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Sleep and Circadian Rhythm Dysfunction in Alzheimer's Disease

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THE PROBLEM: WHY IS ALZHEIMER'S DISEASE SO SEVERE AND PROGRESSIVE?

DEMENTIA: A DEFINITION

While it is common to label memory loss as the primary symptom of dementia, memory functioning only accounts for one the many factors associated with a dementia diagnosis (Hugo, 2014). Dementia symptoms also involve impairment in regard to attention, executive functioning, learning, language, and visuo-spatial abilities (Hugo & Ganguli, 2014). Thus, dementia is characterized by a clinically significant and severe cognitive impairment, affecting a patient's functionality in many different ways (Lane et al., 2018). While some cognitive impairment is not unusual with aging, clinicians agree that the impairment experienced in dementia patients affects multiple cognitive areas and must impede daily functioning, even socially (Hugo & Ganguli, 2014). Of course, the shift from normal cognitive functioning to a severe level of cognitive impairment occurs on a spectrum; in fact, the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders includes a separate diagnosis for the intermediate state of cognitive decline, Mild Cognitive Impairment (MCI) (Chagas et al., 2018). These patients do not display the functional impediments seen in true dementia patients (Karantzoulis et al, 2011).

Strict guidelines and testing strategies are also being developed to ensure accurate diagnosis and proper indication of significant changes in the severity of symptoms, most often initiated by a demonstrated concern by the patient or the patient's loved ones (Albert et al., 2011). However, it must be noted that the cognitive tests used to assess cognitive status are not very reliable, with results varying based on the presence of external factors affecting baseline conditions (Albert et al., 2011). Age is a particular variable of interest, as scores on generalized cognitive tests may be skewed for the elderly at baseline (Albert et al., 2011). This highlights an

obstacle neurologists face when evaluating any neurological or psychiatric disorder, as a patient's presentation rarely warrants a textbook diagnosis; for this reason, treatment and research in these fields is quite complex. Additionally, dementia and MCI can be caused by trauma and other external factors, and the pathology of dementia is often comorbid with conditions like cardiovascular disease, so the underlying causes of dementia are also often difficult to determine (Albert et al., 2011). Early detection of dementia is necessary for effective treatment; unfortunately, due to these discrepancies, there are many cases where symptoms of cognitive impairment are overlooked and, therefore, undiagnosed (Atri, 2019). In fact, a study showed that primary care physicians ignored early onset symptoms in two thirds of dementia patients (Valcour et al., 2000). The complicated nature of the disease is thus made even further complex due to poor recognition of symptoms during such a critical period of potential treatment.

There are several types of dementia, each with different etiology, affecting different domains of cognitive impairment (Dening & Sandilyan, 2015). Vascular dementia, also called vascular cognitive impairment, is an extremely common form of dementia, second only to Alzheimer's Disease (O'Brien & Thomas, 2015). As the name implies, this form of dementia is characterized by poor blood circulation to the brain (Dening & Sandilyan, 2015). There are many underlying risk factors for vascular dementia such as cardiovascular disease, hypertension, and stroke. Importantly, post-stroke dementia is actually only one of the subtypes of vascular dementia as there are many cases of vascular dementia that present without history of stroke (O'Brien & Thomas, 2015). Patients typically exhibit impairment in language, memory, executive functioning and attention; however, as there are many variants of vascular dementia, presentation can vary and therefore, diagnosis and treatment are challenging (O'Brien &

Thomas, 2015). The third most prevalent form of dementia is Lewy Body dementia, characterized by the presence of alpha-synuclein protein aggregates, also known as Lewy Bodies, in the brain (Dening & Sandilyan, 2015). With many similarities to Parkinson's Disease, patients may exhibit symptoms such as trembling of extremities and a shuffled gait pattern (Dening & Sandilyan, 2015). Other symptoms include disturbed sleep, visual hallucinations, memory loss, visuospatial difficulty, and impaired executive function (Dening & Sandilyan, 2015). While dementia is often a late complication of Parkinson's Disease, the two are considered distinct disorders (Garcia-Ptacek & Kramberger, 2016). Frontotemporal dementia, a much less common form of dementia, is a label given to dementias that affect the rostral portion of the brain (Dening & Sandilyan, 2015). Unlike other forms of dementia, the onset of frontotemporal dementia can occur as early as ages 30-40 (Olney et al., 2017). Subcategories include behavioral variant frontotemporal dementia, categorized by profound behavior changes, and primary progressive aphasia, demonstrated by significant language and speech impairment (Dening & Sandilyan, 2015). These categories of dementia are not firmly defined, and there is some overlap in pathology, especially between vascular dementia and Alzheimer's Disease, which are often comorbid (O'Brien & Thomas, 2015). In fact, when more than one form of dementia is present, a patient is given a diagnosis of Mixed Dementia (Dening & Sandilyan, 2015). Additionally, there are other forms of progressive dementia that do not fit into these categories, including Multiple Sclerosis, Creutzfeld-Jakob disease, and Huntington's Disease (Dening & Sandilyan, 2015).

Essentially, there are many types of dementia that overlap, indicating the complex mechanisms underlying the development and progression of these diseases, especially considering the presence of comorbid disorders and many risk factors involved. Genetics also

plays an integral role in each dementia diagnosis, each to a varying degree; for example, Huntington's Disease is grossly hereditary, while certain biomarkers may only suggest that an individual is more susceptible to developing Alzheimer's Disease (Dening & Sandilyan, 2015). Most importantly, the prevalence of dementia is increasing on a global scale, and researchers expect that there will be 115.4 million people diagnosed with dementia in 2050 (Hugo & Ganguli, 2014). Thus, continued research and the development of innovative treatment plans is imperative for the future of dementia disorders.

ALZHEIMER'S DISEASE: A GENERAL OVERVIEW

By far, Alzheimer's Disease (AD) accounts for the majority of dementia cases, affecting approximately 70% of dementia patients over the age of 65 (Ljubenkov & Geschwind, 2016, 2016). The disease almost exclusively affects elderly individuals, as the prevalence AD cases doubles every five years after age sixty-five (Lane et al., 2018). In addition, females are about 1.5 times more likely to develop Alzheimer's Disease compared to males (Atri, 2019). From a biological perspective, Alzheimer's Disease is associated with abnormalities in the function of multiple different classes of neurotransmitters, indicating the complex brain mechanisms involved in the pathology of the disease (Selkoe, 1991). In terms of symptoms, a diagnosis of AD is preceded by a diagnosis of MCI, and patients commonly demonstrate impaired episodic memory, spatial orientation, language abilities, and executive functioning (Karantzoulis et al., 2011). Eventually, patients experience a more progressive and comprehensive cognitive decline, which results in extreme difficulty with multitasking and completing daily tasks.

In addition, there are fundamental structural abnormalities in the brain that characterize degeneration of brain tissue seen in AD, including the presence and accumulation of β-amyloid

plaques (Selkoe, 1991). As supported by the Amyloid Hypothesis, this pathology is widely considered as one of the primary causes of the impaired function of neurotransmitters, cognitive dysfunction, and the disruptions of homeostasis that characterize AD (Hardy & Selkoe, 2002). Along with the discovery of an accumulation of neurofibrillary tangles of tau proteins, these factors have since been used as biomarkers for identifying early-onset Alzheimer's Disease and differentiating AD from other forms of dementia or cognitive impairment (Hardy & Selkoe, 2002). However, the mechanisms underlying the presence of these of β-amyloid plaques and tau proteins are still being investigated and the origins of this pathology are still unclear (Lane et al., 2018). As a result, the true relationship between these biomarkers and the cognitive changes seen in AD is unknown (Ferreira-Vieira et al., 2016). Nonetheless, the contribution of the discovery of these biomarkers to diagnosis of AD has also proven to be very effective for determining progression of the disease (Lane et al., 2018).

Another biological characteristic of AD is the dysfunction of the cholinergic system in the brain, which is an important component of cognition, affecting neural plasticity as well as learning and memory (Hampel et al., 2018). There are multiple cholinergic pathways in the brain, but scientists have discovered that the main area of cholinergic degeneration in AD is the nucleus basalis of Meynert, which is located in the basal forebrain (Hampel et al, 2018). Acetylcholine receptors, categorized as either muscarinic or nicotinic, function in multiple areas of the brain and are very important for cognitive functioning, response to stress, attention, and the sleep-wake cycle (Ferreira-Vieira et al., 2016). Muscarinic receptors, labeled M1-M5, are involved in many complex signaling cascades that affect the regulation of proteins in brain areas affected by AD, including the hippocampus, prefrontal cortex, and thalamus (Ahmed et al., 2017). Amyloid precursor proteins are under regulatory control of the cholinergic system, so

researchers have speculated that fluctuations of the cholinergic neurons lead to dysregulation of proteins in the brain and, potentially, the cognitive impairments seen in AD (Ahmed et al., 2017). Treatment methods using cholinesterase inhibitors are very effective and are a widely used treatment method for the symptoms of Alzheimer's Disease (Hugo & Ganguli, 2014). However, I argue that behavioral methods may be more effective for long-term improvement and recovery from AD-associated neuronal cell death in the cholinergic system.

A diagnosis of Alzheimer's Disease warrants brain imaging, as AD patients commonly present with bilateral symmetrical atrophy to medial brain regions in the temporal lobes (Lane et al., 2018). Extensions of this atrophy are presented in later stages of the disease (Karantzoulis et al., 2011). In addition, imaging allows clinicians to rule out other potential causes of cognitive impairment, such as lesions to brain regions as well as other possible neurological disorders (Lane et al., 2018). Genetic testing is also effective, as a family history of AD has been linked to about seventy percent of the risk of developing the disease (Lane et al., 2018).

WHY STUDY ALZHEIMER'S DISEASE?

Alzheimer's Disease is recognized as one of the top ten leading causes of death for the United States; however, the CDC has released data showing that establishing death rates for Alzheimer's Disease is challenging because the death of many AD patients is frequently attributed to complications that arise from the disease, such as decreased mobility, dysphagia, or malnutrition that increase their susceptibility to serious infections such as pneumonia (Alzheimer's Association, 2016). In fact, Medicare released data demonstrating that approximately one third of the annual deaths of Americans older than age 65 have a medical history of dementia (Alzheimer's Association, 2016). Thus, the progression of Alzheimer's

Disease is an extremely relevant factor in regard to health complications and, unfortunately, even death of AD patients.

Public health systems around the world are not equipped to handle the pervasiveness of Alzheimer's Disease in terms of seeking out a cure as well as treating a perpetually increasing number of patients annually (Wortmann, 2012). With such high prevalence, AD has become an economic issue as a result of healthcare costs and the loss of members of the workforce due to caregiver necessity (Wortmann, 2012). The World Health Organization highlights that this public health problem stems from the stigma associated with it, also reflective of how socioeconomic status may impact the way patients, families, and practitioners approach and ultimately endure the progression of AD (World Health Organization, 2012). It is clear that AD has made an extreme impact on healthcare, emphasized by the continued challenges researchers face in determining its etiology, developing effective treatment plans, and ultimately finding a cure. Alzheimer's Disease differentially affects all parties involved, and, with such social value, continued education of the public is absolutely necessary.

A POTENTIAL SOLUTION: THE ROLE OF THE CIRCADIAN SYSTEM IN ALZHEIMER'S DISEASE

As mentioned above, key symptoms of AD include disturbed sleep (Dening & Sandilyan, 2015) and dysfunction of brain areas like the cholinergic system, which regulates the sleep-wake cycle (Hampel et al., 2018). These factors, therefore, play integral roles in both the pathology and treatment of the disease. Dysfunction of human circadian rhythms have also been correlated with many other disrupted health conditions, including cardiovascular disease and lung cancer, reflecting the importance of its role in multiple body systems (Bollinger & Schibler, 2014). As Alzheimer's Disease often co-occurs with other chronic medical conditions, the relationship between circadian rhythm abnormalities, sleep dysfunction, and Alzheimer's Disease is clinically and socially relevant. This interaction highlights the significance of the role of these homeostatic functions in the features of Alzheimer's Disease, both individually and globally.

SLEEP AND CIRCADIAN FACTORS: AN OVERVIEW

The rhythmic oscillations of many body processes, such as metabolism, body temperature, and hormone secretion are endogenously generated by the circadian system in mammals and driven by molecular oscillators (Bollinger & Schibler, 2014). These circadian rhythms, either behavioral or physiological, are clinically significant as they modulate the body's activity on a twenty-four hour cycle and allow the effective use of metabolic resources without explicitly relying on the presence of external cues (Weaver, 2016). However, the external light-dark cycle plays an integral role in circadian function as it entrains the body's endogenous circadian cycle, allowing for external regulation of these rhythms (Bollinger & Schibler, 2014; Weaver, 2016). This indicates the significance of light exposure to the sleep-wake cycle, a functionally important circadian rhythm. Abnormal patterns of light exposure, seen in hospital

or institutional settings as well as in patterns of shift work hours, therefore have the ability to completely disrupt the body's circadian sleep cycle, dysregulating bodily processes and, likewise, affecting health outcomes (Reitz & Martino, 2015).

The brain region considered responsible for controlling these endogenous mechanisms, called the brain's master clock, is the suprachiasmatic nucleus (SCN) of the hypothalamus, which also happens to be anatomically located above the optic chiasm (Bollinger & Schibler, 2014; Weaver, 2016). This further indicates the importance of the communication between these brain areas for optimal circadian functioning (Weaver, 2016). In addition, the SCN plays a role in regulating the rhythmic activity of peripheral oscillators throughout the body through multiple transcriptional-translational feedback loops, essentially allowing for the generation of complex and cooperative circadian rhythm control (Weaver, 2016). The SCN, notably, is an area of severe degeneration in Alzheimer's Disease (Coogan et al., 2013); thus, SCN degeneration is a proposed mechanism for disrupted circadian activity in AD patients, as its decreased functioning inhibits the effective communication of the SCN with peripheral oscillators. As such, it is clear that disruptions in circadian rhythms as well as daily light exposure are relevant to Alzheimer's Disease.

Just as the circadian sleep-wake cycle is clinically relevant, the sleep cycle itself, which is an ultradian rhythm, likewise has health-related effects (Baghdoyan & Lydic, 2012). While there is a lot of evidence underlying the neurochemical regulation of sleep and wakefulness, it is important to note that the explicit function of sleep is unclear and difficult to determine experimentally (Baghdoyan & Lydic, 2012). Nonetheless, it is well-known that sleep is necessary for survival and that disturbed sleep as well as sleep deprivation are strongly associated with adverse health effects as well as significant cognitive impairment (Brown et al.,

2012). The sleep cycle consists of two main phases, rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep, each of which is thought to play a different role in memory consolidation (Brown et al., 2012; Ackermann & Rasch, 2014). While the mechanisms of memory consolidation during sleep are unclear, researchers know that sleep aids in the formation of memories (Ackermann & Rasch, 2014). In addition, activation of cholinergic neurons is thought to be important for memory consolidation during REM in the elderly (Hornung et al., 2007). REM sleep is also associated with dreaming, indicating that dreams themselves may play a role in this processing (Lamberg, 2004). This is extremely relevant for Alzheimer's Disease because, as mentioned earlier, memory loss is a primary symptom of AD (Hugo & Ganguli, 2014), and AD is strongly associated with degeneration of cholinergic neurons (Hampel et al., 2018).

In terms of sleep-wake cycle abnormalities, Alzheimer's patients typically demonstrate increased daytime sleep and frequent awakening from nighttime sleep (Coogan et al., 2013). This dysregulation of the sleep-wake cycle is further exacerbated in long-term care facilities such as nursing homes, in which patients receive decreased exposure to natural light (Coogan et al., 2013). In addition, it can be inferred that seasonal changes of daylight hours in some geographic areas may also have increasingly harmful effects. The implications of such abnormalities are extensive, considering that adults ideally need seven to eight hours of healthy sleep each night for proper daily performance and optimal health (Watson et al., 2015). Further, researchers state that excessive sleep may often be as harmful as sleep deprivation in adults (Watson et al., 2015). Individuals with Alzheimer's Disease, who are clearly experiencing unhealthy sleep, are thus at a critical health disadvantage. To make matters worse, sleep is largely undervalued in today's society, despite extensive research indicating the importance of sleep for overall mental and

physical health. Thus, the clinical implications of circadian dysfunction and sleep dysregulation ought to be emphasized even further, especially as they relate to debilitating and often fatal conditions such as Alzheimer's Disease.

ALZHEIMER'S DISEASE, SLEEP, AND CIRCADIAN RHYTHMS: THE PATIENT

Every case of Alzheimer's Disease progresses differently, as some patients die in as little as four years after onset while others live twenty years past their original diagnosis (Atri, 2019). As mentioned previously, diagnosis is often delayed (Atri, 2019). A study in China stated that there is a 1-2 year period between onset of symptoms and seeking out neurological treatment (Zhao et al., 2016). Of course, this can be a result of many external factors such as socioeconomic status and education level. Regardless of its cause, though, this latency of treatment can have a profound effect on patient outcomes. The timeline is largely dependent on the patient as well as the presence or absence of other risk factors, many of which are affected by circadian rhythm dysfunction (Bollinger & Schibler, 2014). Cardiovascular disease, a prominent risk factor for developing AD (Zhong et al., 2015), often results from dysfunction of circadian rhythms, which can be attributed to instances of myocardial infarction and even cardiac death (Reitz & Martino, 2015). In addition, because circadian rhythms affect the modulation of the body's response to inflammation, this system also aids in the functional and structural changes of the heart during recovery from myocardial infarction (Reitz & Martino, 2015). As the inflammatory response is a key component of the immune system, disruptions in the immune system can also be associated with other health conditions beyond those associated with the cardiovascular system. This role of the immune system has gained increasing attention in recent years, as researchers have found that the neuroinflammation that characterizes AD is a result of

chronically activated microglia due to dysregulation of the immune response (Sarlus & Heneka, 2017). Additionally, it is hypothesized that this chronic activation may play a role in propagating aggregated tau proteins in the brain as well as disrupting neuronal signaling in the nervous system (Sarlus & Heneka, 2017). Thus, this could become a more relevant target for treatment of AD in years to come.

There are many other risk factors that contribute to both cardiovascular disease and Alzheimer's Disease including obesity, hypertension, and diabetes mellitus (Alzheimer's Association, 2016). Diabetes mellitus patients exhibit a more rapid cognitive decline with AD, and abnormalities in glucose metabolism can affect the presence of amyloid plaques as well as brain atrophy (Shinohara & Sato, 2017). There is a circadian component to this as well, as these abnormalities can be a result of misaligned feedback communication between the SCN's modulation of glucocorticoid release and the peripheral oscillatory response of target endocrine organs (Oster et al., 2016). As discussed previously, this ineffective circadian communication thus adversely impacts the functioning of multiple body systems (Oster et al., 2016; Weaver, 2016).

Smoking status also contributes to the progression of AD, serving as a competitive death risk, meaning that deaths that are smoking-related may occur earlier in life and may also overshadow an underlying case of AD (Chang et al., 2012). Studies have also shown that this survival bias may affect incidence rates of dementia because non-smoking patients generally live further into their elderly years when AD symptoms typically arise (Chang et al., 2012). There is also a biological element to this risk, as the oxidative stress that smokers are subjected to has the potential to affect the presence of neurofibrillary tangles that characterize dementia (Zhong et al., 2015). The vascular risk associated with smoking further supports the association between

smoking and AD (Zhong et al., 2015). Although there are many negative side effects of tobacco use, studies have shown that nicotine, a nicotinic acetylcholine receptor agonist, improves cognitive functioning; one study demonstrates that administration of nicotine prevents the development of memory deficits and preserves plasticity in rodents with drug-induced AD-like dysfunction (Esteves et al., 2017). As cholinergic drugs have already proven to effectively slow the progression of AD symptoms, there are several proposed benefits of nicotine treatment of AD (Esteves et al., 2017). However, the negative side effects of nicotine use are well-known, and further research must be done before this could be feasible and well-regulated.

Obstructive sleep apnea (OSA), a sleep disorder, is often comorbid with Alzheimer's Disease and also associated with major AD risk factors such as cardiovascular disease and hypertension (Liguori et al., 2017). However, the relationship between OSA and AD is not clearly defined, as both OSA and AD are common in the elderly and intimately related to cardiovascular health (Brzecka et al., 2018). As a sleep disorder, OSA disrupts normal sleep and specifically results in increased sleep fragmentation due to increased periods of arousal with apneas (Brzecka et al., 2018). For patients with OSA, hypoxia during sleep results in oxidative stress that, as discussed previously, has been linked to Alzheimer's Disease (Liguori et al., 2017). There is a circadian factor at work here as well, as the various enzymes and antioxidants involved in the body's defense response to oxidative stress exhibit circadian rhythms (Wilking et al., 2013). For example, melatonin, a major sleep-promoting hormone involved in regulating the sleep-wake cycle and controlled by the circadian clock, has been discovered to have antioxidant properties as well as a role in lowering blood pressure, further indicating the complex relationship between circadian rhythms and the cardiovascular system (Wilking et al., 2013). More importantly, this also highlights the impact of the dysfunction of circadian rhythms in AD,

as the oxidative stress and metabolic dysregulation that results from OSA have been associated with the promotion of the neurological degeneration and cognitive impairment seen in AD (Liguori et al., 2017; Brzecka et al., 2018).

Sleep hygiene, which involves modifiable behaviors such as restricting time in bed, limiting caffeine and alcohol intake, and establishing a dark and quiet sleep environment, is important for optimal sleep and, therefore, overall health (Homolak et al., 2018). Poor sleep hygiene is frequently seen in AD patients, as these elderly individuals naturally have more unstructured daily schedules and spend more time in bed; in addition, the atmosphere of nursing homes is normally fairly loud, patients are often exposed to bright light during the night, and sleep is often disrupted by nighttime monitoring by staff (Homolak et al., 2018). While it is true that Alzheimer's Disease is characterized by internally driven sleep abnormalities and dysfunction of the sleep-wake cycle, sleep quality is often further reduced due to the poor sleep hygiene of AD patients (Bollinger & Schibler, 2014; Dening & Sandilyan, 2015).

Thus, it becomes explicitly clear that there is a complex relationship between all of these variables: while the development of several major AD risk factors is strongly associated with circadian rhythm dysfunction and reduced sleep quality, these abnormalities are also considered symptoms of Alzheimer's Disease itself. In addition, many commonly used medications for conditions like hypertension and diabetes disrupt the normal sleep cycle, so it must be considered that any sleep abnormalities AD patients experience could be secondary to or exacerbated by these medications (Naiman, 2017). The presence of these interconnected relationships is a key component of the complexity of Alzheimer's Disease and indicates that many of the risk factors associated with AD may also impact its progression due to the effects of circadian disruptions and decreased sleep quality on these preexisting health conditions. In addition, this deleterious

cycle, with many factors negatively affecting overall health, may also contribute to the timing and cause of death in AD patients.

Health risks aside, the progression of AD undoubtedly has a profound effect on quality of life of the patient. One particular study shows that patient interactions with strong networks of friends is correlated with improved cognitive ability (Balouch et al., 2019). Studies have also shown that groups of elderly females who regularly participate in social activities have a lower incidence of developing dementia (Hugo & Ganguli, 2014). However, this is undoubtedly a bidirectional relationship, as a decline in cognition may also result in fewer social interactions with friends (Balouch et al., 2019). Additionally, patients with dementia are often socially isolated, which can either be a cause or effect of depression and loneliness in dementia patients (Sun et al., 2019). They also experience changes in the ways they engage with their interests, especially in terms of hobbies or exercise (Atri, 2019). While this may be a result of memory loss, a trend toward isolation is largely to blame, as the nature of the patient's self-confidence is diminished with dementia (Atri, 2019). Of course, this may be attributed to a patient's living accommodations as well as a decreased sense of independence and autonomy (Sun et al., 2019). Thus, mental health is extremely relevant for the treatment of patients battling Alzheimer's Disease, as cognitive impairment and decline in mental health are very much related. This is coupled with the fact that many Alzheimer's Disease patients are largely unaware of the functional difficulties they are experiencing with daily tasks, and they frequently attribute any awareness of cognitive decline to other external factors rather than labeling them as symptoms of Alzheimer's Disease (Emery et al., 2018). Agitation is also often a symptom of AD, which impacts patients' overall quality of life as it may potentially create tension in the home (Senanarong et al., 2004). Psychiatric disorders such as post-traumatic stress disorder, anxiety,

and depression are also considered risk factors of dementia, further indicating a bidirectional relationship between mental health and development of AD (Hugo & Ganguli, 2014). Thus, as a complex and degenerative cognitive disease, the mental health symptoms afflicting these patients are likewise multifactorial.

ALZHEIMER'S DISEASE, SLEEP, AND CIRCADIAN RHYTHMS: THE FAMILY/CAREGIVER

Patients, especially those in the later stages of the disease, will generally live in a nursing home or with a full time family caregiver (Lane et al., 2018). This is largely because of the difficulty of implementing patient-centered care in a hospital setting, where the focus is on short term stays due to the increased risk of urinary tract infection, pneumonia, and other illnesses in AD patients with extended stays (Toye et al., 2019). As patients develop a state of complete dependence, the role of the caregiver thus becomes increasingly important for daily functioning of the patient. Quality of life is a priority for the continuity of care of AD patients, and the impression of a patient's overall quality of life is generally very different for the family and health care staff, as education level as well as personal relationship with the patient largely affect their opinions (Robertson et al., 2019). Nonetheless, the role of the family is vital to the experience of the patient, as effective communication with health care staff is best achieved via family caregivers who have a close relationship with the patient as well as knowledge of the patient's medical history and baseline functioning (Toye et al., 2019).

As a result, there is a heavy responsibility and burden placed on caregivers, which has become a significant topic of discussion in the patient care aspects of treating neurodegenerative disorders such as AD. While many caregiver tasks largely involve assistance and guidance with

daily tasks, the work required of family caregivers requires much sacrifice and far exceeds the normal expectations of daily living (Seaman, 2018). It is common for caregivers of AD patients to experience increased stress and anxiety as a result of the emotional burden of their roles, and there is evidence supporting the need for those treating AD patients to better consider the effects of treatment on the caregiver, as this ultimately impacts outcomes for patients themselves (Savundranayaham et al., 2010). Further, the emotional stress can lead caregivers to become more focused on the inevitable health outcomes of AD, adopting complacent attitudes and believing that their intervention does not affect the end result (Seaman, 2018). In addition, the sleep fragmentation and circadian disturbances experienced by AD patients affects caregivers as well, which can also impact their health, affecting their ability and potentially even their willingness to care for the patient in the home (Homolak et al., 2018). This makes the decision of caring for AD patients in the home versus arranging care in nursing homes much more complicated, as there are conflicting viewpoints about the best routes for achieving the highest levels of patient care, including the effectiveness and ethicality of institutionalization.

ALZHEIMER'S DISEASE: TREATMENT AND PREVENTION

As Alzheimer's is currently incurable, treatments are aimed at symptoms of the disease and slowing its progression rather than reducing or eliminating the neurological damage associated with AD (Lane et al., 2018). Effective treatment and management of AD goes beyond the patient and physician, involving the patient's family members, caregivers, etc. (Atri, 2019). Additionally, providers must pay particular attention to regulating psychiatric and behavioral symptoms through regular psychiatric screening as well as regular education of both the patient

and the caregiver of the appropriate expectations regarding progression of the disease (Atri, 2019).

In recent years, there has been increasing support for the use of music therapy in management of cognitive decline in Alzheimer's Disease, especially considering the role of these sensory cues in involuntary memory recall (Leggieri et al., 2019). Morning light therapy has also been shown to have a significant effect on the stabilization of circadian rhythm abnormalities in AD patients (Coogan et al., 2013). However, a more interventional approach for symptomatic regulation is a main focus of managing Alzheimer's Disease. As mentioned previously, cholinesterase inhibitors are a common and effective medication used for Alzheimer's treatment (Hugo & Ganguli, 2014). These medications effectively inhibit the breakdown of acetylcholine in an effort to counter the effects of degeneration of cholinergic neurons in AD patients (Atri, 2019). Acetylcholine is an excitatory neurotransmitter in the brain that helps regulate the sleep-wake cycle as well as aid in learning, memory, and attention (Baghdoyan & Lydic, 2012). Thus, enhancing the role of this neurotransmitter is indicated for partial improvement of symptoms such as cognitive decline; however, it must be noted that these symptoms are not reversed by any of the AD medications used today (Lane et al., 2018). There are limited options for pharmacological management of Alzheimer's Disease, largely due to the cost of engineering new drugs and the lengthy process of determining the overall effect on the patient (Lane et al., 2018). As AD is strongly related to cardiovascular disease and other chronic medical conditions (Bollinger & Schibler, 2014), drug interactions must also be considered when planning a course of Alzheimer's treatment, both for regulating other chronic health conditions and managing AD symptoms (Atri, 2019). In my opinion, though, the most important factor of AD treatment involves the principle that any interventions or conversations should be carried out

with the patient in mind, with modifications based on progression of the disease, as the patient's ability to engage in discussions about his/her care may be diminished as the disease progresses.

In terms of preventative approaches for Alzheimer's Disease, exercise is cited as a prospective method for prevention, notably for those at risk for AD (Cass, 2017). It has also been proposed that regular exercise could also potentially be effective for management of MCI as well as AD (Ströhle et al., 2015). In my opinion, this may be due to the more generalized beneficial health effects of regular exercise on cardiovascular health, etc. However, the relationship between exercise and cognition should not be ignored, as studies have shown that cognitive functioning is improved by exercise in non-AD subjects (Smith et al., 2010). One study also shows that exercise aids in the regulation of circadian rhythms in elderly individuals, so this could be a possible mechanism for the benefits of exercise for the prevention and management of AD (Van Someren et al., 1997). Further, the time of day may also impact the effect of exercise on the circadian system. Another study highlights that the effects of exercise and light exposure on circadian rhythms may be synergistic, so outdoor exercise could even enhance the effects of exercise on regulating circadian rhythms (Barger et al., 2004). Of course, these behaviors will impact the sleep-wake cycle as well, so the effects of these nonpharmacological interventions may surely be additive. In addition to the role of physical exercise, studies have shown that a generally healthy and active lifestyle in which persons have regular cognitive exercise can be very preventative in terms of cognitive impairment and AD (Alzheimer's Association, 2016).

CONCLUSION: WHAT NOW?

While Alzheimer's Disease researchers have not been successful in finding a cure, it is important to note that the is a great deal that has yet to be discovered about the human brain. Treatment methods are still being developed and modified, and there is much to look forward to for the future of Alzheimer's Disease research. While pharmacologic treatments are a standard and effective form of treatment of AD symptoms, I argue for a more unconventional focus looking forward. The profound role of circadian rhythms as well as sleep quality indicates a need for treatment approaches to better manage and regulate patients' sleep-wake cycles as well as the activity of their entire circadian system. As demonstrated throughout this paper, these factors are intimately related to Alzheimer's Disease as well as many other diseases that are comorbid with AD. While this nonpharmaceutical approach may not be the most effective form of treatment on its own, treatment ought to be more concentrated on factors such as the effects of behavioral management, light exposure, quality of home life, caregiver wellbeing, sleep hygiene, etc. In addition, as cost-effective treatments are difficult to develop, this holistic approach to detection and treatment of AD and AD-like disorders may likely be one of the more effective approaches for preventive medicine, both in terms of prevention of the disease itself and prevention of its rapid progression.

Adopting a more holistic approach to treatment may pose several challenges, though, particularly because it is difficult to prove that any causal relationship exists between certain circadian and sleep-related factors and Alzheimer's Disease. As the brain is a complex organ, any correlations must not be overstated, but they should be considered. However, it is possible that patients and their loved ones may be less supportive of some nonpharmacologic treatments, especially because these outcomes are extremely variable for each individual. Nonetheless, it

should become standard for important behavioral and environmental factors such as light exposure, sleep hygiene, and exercise to be included in patient care, particularly in nursing home facilities where these factors can be effectively monitored.

While there is no clear solution to the problem of Alzheimer's Disease, these modifications of existing treatment methods could improve quality of life of the patient, if nothing else. Of course, more research is also needed in many areas, including the extent of the role of the immune system in Alzheimer's Disease. Most importantly, though, engaging the public in the conversation about Alzheimer's Disease and treatment options is essential for improving early detection and management of AD. This also includes spreading awareness by encouraging society to value the importance of certain unappreciated factors such as sleep in regard to their overall health as well as the management of existing health conditions. It is important to note, however, that the goal of this focus is not a cure. Rather, it offers new direction that may unlock the potential for better management of Alzheimer's Disease and dementia as a whole.

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