COMPREHENSIVE REVIEW ON DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE: CURRENT CHALLENGES

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Abstract:
Degeneration of brain cells is a hallmark symptom of Alzheimer's disease (ad). It's the main cause of dementia, which is typified by a loss of curiosity and autonomy in one's day-to-day life. It has been observed that the only therapies for ADS are symptomatic treatments, but no cure. Alzheimer's disease is a kind of neurodegeneration first identified by Alois Alzheimer in 1906; neurodegenerative diseases are a major challenge for the current health care system. It's a complicated disease with many unknown causes, although neuronal damage, memory problems, and other symptoms are common. The pathological hallmarks of Alzheimer's disease include acetyl cholinergic neuron dysfunction, neurofibrillary tangles, and amyloid- (A) plaque deposition across neurons. Age, genetics, head trauma, AMI, infections, and environmental factors are all potential contributors to the development of this illness. Physical activity and healthy eating have both been linked to decreased risk and protection against the condition. Biomarkers in cerebrospinal fluid, positron emission tomography, computed tomography, magnetic resonance imaging, and electro encephalography are used for prognosis. Drugs including tacrine, donepezil, rivastigmine, galantamine, and N-methyl-D-aspartate glutamate antagonist (NMDA) memantine are currently available as FDA-approved, standard pharmaceutical treatments for Alzheimer's disease (AD). This evaluation discusses presently available drugs and different methods to the diagnosis of AD and varoius mode of treatment of AD.

Keywords: Alzheimer's disease, pathology, defensive elements, biomarkers, pharmacotherapy

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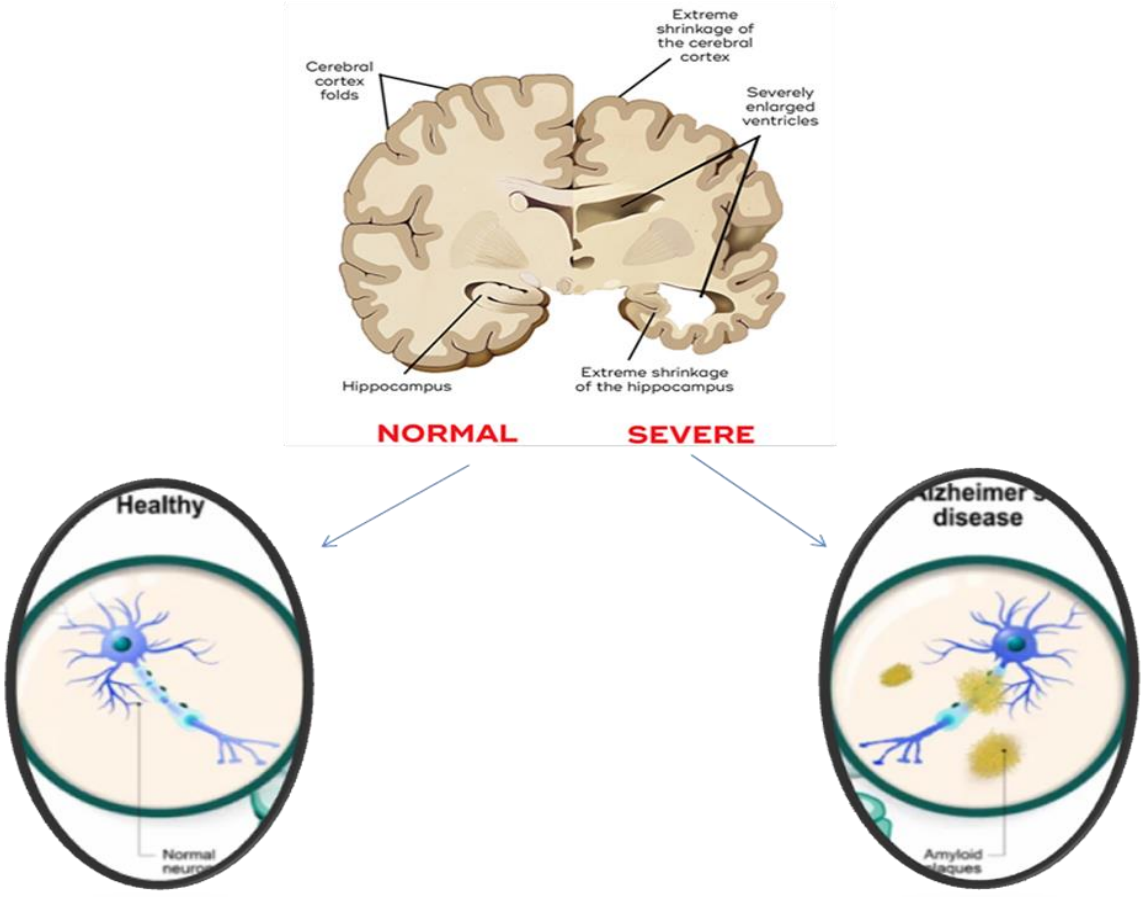
Introduction

Alzheimer's disease is one of the many neurodegenerative disorders now challenging the modern health care system. Alzheimer's disease (ad; named after German psychiatrist Alois Alzheimer) is the most common form of dementia and is characterized by the accumulation of amyloid-beta peptide (A) in the brain's medial temporal lobe and neocortical structures, resulting in neuritic plaques and neurofibrillary tangles (figure 1).



(a) (b)

Figure 1. The physiological shape of the brain and neurons in (a) healthful mind and (b) Alzheimer's disease brain

After studying the brain of his first patient, who had experienced memory loss and a change in personality before to death, Alois Alzheimer announced the presence of amyloid plaques and a massive reduction of neurons, describing the situation as a severe disease of the cerebral cortex. In his eighth edition of his psychiatric textbook, Emil Kraepelin gave this condition its now-famous name, Alzheimer's disease (Cipriani et al., 2011). Brain diseases like Alzheimer's disease (advert) and other factors like intoxications, infections, abnormalities in the pulmonary and circulatory systems that reduce oxygen supply to the brain, nutritional deficiency, vitamin B12 deficiency, tumors, and so on can all lead to cognitive decline.

Several studies conducted in recent years have produced some compelling theories, such as the cholinergic hypothesis (Craig et al., 2011), the Amyloid cascade hypothesis (Karran et al., 2011), the tau hypothesis (Maccioni et al., 2010) and many more. Drugs that block acetylcholinesterase (AChE) are being used to treat Alzheimer's disease. These include Donepezil (Aricept), Rivastig0.mine (Exelon), and Galantamine Hydrobromide (Razadyne, previously Called Reminyl). (Bartus et al., 1982).

Beta amyloid plaque depositions outside of cells and neurofibrillary tangles of hyper-phosphorylated tau inside of cells make up the neuropathology of AD. Although biomarkers in cerebrospinal fluid (CSF) and positron emission tomography (PET) can improve diagnostic accuracy, advert is still diagnosed clinically. Modern medications, like as cholinesterase inhibitors and memantine, improve quality of life but do not manage or slow the progression of the disease. Current research aims to understand the pathophysiology of AD in its early stages in humans and to implement therapies at that point.

There are already roughly 50 million ad victims worldwide, and this figure is expected to quadruple every five years, reaching 152 million by 2050. As ad's victim count rises, so does the cost of providing for those in need. The goals of this review are to (1) highlight the most recent advancement in chemicals that may prevent or treat AD, and (2) provide a concise summary of AD diagnosis, pathology, causes, and present treatments.

Alzheimer's disorder Diagnostic standards

Addiction has defined medical diagnostic criteria in the United States. Originally published in 1984, they underwent revisions in 2011 and 2018 to highlight the use of biomarkers in AD diagnosis and to generate distinct diagnoses for the preclinical, moderate cognitive impairment (MCI), and dementia levels of AD.

In 1984, a committee comprised of experts from the NINDS and the AD/ADRD established to establish clinical diagnostic guidelines for Alzheimer's disease. This organization is known as the NINDS-ADRDA.

(1) Probable Alzheimer's disease, as determined by dementia confirmed by neuropsychological tests, progressive memory loss, impaired daily-lifestyles interest, and additional symptoms such as aphasia (language impairment), apraxia (motor talents disease), and prefer aphasia (language impairment), apraxia (motor talents disease), and agnosia (loss of perception). In the absence of other diseases, such as those affecting the nervous system or the brain, the onset of these symptoms can occur as early as age forty-ninety; (2) a diagnosis of probable Alzheimer's disease can be made in the absence of neurologic or mental illness; (3) in the presence of other diseases, such as those affecting the nervous system or the brain, but these are not the primary cause of dementia; and (4) definite Alzheimer's disease, which is confirmed by histopathologic confirmation obtained from A number of neuropsychological assessments, such as the Mini Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR), were begun by a person who may have Alzheimer's disease. Neuropsychological evaluation is a straightforward, painless, and diagnostic method that may be taught to non-specialist trainees. As a result, the national burden of cognitive decline can be mitigated by early diagnosis and proper referral to therapy if the same is implemented at primary health facilities (Sharma et al., 2007). Besides the patient's clinical and family history, additional evaluations may include neuroimaging techniques like positron emission tomography, computed tomography for neuronal activity, electroencephalography (EEG) for cortical activity and laboratory examinations compromising of regime B12, (Cho et al., 2018)

Stages of Alzheimer's

Alzheimer's disease is diagnosed on the basis of the patient's characteristic symptoms, which include a progressive impairment of learning and memory. Problems with language, executive processes, perception (agnosia), or motor execution (apraxia) may be more noticeable than memory issues in a subset of the population. Problems with language are defined by a decline in both oral and written communication, with a corresponding reduction in vocabulary and word fluency. Memory loss worsens during the mild stage, and it's not uncommon for patients to fail to identify close family members. Neuropsychiatric and behavioural changes become more habitual. Wandering, irritation, and labile affect can lead to weeping, accidental provocation, or resistance to caregiving, and are common symptoms.

In the last phases of life, patients become completely dependent on their carers. Addiction is a major worldwide issue for a number of reasons, including (i) an aging population, (ii) a rising life expectancy, and (iii) a dearth of effective pharmacotherapy options. People with ALS are unable to care for themselves in any significant way since their muscles and movement deteriorate to the point that they are bedridden and unable to feed themselves. Infections of pressure ulcers or pneumonia are common outside factors that lead to death rather than the disease itself (Förstl and Kurz 1999)

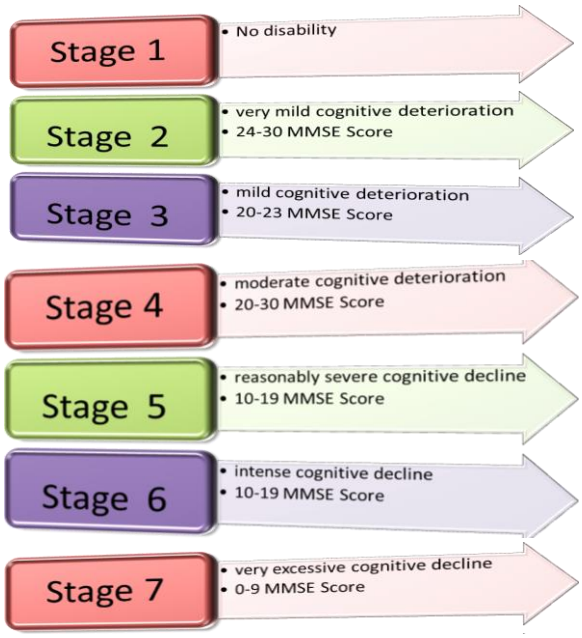


Figure 1. Special tiers of Alzheimer's disorder

According to research by Sharma et al. (2007), people with Alzheimer's disease (AD) had a distinct pattern of higher clinical dementia rating (CDR) scores compared to those with moderate cognitive impairment and normal health. MCI patients fare somewhat well on the memory tests for words and pictures, but poorly on the semantic memory test. The score on the attention task was similar to, but higher than, AD. In mild cognitive impairment (MCI), working memory may be the first cognitive area to deteriorate (Sharma et al., 2007). (Fig. 2)

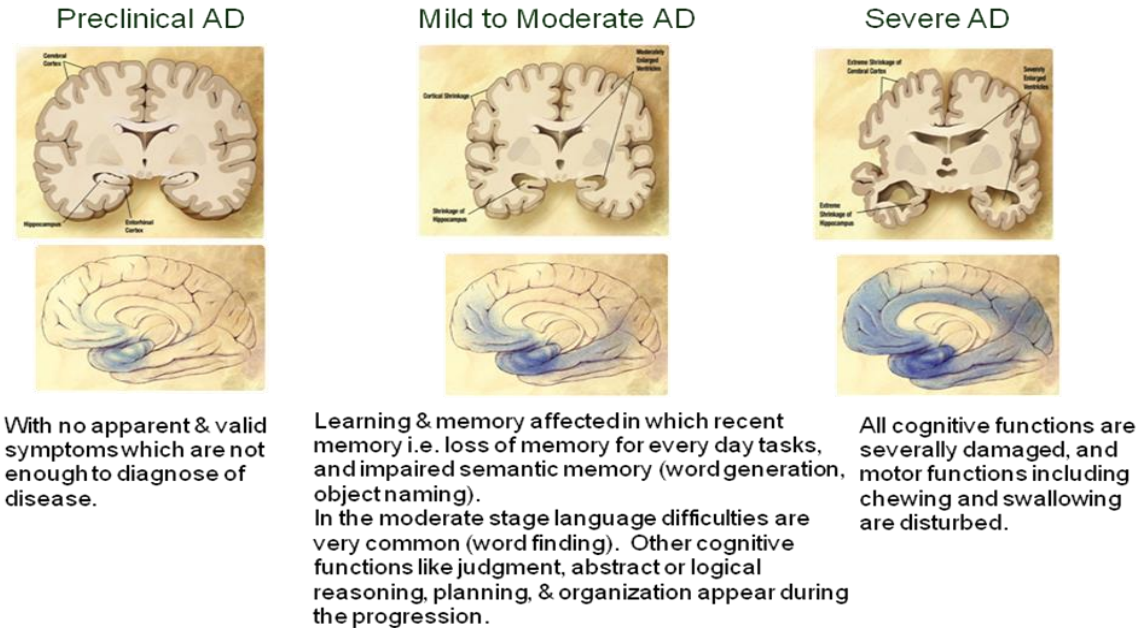


Fig. 2. Clinical Symptoms of AD

Alzheimer's disorder's Neuropathology

Because Alzheimer's disease is a polygenic and multifactorial condition, its pathology is not always fully understood. Here are some of the most prominent neuropathological features of Alzheimer's disease:

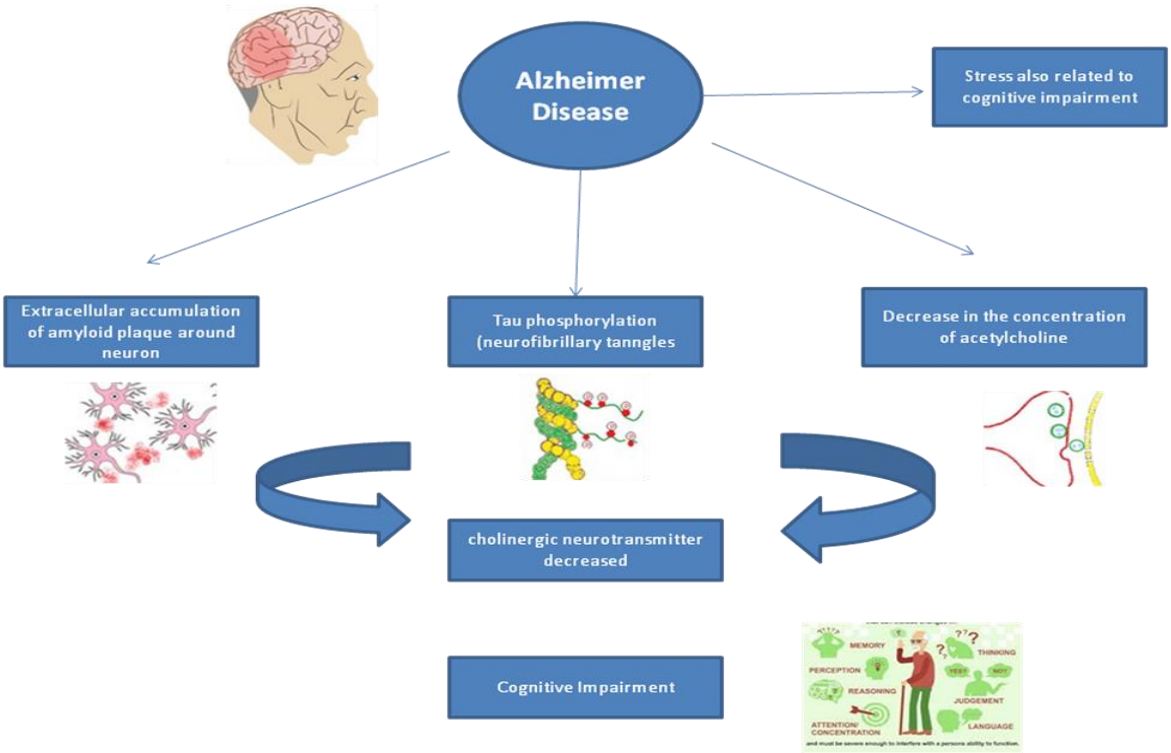


Fig. 3: Few crucial Alzheimer's Pathologic Conditions

The hallmarks of Alzheimer's disease are a progressive buildup of amyloid- (A) proteins in and around neurons, manifesting as plaques; the formation of neurofibrillary tangles (NFTs) due to hyperphosphorylation of tau proteins; and a decrease in the level of acetylcholine (ACh). The neurotransmitter acetylcholine is produced by the brain's cholinergic neurons and aids in the transmission and delivery of signals and messages inside the brain (Pope and Brimijoin 2018). It hints to a crucial function in both knowledge acquisition and retention (Francis, 1999). Degradation of cholinergic neurons in the hippocampus and cortex, as well as a decrease in acetylcholine levels, is hallmarks of Alzheimer's disease pathology (Lombardo and Maskos 2015). Cholinergic dysfunction causes unregulated cholinergic signal transmission, which is accompanied with Alzheimer's disease. It has been shown that pathogenic components of advertisements, including as the A plague, NFTs, inflammation, and oxidative status, combine with dysfunction in cholinergic policies originating in the basal forebrain to impair cognition (Muir JL, 1997).

Diagnosis Symptomatic characterization:

Only through a brain autopsy can Alzheimer's disease be diagnosed. However, 90% of the time, doctors may correctly diagnose AD with the use of psychological and behavioral examinations in addition to physical exams (American Health Assistance Foundation, 2010). The Psychiatric Association's Diagnostic and Statistical Manual of Mental illness, Third Edition (DSM-III) is where you may find diagnostic criteria for mental illnesses. Dementia with a slow, progressive onset is a diagnostic hallmark. Deterioration, with no further cause for concern based on patient history or physical examination (American Psychiatric Association, 1980).

Dementia with a slow, progressive onset is a diagnostic hallmark. Obtaining patient information is the first step in seeking an analysis. At some point during this window, the doctor will make a diagnosis based on the patient's symptoms, when they first appeared, and how far along they are now. Personal experiences with contamination in the family also matter. The clinical physician will do a complete physical examination, including laboratory tests. This is done to rule out endocrine disturbances, vitamin deficiencies, and urogenital infections as possible causes of dementia. Tumors, cerebrovascular diseases, traumatic brain injuries, and infections will all be ruled out by brain scans. Those scans can also be used to detect the tangles and plaques characteristic of Alzheimer's disease. Information regarding the size and shape of the brain may be gleaned through structural imaging studies, which join the likes of MRI, EEG, and CT in providing such data.

Neuroimaging as a diagnostic tool for Alzheimer's disease is an emerging field of study. Several imaging modalities, such as PET, MRI, EEG, and CT scans, can be used to detect abnormalities inside the brain. Each scan employs a different method, allowing researchers to zero in on specific brain regions and anomalies. Although brain imaging is not yet often employed in AD diagnosis, recent medical studies have shown promising outcomes that may one day replace the method now used by doctors.

Positron emission tomography (PET)

According to Health News (2009), PET creates a full-color, three-dimensional image of the human body by using radiation signals. A radiotracer, or radioactive drug that is specific to a naturally occurring molecule, is injected into the patient. Glucose is a typical substance used for AD monitoring. The radioactive tracer moves to the parts of the body that make use of the target chemical. Positron emission results from metabolic clearance of the molecule. The PET scan detects the positrons' electric charge and produces a visual representation of the data. The degree to which the radiotracer is metabolized in this image is indicative of the patient's physiology. Positron emission yields a spectrum of colors and intensities reflective of the brain's functional strength. According to Health News (2009), a PET scan can reveal alterations in metabolic rate, blood flow, and cellular communication processes in the brain.

A PET experiment was used to detect changes in glucose metabolism in the brain of an Alzheimer's disease patient, according to a study published in 1996 in the journal scientific Psychiatry. An unusually low glucose metabolic rate was found in the parietal, temporal, and posterior cortices. Patients with advanced stages of AD and more brain lesions were reported to have a slower rate of glucose metabolism (Small, G. W. 1996). The changes in glucose metabolism that Small and his colleagues suspected would occur before the onset of clinical symptoms were found using a PET experiment. A pet's picture, much like a prognosis, may be used to gauge the efficacy of different advertising strategies.

Merits and Demerits of PET

Because it can find several metabolic methods and be used with a wide variety of labels, a PET scan can be a powerful tool in the diagnosis of Alzheimer's disease. This method, however, is invasive since it uses radioactive isotopes. Also constrained by the type of radiotracer utilized is the choice made on the image.

A computed tomography (CT)

The body is photographed in cross-section several times during a computed tomography (CT) study (Beyenhof, Lauren 2010). This method is helpful since it can be used to convert a scan from any individual into a high-quality computer image. The CT scan provides data to the clinician about the average density of body tissues. An evaluation dye is injected to help differentiate between tissues of the same kind for better viewing.

Merits and Demerits of PET

When compared to other neuroimaging methods, CT scanning is quite cheap. This noninvasive approach generates high-resolution pictures of the skeleton and soft tissues in only a few minutes. Some danger is inherent even in this treatment. Some people may have an adverse reaction to the irradiated and recycled dye.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) was first used in 1977 to create two- and three-dimensional pictures of the body for the purpose of diagnosing injuries and illnesses. The superconducting magnet is crucial to the MRI machine because it generates a strong magnetic field that is consistent throughout time. The magnetic field produced by the MRI system's tiny magnets is much weaker.

The various bodily parts may be located with the help of this magnet. There are billions of atoms in a human body. However, the magnet just displaces hydrogen atoms. Hydrogen atoms spin arbitrarily about their own axes, but molecules align themselves with the MRI's magnetic field. The atoms are split along the middle, with half pointing to Patient's head and the other half to his feet. The number of atoms in a million is not compensated for. The equipment then sends out pulses of radio energy at hydrogen's particular frequency, changing the spin of the protons. When the proton spinning ends, the stored energy is released. varying textures have varying color responses and are displayed as varied shades of gray (Health News, 2009).

Researchers are able to identify the structural abnormalities and cellular death in the brains of AD patients with the use of MRI scanning. The hippocampus frequently atrophys in AD patients, even in the absence of clinical symptoms (Emilien et al., 2004). After 56 people with varied degrees of mental disability died, their brains were scanned using MRI. Detection of hippocampus volume and its importance as a biomarker of AD neuropathology was achieved using magnetic resonance imaging (MRI). The findings suggested that the scans may be used to detect healthy older people with AD neuropathology but no overt symptoms of dementia or memory loss. Doctors may be able to delay the advancement of Alzheimer's disease by treating people at high risk for developing the condition years before the onset of symptoms.

Merits and Demerits

There are advantages and disadvantages to using this method. This treatment may be preferable to X-rays since it does not cause discomfort and can identify extremely subtle abnormalities. High spatial resolution is another benefit of this process. However, this procedure can cost a lot of money and isn't always covered by medical plans. Examining a patient who is afraid of enclosed spaces might be challenging due to the design of the equipment. Patients with metallic things in their bodies cannot get an MRI scan because of the system's powerful magnetic field.

Electroencephalography (EEG)

The electroencephalogram (EEG) documents the propagation of postsynaptic potentials from vast groups of pyramidal cells in the cerebral cortex to the extracellular space. After being filtered through the skull, this activity is picked up by electrodes placed on the scalp. The electrical activity of pyramidal neurons in the cerebral cortex may be recorded by electroencephalography (Monllor et al., 2021). It is generally accepted that Alzheimer's disease causes alterations in EEG synchronization and a decrease in the complexity of EEG signals. Differential characteristics based on these EEG changes have been utilized to diagnose AD (Nesma et al., 2018). The cultural and educational barriers that may make administering neuropsychological tests impractical can be surmounted by using EEG versions [i.e., event-related potential (ERP)] (Polich and Corey-Bloom, 2005). In reaction to particular stimuli or events, the brain's electrical activity produces tiny voltage spikes called event-related potentials (ERPs). Time-locked peaks in the voltage of ERP

signals are reflective of human perception, cognition, and experience. As a result, ERPs can reveal both normal and abnormal aspects of human cognition (Jungmi et al., 2023) in a physiological and pathological context.

Merits and demerits

Electroencephalograph (EEG) data have been regarded a viable means of assessing aberrant brain patterns associated to AD at the cortical level because of their low cost, non-invasive nature, and portability. The capacity to see brain activity in real time, down to the millisecond (a thousandth of a second), is a major benefit of EEG/ERP. The greatest drawback of scalp EEG is that the collected signals become blurry owing to the wide separation between neurons within the skull and the electrodes.

Treatment of Alzheimer's disease

Although there is presently no treatment for Alzheimer's disease (AD), there are some medications that have been shown to reduce disease development and treat associated symptoms. According to the Alzheimer's Association (2010), doctors classify AD patients' symptoms as either "cognitive" or "behavioral and psychiatric" before beginning therapy. This allows for more targeted therapy of the underlying problems. Memory, communication, and judgment are all negatively impacted by cognitive disorders. A patient's behavior and emotions are affected by their behavioral symptoms. Cognitive Symptom Treatment Chemical messengers in the brain are targeted in the treatment of cognitive disorders. Two medications have been found to be effective in this regard and have been authorized by the FDA (Alzheimer's Association, 2010). One class of drugs blocks an enzyme necessary for the breakdown of the neurotransmitter acetylcholine. The neurotransmitter acetylcholine has a crucial role in both learning and memory. Age-related forgetfulness results from a natural decline in acetylcholine concentration. However, in AD, the concentration can be reduced by as much as 90%, leading to serious memory and behavioral changes. The purpose of these medications is to boost acetylcholine levels to aid in nerve cell communication. Donepezil, galantamine, and rivastigmine are the three most often prescribed cholinesterase inhibitors at the moment. Memantine, like cholinesterase inhibitors, is a medicine that has been licensed for the treatment of Alzheimer's disease. Memantine controls glutamate levels in the brain. Learning and memory are facilitated by glutamate, an excitatory neurotransmitter. Excitotoxicity, or the excessive stimulation of neurons, may be responsible for the neuron degradation found in AD. N-methyl-D-aspartate (NMDA) receptors are found on the surface of neurons and are activated when glutamate binds to them. Memantine protects neurons from the damaging effects of too much glutamate activation by inhibiting NMDA receptors. Memantine is useful for treating moderate to severe Alzheimer's disease because it slows the progression of cognitive symptoms.

Donepezil hydrochloride (Brand name Aricept)

The breakdown of acetylcholine in the brain is prevented by this medication, making it suitable for use in all stages of Alzheimer's disease. Donepezil is an acetylcholinesterase (AChE) antagonist that is both highly selective and reversible. Due to its long half life and favorable pharmacokinetic profile, a single daily dose is sufficient. The results of this treatment were studied in a 1998 article published in the Archives of Internal Medicine. The patients were classified as having mild to moderate AD based on their scores on the Mini-Mental State Exam and the Clinical Dementia Ratings (Rogers et al., 1998). Patients with any preexisting conditions that could potentially affect the trial were not included in the study. The subjects were split up into three different groups. Two placebo tablets were given to one group. A second group took both a placebo and a donepezil tablet, each containing 5 milligrams. The last group took two donepezil tablets, each containing 5 milligrams. 32% of those given the drug at 5 mg showed clinical improvement on various psychiatric and mental scales, while 38% of those given 10 mg did so as well. The only cholinesterase inhibitor with FDA approval to treat advanced AD is donepezil. Studies have shown that this medication is useful in preventing cognitive decline.

Galantamine hydrobromide (Brand name Razadyne)

By inhibiting hydrolysis and elevating acetylcholine levels, galantamine is useful for treating mild to moderate AD. Since the half-life of galantamine is only seven hours24, it must be taken twice daily in contrast to donepezil's once-day dosing. Loy and Schneider 26 ran a study to see how long it took for galantamine to alleviate cognitive problems. Patients receiving daily dosages between 18 and 32 mg saw the most dramatic improvement at both points in time. After six months of therapy, the benefits were more pronounced and the individuals' results on cognitive examinations improved (Loy and

Schneider, 2006). Galantamine can delay the deterioration of cognitive function, with side effects occurring in a small percentage of patients, according to a meta-analysis of AD therapy studies conducted by Hansen and colleagues (Hansen et al., 2006).

Rivastigmine tartrate (Brand Name Exelon)

When compared to other cholinesterase inhibitors, this drug is given for mild to severe AD less frequently. The efficacy of rivastigmine was studied over a range of doses and time frames in a 2009 study (Lanctot) from the Department of Psychiatry at Toronto's Sunnybrook Health Sciences Centre. The effectiveness of daily doses of 1–4 mg and 6–12 mg was compared over the course of 12, 18, and 26 weeks. Over the course of all time points, the group receiving the maximum dose improved the most on cognition tests and ADLs. Only after 26 weeks did the reduced dose show any improvement, and it had no effect on ADL performance. A smaller percentage of people getting the higher dose than those taking the placebo reported experiencing side effects. Taking 6-12 mg of this medicine every day for a long time has been shown to be useful in treating the cognitive symptoms of AD (Lanctot, 2009).

Memantine (Brand Name Namenda)

The NMDA receptor antagonist memantine has been proven effective in treating moderate to severe Alzheimer's disease (Lippincott et al., 2010). Researchers found that by controlling the activity of NMDA receptors, memantine might slow the progression of AD and relieve its symptoms (Reisberg et al., 2003). Only 181 people out of 345 who started the double-blind study made it to the end after 28 weeks. All of the individuals were fifty or older and had been diagnosed with moderate to severe Alzheimer's disease. Each has also undergone an MRI and CT scan within the past year. Patients in the memantine group responded well to the treatment 29% of the time, whereas just 10% of those in the placebo group did so. Nearly every participant experienced some sort of negative side effect; however the vast majority of these had nothing to do with the medicine. Agitation was the most often reported adverse effect. Results were shown in a smaller sample size than in investigations of cholinesterase inhibitors, although this was to be expected. Patients in those studies had AD that was considered mild to moderate (Reisberg, et al., 2003), therefore they were more amenable to therapy and more likely to improve). The collected evidence suggests that memantine can successfully slow the worsening of AD symptoms in individuals.

Treatment for Behavioral and Psychiatric Symptoms

The mental and behavioral symptoms of Alzheimer's disease can be just as debilitating as the disease's effects on cognition and function. Anxiety, insomnia, agitation, hallucinations, and delusions are all signs of Alzheimer's disease (Alzheimer's disease Fact Sheet). Both drug-based and non-pharmaceutical approaches to alleviating symptoms might be considered. According to the Alzheimer's Association (2010), one non-drug method is making changes to the environment to reduce risk. Another option is to look into the patient's medication history for any possible drug interactions that might have a negative impact on the patient's behavior or mental health. If the symptoms persist after these measures, medication may be necessary. Depending on the signs and symptoms, a variety of drugs are available. Antidepressants like Prozac and Zoloft might be recommended if the doctor determines that the patient is suffering from depression. There are medications that can help with hallucinations and anxiety (Alzheimer's Association, 2010): antipsychotics and anxiolytics.

Conclusion

There is an urgent need to discover and deploy novel therapeutics for dementia due to the disease's increasing incidence and the relatively insufficient nature of present pharmaceutical therapy. Though promising, recent trial outcomes of medicines in AD with possible disease-modifying benefits require caution. However, we are still quite some distance from having access to clinically effective disease-modifying medication, which might postpone the onset of dementia and significantly lessen its prevalence and effects. One can only hope that this becomes a practical aim in the near future with the development of neuroimaging technologies, molecular biomarkers, and a deeper knowledge of the underlying pathogenic processes involved. Dementia is a diverse, complicated disease that, by its very nature, dictates a need for a multidisciplinary approach to care, so although attention to the development of novel medicines is highly welcome, we must also be cognizant of this. All of the complex biopsychosocial facets of caring for this population of patients, not simply the pharmaceutical therapy, must remain central to our attention in the management of those with dementia.

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