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Lifestyle Factors that Impact Progression of Alzheimer's Disease

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Abstract

While there have been decades of research looking into the causes of Alzheimer's disease (AD), the true underlying pathogenesis continues to be a focus of active mechanistic studies. Even so, there is little holistic understanding of what processes or therapies help alleviate the decline of memory and cognition. As a result, it is difficult for caregivers and healthcare providers to have tangible actions to focus on that are validated to maintain or improve an Alzheimer's patient's function and quality of life. Here, we present a literature review of the currently available research to examine which social and physiological factors, such as music, exercise, diet, and more, affect the disease progression and, of those, which slow it. We then summarize the currently available treatment options for Alzheimer's dementia based on the previous findings. For example, melatonin improves disrupted circadian rhythms, while aerobic exercise and Mediterranean diets give neurons protection against beta-amyloid dysfunction through increased brain derived neurotrophic factor (BDNF). Additionally, SSRI drugs can help maintain brain mass while music therapy can temporarily activate preserved brain regions that enable positive moods.

Keywords: Alzheimer's Disease, Dementia, Caregivers, Cognition

1. Introduction

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders, affecting 5.8 million people in the US (Matthews et al., 2019), according to the CDC, and more than 50 million worldwide (Hebert et al., 2013). In 2020, treatment costs added up to $300,000,000,000 in the US and is thought to increase substantially as the disease progresses in patients with AD (Wong, 2020). Additionally, about 4% of the population in the US acts as an unpaid caretaker to someone with AD ("Caregiving for a Person with Alzheimer's Disease or a Related Dementia," 2019).

While the cause of the disease is still widely disputed, one of the main physiological characteristics is the buildup of beta-amyloid (plaques) and the tau protein (tangles) in the brain (Gulisano et al., 2018; Mena et al., 1995; Seeman & Seeman, 2011; Takahashi et al., 2017). In tandem, there is disruption of neural networks, resulting in memory loss and cognitive decline. The buildup also affects glial cells, which act as the protector cells of the brain. The glial cells help to maintain homeostasis and provide support and protection to the neurons. The plaques and tangles have been associated with glial cell destruction, which then results in brain atrophy. Comparison of an unaffected brain versus one with Alzheimer's shows a significant decrease in volume and mass, particularly in the hippocampal regions. As a result, many brain systems are interrupted leading to the symptoms of memory loss and cognitive decline. Often, people with the disease rely on others to help facilitate daily life.

With the lack of knowledge on an optimal treatment or therapy for AD, caregivers often feel

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overwhelmed. 80% of people with Alzheimer's receive in-home care, and some studies support the idea that caregiving is important to treatment of AD (Vernon et al., 2019), however there are very few studies done on that topic. There are social and physiological factors that have been scientifically shown to help outcomes of disease progression for AD. We chose these factors based on the idea that each is a highly variable process that has been shown to affect an individual's experience with AD based on the way they experience it.

The objective of the review is to summarize from available literature on how social and physiological factors impact the progression of AD and explore currently available treatment options based on the findings. Our hypothesis is that awareness of these factors is important so caregivers can either minimize the adverse effects or maximize the potential therapeutic benefit to deal with a non-reversible condition (Iqbal et al., 2010) Additionally, viable treatment options can be sourced from these factors by sourcing the beneficial aspects and regulating them into a therapy or treatment. For example, in the realm of sleep, caregivers can administer melatonin to a patient to improve disrupted circadian rhythms while aerobic exercise and Mediterranean diets improves production of BDNF, which gives neurons protection against beta-amyloid dysfunction. In patients with a history of depression, SSRI drugs can help maintain brain mass which normally decreases in AD. Finally, music therapy could be used as adjunct therapy for patients who are in the late stages of the disease with confusion or depression. This review was limited by a variety of factors such as small sample sizes and lack of uniformity in metrics.

2. Social and physiological factors that affect disease progression, cognition, and quality of life

In this section, we explore the social and physiological factors in greater detail with emphasis on prior studies and their impact on the progression of the disease. Those covered are sleep, exercise, diet, mental health, and exposure to music, each of which has been studied in relation to the advancement of the disease and are extremely mutable processes.

2.1 Sleep

In Alzheimer's disease, sleep disturbance is common, due to both environmental and genetic factors. Multiple studies have explored the relationship between sleep quality and functional independence. In particular, studies have demonstrated that greater independent activities of daily living (IADL) function were associated with higher objective sleep efficiency (OSE) and a higher Pittsburgh Sleep Quality Index (PSQI), (Hodgson et al., 2014; McCurry et al., 2006; Zhou et al., 2019). Furthermore, Zhou et al. (2019) found that people who had a better sleep quality also were more likely to have better cognitive function, while Hodgson et al (2014) found that people who had better PSQI had improved quality of life with regards to the categories of "Feelings" (which encompass self- concept) and "Everyday life" (which describes the patient's ability to independently navigate their life). Interestingly, research in this field has also demonstrated a positive relationship between daytime sleep and severity of cognitive decline, including results from other studies (Bonanni et al., 2005; Ohadinia et al., 2004). However, sleep disturbance doesn't correlate with AD severity in all studies, indicating that genetic susceptibility may play a role in these heterogeneous results (Fernandez-Martinez et al., 2002). In conclusion, sleep in Alzheimer's dementia is an important factor that can regulate a patient's quality of life, particularly with regards to their independent function and other aspects of their social lives.

Many medications have been introduced to enhance sleep in Alzheimer's dementia. A negative relationship between melatonin and amyloid effects have been found in many studies (Cardinali et al., 2005; Lin et al., 2013; Pandi-Perumal et al., 2005). Interestingly, melatonin decreased sleep latency significantly relative to placebo treatment (Cruz-Aguilar et al., 2018). Further research would have to be done to see if it helped with cognitive decline. Additionally, antipsychotics are prescribed for the behavioral manifestations of AD which have been effective as a last resort; however, they can increase the risks of falls and cardiac side effects (Katz et al., 1999; Rocca et al., 2007; Rocha et al., 2006). Serotonergic agents did not show benefits to

cognitive deterioration in AD (Atri et al., 2018; D. A. Bennett, 2018; Severino et al., 2018). Both norepinephrine and formoterol are commonly available medications that are now in preclinical and clinical trials, with future results to be released regarding efficacy (Dang et al., 2014). Donepezil has many varying results on clinical efficacy with many inconsistencies, but one generally agreed upon finding is that it improves REM sleep percentage (Cooke et al., 2006; dos Santos Moraes et al., 2006; Naharci et al., 2015). According to those same studies, galantamine has had little to no benefit when it comes to improvement of sleep architecture; many studies so far demonstrating efficacy have been non-randomized trials, therefore future randomized controlled trials (RCTs) are needed to probe this therapy further. Interestingly, rivastigmine, despite being a popular treatment for AD, has not been studied in a large enough capacity to determine the exact effect, although it has been suggested that it decreases PSQI insignificantly. A non-medication option is bright light therapy (BLT), which various studies showed can be helpful to regulate sleep schedules and has no serious adverse effects (Ancoli-Israel et al., 2003; Fetveit & Bjorvatn, 2005). In conclusion, these medications have been beneficial in improving sleep quality, independent functioning, and quality of life; however, there is still little to no evidence that these therapies prevent disease progression.

2.2 Exercise

Many studies have validated that exercise does help in prevention of AD and help stagnate the progression of AD. Exercise does not affect cognitive decline in AD; the study that supported this opinion was not randomized so further research will have to be done to fully support it (Borges-Machado et al., 2019). Additionally, quality of life was unaffected as a result of the intervention. Exercise also produces necessary proteins to protect against AD, specifically brain-derived neurotrophic factor (BDNF). Many studies cite a negative correlation between BDNF levels and the progression of AD (Connor et al., 1997; Holback et al., 2005; Holsinger et al., 2000; Nigam et al., 2017; Peng et al., 2005; Phillips et al., 1991). BDNF also acts as a catalyst for antioxidant enzymes, so a lack of this factor could predispose a neuron to beta-amyloid dysfunction. Wrann et al. (2013) also supports this claim while also detailing that exercise specifically induces the PGC-1α/FNDC5 pathway, which can increase BDNF production. Additionally, in a simulation with AD mice, those with increased exercise were found to have less neurogenesis impairment, due to a higher number of BrdU/NeuN+ cells which is theorized to help stop the progression of AD. Of note, this work has not yet been replicated in humans (D. Kim et al., 2019). In summary, BDNF production is why exercise is important in the regulation of AD and BDNF itself could possibly be further researched as a possible treatment option for AD.

Aerobic exercise has been shown to be significantly effective as an adjunct treatment for AD. In a study done by Sampaio et al. with AD patients with a neurocognitive disorder and other health issues, increased aerobic capacity resulted in the greatest improvement of cognition (Sampaio et al., 2020). Adversely, lower body flexibility, agility, and dynamic balance were not associated with cognition at all. Additionally, many studies suggest aerobic exercise improves executive control, working memory, visuospatial memory, retention and reaction time in humans (Chaddock et al., 2010; Churchill et al., 2002; Herting & Nagel, 2012; Hillman et al., 2008; Skriver et al., 2014; Spirduso & Clifford, 1978; van Praag et al., 1999). Similarly, in a study by Vidoni et al. (2019), aerobic exercise was shown to be significantly better compared to stretching and toning on the Disability Assessment for Dementia (DAD), showing more stability for functional independence and increasing IADL and ADL independence. Additionally, oxygen uptake increased in an intervention group who performed aerobic exercise regularly in Sobol et al by 13%; however, in this study there was no additional mechanistic experiment to determine whether increased oxygenation improved AD quality of life (Sobol et al., 2018). Finally, in a study by Liu et al. (2013), a mouse model of Alzheimer's, treadmill workouts for five months decreased the progression of plaque buildup in their brains and also soothed behavioral problems. Further research will have to be done to

see if these same results of exercise improving AD pathophysiology can be replicated in humans. To summarize, aerobic activity tends to be far superior to other forms of exercise and could be used as a preventative option for patients who still have the capability of motion or patients who are still in the early stages of the disease.

2.3 Diet

Diet is an important factor in preventing AD and also slowing the progression of AD. A number of factors could be at play, including vitamin deficiencies, ratios of macronutrients, and genetic contribution to diet response. One prospective cohort study found that lower concentrations of vitamin B12 and folate (B9) were associated with a two-fold increase in likelihood to develop AD compared with higher concentrations (Wang et al., 2001). Of note, while there is currently limited mechanistic information as to how B12 and folate deficiencies can contribute to AD, it has been well-established that B12 deficiency leads to homocysteine buildup, which is neurotoxic (Bhatia & Singh, 2015; Obeid & Herrmann, 2006). In addition, vitamin D3 deficiency has been inversely correlated with the risk of AD, as it increases phagocytosis of beta-amyloid. In rodents, a ketogenic diet increased the progression of beta-amyloid build-up, whereas intermittent fasting decreased this buildup, compared to a control group of transgenic rats with AD (Ito et al., 2011; Singh et al., 2014). A Mediterranean diet, which consists of olive oil, grains, and vegetables, in unaffected individuals was shown to reduce the chance of having AD by up to 40% (Abuznait et al., 2013; Daccache et al., 2011; Miquel et al., 2018; Scarmeas et al., 2006; Szczechowiak et al., 2019; A. Wu et al., 2004). Also, the Mediterranean diet can be paired with exercise to increase BDNF production, which negates the progression of AD. Finally, in a study done by Luchsinger et al. (2002), people who were in the highest percentile for consumption of fats and calories who also possessed the APOE 4 allele, an allele that has been well- associated with AD, were found to have increased risk of AD. Overall, diet should be carefully examined in individuals with a family history of AD and in the early stages of AD to ensure adequate nutritional balance.

2.4 Depression

Major depressive disorder, commonly referred to as depression, has been thoroughly researched in recent years as a response to increased publicity of mental health. In a case-control study of 125 people, episodes of depression, particularly those in older adults, were positively correlated with a higher risk of Alzheimer's disease/dementia compared to non-depressed individuals (Cantón-Habas et al., 2020). Additional research suggests the reason behind this trend, with protein metabolism being correlated with symptoms of depression (K.-Y. Wu et al., 2018; Zvěřová et al., 2013). Cortisol levels have also been suggested to be associated with cognitive decline in people with AD and symptoms of depression. Depression and dementia are also theorized to have similar pathophysiologic pathways; an alternate hypothesis is that depression is a prodromal symptom of dementia (Amieva et al., 2008; S. Bennett & Thomas, 2014; Wilson et al., 2008). Overall, depression is more than likely a major risk factor for AD and dementia, making it important to be aware of by caregivers.

Different depression treatments have been shown to help slow the progression of AD. Selective serotonin reuptake inhibitors (SSRI) are drugs that stop the reabsorption of the neurotransmitter serotonin back into the presynaptic neuron. Fluoxetine, commercially known as Prozac, is an SSRI drug that has been associated with treatment of AD. In many studies, use of fluoxetine has been positively associated with the mass of the hippocampus, hypothalamus, and anterior cortex (Bath et al., 2012; Chen et al., 2007; Imoto et al., 2015; Jin et al., 2017; Mendez-David et al., 2014; Phillips et al., 1991; Reynolds et al., 1995; Santarelli et al., 2003). Interestingly, in Alzheimer's disease there is atrophy of the frontal and temporal cortices. Thus, hippocampal mass preservation, in the temporal cortex, could demonstrate a structural basis of therapeutic effect of antidepressants in the therapeutic efficacy for both depression and Alzheimer's disease. BDNF levels have also been positively correlated with fluoxetine, providing

evidence towards additional neuropharmacological benefits. Other SSRI drugs, including sertraline, citalopram, trazodone, and moclobemide, have also been similarly effective. Buspirone, and mirtazapine have not been studied enough to come to a conclusion (Buhr & White, 2007; Herrmann & Lanctôt, 2007; Lyketsos et al., 2003; Sink et al., 2005; Starkstein & Mizrahi, 2006).

Some studies have found that while psychotherapy is effective initially, therapeutic benefit decreases over time; thus they recommend psychotherapy as a short-term option for comorbid depression and Alzheimer's disease. However, other studies demonstrate long-term efficacy in psychotherapy treatment of depression in the elderly, thus further large-cohort studies are needed to demonstrate true effect (Farina et al., 2017; Leong, 2014). In the study by Wilkins et al. (2010), it was especially found that efficacy of cognitive behavioral therapy (CBT) was dependent on note-taking and frequent summaries in patients with dementia to account for memory loss, in order for therapy to be effective. This perhaps could have contributed to the decreasing efficacy seen in other studies. In conclusion, SSRI therapy can be considered a first-line therapy for patients with comorbid Alzheimer's and depression, but psychotherapy could also be a beneficial second-line therapy.

2.5 Music

Music therapy has been researched as a short-term therapy for AD patients. In general, long-term music-related memory remains more preserved, whereas short-term and autobiographical long-term memory are relatively more affected in patients (Dahms et al., 2021). The latter two are represented in the hippocampus, which is very quickly atrophied in AD. As a result, patients with AD show the most intense response to music that they prefer and are familiar with, as it activates the supplementary motor area of the brain that is not affected in the early progression of AD. Additionally, emotionally charged music was shown to recall autobiographical memory efficiently, especially events that were emotional or important to the patient (Guetin et al., 2013). Music therapy also slows the decrease in Mini-Mental State Exams (MMSE) scores. In one study, MMSE scores of a patient group who had received music therapy was significantly better than the control group. In a study done in China, Mozart and Liangzhu music, ancient Chinese orchestral music, were shown to be the most effective at improving quality of life indices. This may be because the population studied was an elderly Chinese population and therefore could have been exposed to this music in their childhood and adolescence. Indeed, Arroyo-Anlló et al. (2013) demonstrated that while patients with AD experienced a decline in MMSE scores with unfamiliar music exposure, those who were exposed to familiar music had no change in MMSE scores. In a case study from Japan, while music therapy improved a client's social interaction, it did not affect the client's depression and progression of dementia. Finally, other studies have also linked music therapy with increased global cognition, decreased anxiety and irritability, and interestingly improved quality of life of caregivers (Bruer et al., 2007; Gómez Gallego & Gómez García, 2017; Herholz et al., 2013; H.-J. Kim et al., 2016). Overall, while there is no strong evidence that music therapy slows the progression of AD pathology, it can be used as a method for improving quality of life for both AD patients and caregivers as well as caregivers, although there is no strong evidence towards slowing the progression of the disease pathology.

3. Discussion

This review highlights some of the keyways that caregivers can approach helping patients with Alzheimer's disease (AD). We found many ways to improve quality of life in a patient and slow the progression of the disease. For example, in the realm of sleep, caregivers can administer melatonin to a patient to improve disrupted circadian rhythms or aid with falling asleep as it decreases sleep latency. Aerobic exercise should be encouraged in patients who still have full range of movement as it improves production of BDNF, which gives neurons protection against beta-amyloid dysfunction. Additionally, a Mediterranean diet also is correlated with increased BDNF production while also decreasing the risk of AD by 40%, which can be incorporated into a

patient's daily meals. In patients with a history of depression, SSRI drugs can not only help with mood symptoms, but also help maintain brain mass which normally decreases in AD. Finally, music therapy could be used as adjunct therapy for patients who are in the late stages of the disease with confusion or depression, due to temporary activation of preserved brain regions that enable positive mood and music-related associations.

This review was limited by a variety of factors. For example, the studies examining the role of sleep in AD involved many different metrics for sleep quality, making it difficult to directly compare the results. In many of the studies, rodents were used as the animal model. While rodent brains are useful in simulating many human processes, it is still hard to validate the results as rodent brains still have many significant differences from a human brain. The sample sizes were sufficient in most of the papers, however some, especially those examining the relationship between AD and depression, were not big enough to fully validate the results. While we initially were looking to characterize how best to support patients with late-stage AD, we found that most of the studies, including the ones here, examined effects on patients with early-stage AD. This could be because late-stage AD patients may not be able to participate in a study to the full extent as compared to a patient who has just been diagnosed. Further studies will need to be conducted to further examine whether these lifestyle protective measures also can be therapeutic in late-stage AD.

4. Conclusion

This paper focuses on therapies that are non-invasive and interventions that caregivers can easily administer. The results of this study can be used to facilitate home life of AD patients, as well as make it easier for them to deal with the debilitating effects of the disease in a way that improves quality of life. In particular, we examined the roles of sleep, diet, exercise, antidepressant medication, and music in improving AD symptomatology. We hope that the summarized results provide new tangible ideas for caregivers to help implement to improve the daily lives of patients with AD.

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