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Alzheimer's Disease: Unraveling the Devastating Effects and Promising Treatment Options

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Abstract:

Alzheimer's Disease(AD) is a progressive and neurodegenerative disorder that has come a significant global health concern. Originally described by Alois Alzheimer in the early 20th century, AD is the leading cause of dementia, affecting a substantial portion of the growing population. This article provides an in- depth exploration of the devastating effects of AD on individuals, families, and society. The chronic nature of the disease, its prolonged development period, and the challenges faced by family
and caregivers are highlighted. Current individual approaches, emerging diagnostics, and promising treatment options are discussed, offering a
comprehensive overview of the current state of AD research and management. By understanding the profound impact of AD and exploring the latest advancements in diagnostics and treatment, we aim to contribute to the ongoing dialogue on addressing this complex and pervasive health issue.

Aim :

This article looks into the basic mechanism of Alzheimer's disease in an attempt to provide a thorough examination of the devastating consequences the disorder has on individuals as well as their families. In addition, it aims to provide details about the current status of research and possible treatment alternatives, encouraging hope despite the difficulties this neurodegenerative illness presents. The article aims to deepen awareness of Alzheimer's by shedding light on its complexities and encouraging optimism for future developments in treatment and, eventually, a solution.

Keywords :

Alzheimer's disease ; Dementia; Memory loss; Beta-amyloid plaques; Neurodegenerative disorder; Genetics; Prevention; Care; Risks .

Introduction :

Alois Alzheimer primarily described Alzheimer disease (AD) in 1906s as a progressive and neurodegenerative disorder. Neurodegenerative disorders are one of the crucial problems facing by the modern health care system, and Alzheimer disease is one of those. It is identified as the most ubiquitous form of dementia among geriatric persons from the very beginning of twenty-first century.(1) Alzheimer disease is the most common cause of dementia, worldwide it generally comprises around 60-80% of all dementia events (2), and is characterized by progressive loss of neurons, brain functions and cognition function (3).

The main effects of Alzheimer's disease (AD), a progressive neurological illness, are on memory, cognitive function, and day-to-day activities. Globally, as the population ages older, Alzheimer's disease is having a bigger and bigger influence. This article examines the terrible consequences that Alzheimer's disease has on people, families, and society as a whole. It also provides information on the most recent, promising treatments that give hope for a cure. (4)

Alzheimer's disease is a chronic condition that takes 20 years to fully develop throughout the preclinical and prodromal stages, with an average clinical course of 8 to 10 years. In the population over 65, the disease is predicted to have a prevalence of 10-30% and an incidence of 1-3 percent. The sporadic form of Alzheimer's disease, which affects most people (>95%), has a late onset (80–90 years of age) and is caused by the inability to remove the amyloid-β (Aβ) peptide from the brain's interstitial spaces. Numerous hereditary risk factors for sporadic illnesses have been found. A tiny percentage of patients (<1%) have inherited gene abnormalities that impact Aβ processing and cause the condition to manifest at a significantly earlier age (mean age of ~45 years). Cerebrospinal fluid biomarkers and PET can now be used to detect Aβ buildup in preclinical and prodromal phases. While there are a number of approved medications that can help with Alzheimer's disease symptoms, there are currently no treatments that can change

the fundamental disease mechanisms. Treatment of any co-morbid conditions, such as cerebrovascular disease, and the support of the patient's social networks are the main priorities of management.(5)

UNDERSTANDING ALZHEIMER'S DISEASE:

Epidemiology :

Someone in the world develops dementia every 3 seconds. There are over 55 million people worldwide living with dementia in 2020. This number will almost double every 20 years, reaching 78 million in 2030 and 139 million in 2050. Much of the increase will be in developing countries. Already 60% of people with dementia live in low and middle income countries, but by 2050 this will rise to 71%. The fastest growth in the elderly population is taking place in China, India, and their south Asian and western Pacific neighbours(6). AD is the most common form of dementia, accounting for 60 to 80% of the cases, with less than half expected to be pure AD and the majority expected to be mixed dementias (7). The other most common causes of dementia are frontotemporal lobar degeneration, vascular dementia, Lewy body dementia, Parkinson's disease with dementia, and normal pressure hydrocephalus, each of which accounts for 5–10% of cases. Of these, vascular dementia and Lewy body dementia are most frequently linked to mixed pathology, which includes concurrent AD(8). As the population ages, it is predicted that more than 131 million people will be afflicted by 2050, and these crippling and economically devastating conditions will only become worse by the middle of the century [9]. With the incidence of all dementias doubling every 6.3 years from 3.9 per 1000 for ages 60–90 to 104.8 per 1000 after age 90, aging is the biggest risk factor for AD (10). According to estimates, the prevalence is 10% in those over 65 and 40% in people over 80 (11). Given the rapidly increasing costs connected with the disease, effective pre-clinical diagnostics and treatments are required in order to stop its progression before symptoms appear.

Etiology :

Risk factors both the environment and genes can contribute to the development of AD. Age is a major risk factor. The chance of developing AD is approximately 3% at age 65 and more than 30% by age 85 (12). Estimates indicate that approximately 3% of AD cases occur in individuals under the age of 65, although the exact prevalence is uncertain (12). While the population is getting older generally, age- specific incidence tends to be declining in a number of nations (13&14)

According to the disease's onset and hereditary nature, AD can be categorized. While Late-onset Alzheimer's disease (LOAD) accounts for approximately 95% of cases (15) and manifests after age 65, Early-Onset Alzheimer's disease (EOAD) develops before age 65. Familial AD shows Mendelian (usually dominant) inheritance, while sporadic AD shows no simple familial link (16). As mutations in APP, PSEN1, or PSEN2 cause these circumstances, almost all EOAD are familial, while most LOAD are sporadic. Genome wide association studies (GWAS) and sequencing have now provided more than 20 risk loci in total that contribute to sporadic cases (17), but often there is no identifiable genetic cause.

Pathology:

Pathology of Alzheimer disease is not clearly understood yet because it is a polygenic and multifarious complex disease (18&19). Some important neuro- pathological hallmarks which characterized Alzheimer's disease are as follows:

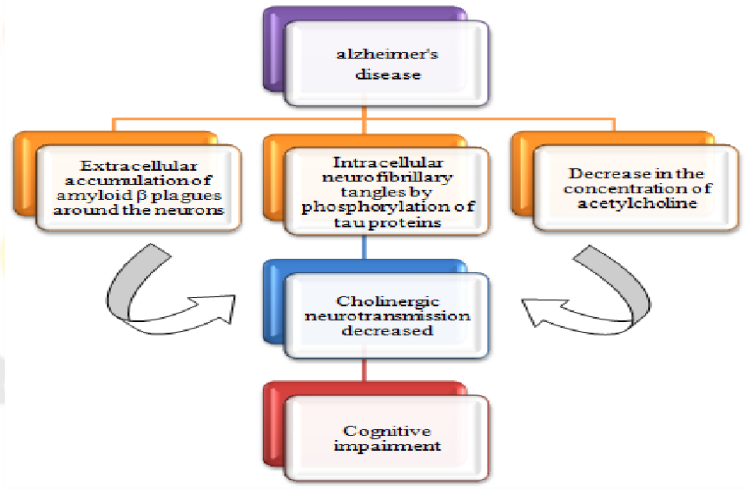

FIG. 1: SOME IMPORTANT ALZHEIMER'S PATHOLOGIC CONDITIONS. (20)(21)(22)

Alzheimer's disease is primarily characterized by the increasing build-up of amyloid-β (Aβ) particles around neurons, which result in plagues; the excessive phosphorylation of tau proteins to create Neuro Fibrillary Tangles (NFTs); and a reduction in the amount of the neurotransmitter Ach(23). A type of neurotransmitter called acetylcholine is produced by the brain's cholinergic neurons and helps in the transport of signals and messages (24). It shows a very crucial part in learning and memory (25). AD pathology relates to the deposition of plaques and neurofibrillary tangles (NFTs) in the brain which leads to degradation of the cholinergic neurons in the hippocampal and cortical part of the brain and decrease in the level of acetylcholine (26). Cholinergic dysfunction is responsible for unregulated signal transmission of the cholinergic pathway which is accompanied by AD (27).Dysfunction in cholinergic regulations originating from the basal forebrain and interact with pathological aspects of AD-like Aβ plague, NFTs, inflammation, oxidative stress to impair cognition (28).

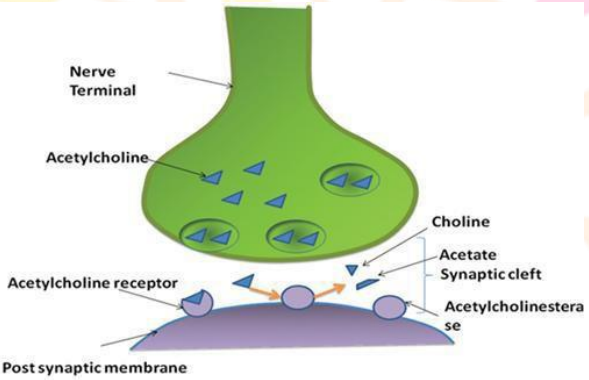

FIG. 2: ACETYLCHOLINESTERASE MECHANISM OF ACTION IN ALZHEIMER'S DISEASE.

The brain cells network degradation resulting in dysregulation of neurotransmitters such as dopamine, serotonin, glutamine, and noradrenaline also affects the function of various additional serotonergic, dopaminergic, glutamatergic, and adrenergic neurons (29).

Macroscopic features :

The most common method for diagnosis in AD remains pathologic diagnosis. however several characteristics of AD can be identified through macroscopic examination, no particular sign or set of traits is particularly distinct, however some features are very suggestive of AD. The limbic lobe and multimodal association cortices exhibit the most significant cortical atrophy in the AD brain, which is frequently at least moderate. Primary motor and somatosensory cortices typically appear intact, while the frontal and temporal cortices frequently exhibit increased sulcal gaps with atrophy of the gyri (30). There is increasing recognitionof atrophy in posterior cortical areas in AD, most notable the precuneus and posterior cingulate gyrus, driven in part by functional imaging studies (31). As a result of this atrophy, there is often enlargement of the frontal and temporal horns of the lateral ventricles as shown in Fig.3, and decreased brain weight is observed in most affected individuals. None of the macroscopic features are specific to AD, and unaffected clinically normal people may have moderate cortical atrophy, especially affecting frontal lobes, with volume loss mostly affecting white matter
(32). Medial temporal atrophy affecting amygdala and hippocampus, usually accompanied by temporal horn enlargement is typical of AD (33), but can be seen in other age-related disorders such as hippocampal sclerosis or argyrophilic grain disease. Loss of neuromelanin pigmentation in the locus coeruleus is another macroscopic characteristic of AD that is frequently noticed, as shown in Fig. 3 (34).

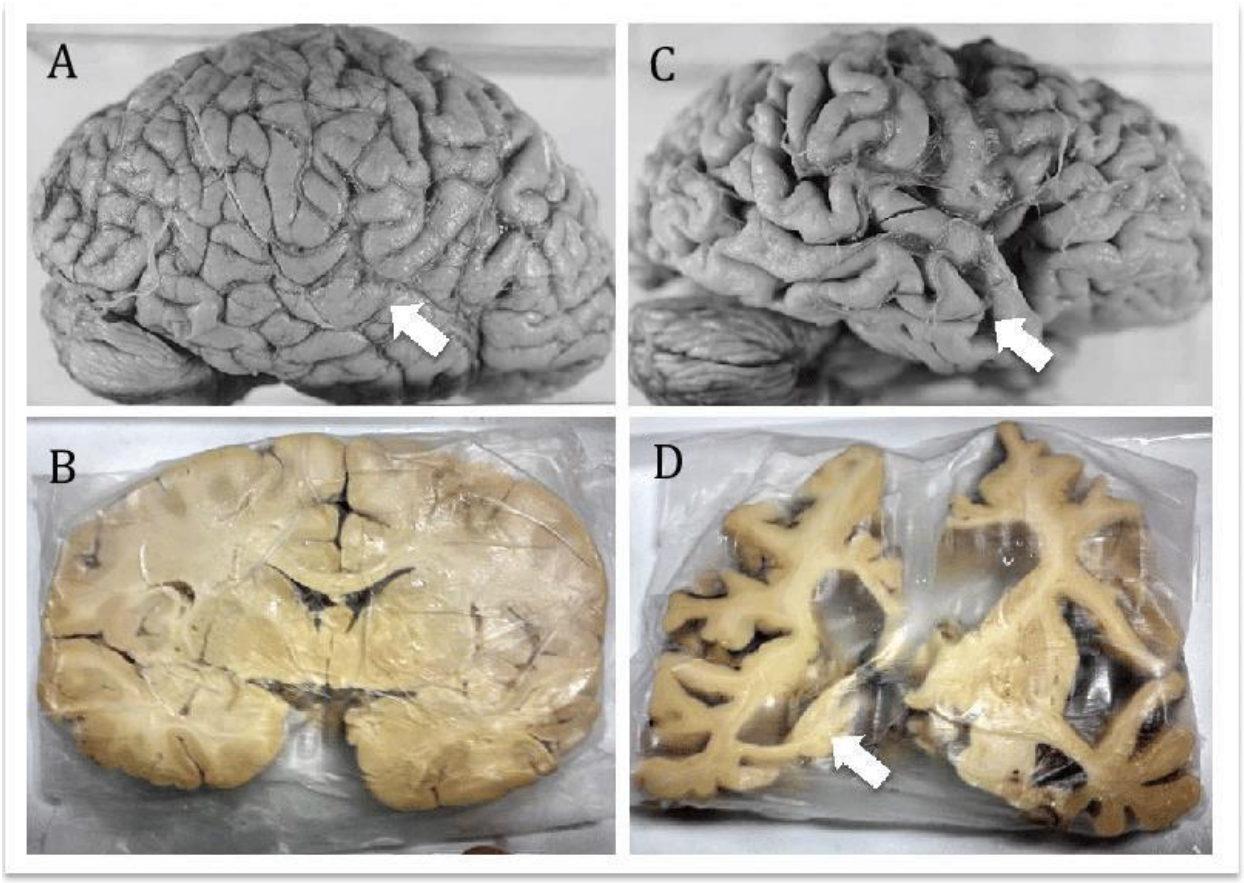

FIG. 3: Gross Brain Anatomy of Alzheimer's Disease. In comparison to a normal brain, a lateral view of an Alzheimer's patient's brain may reveal narrowing of the gyri and widening of the sulcal spaces. The arrowheads suggest that this may be more easily seen in coronal sections, and the arrows highlight that this atrophy is frequently accompanied by enlargement of the lateral ventricles' frontal and temporal horns.

While none of these findings by themselves are unique to AD, they are frequently very encouraging, particularly when other neurodegenerative diseases' outward manifestations of similar changes are absent..

DEVASTATING EFFECTS ON INDIVIDUALS AND FAMILIES:

Alzheimer's is a fatal illness that causes severe symptoms. However, its effects extend beyond people who are affected. Whole families are impacted by Alzheimer's, which causes severe financial challenges(35).

Individuals with Alzheimer's disease and associated dementias are typically looked after by friends or relatives. Eighty percent of those suffering from Alzheimer's disease and associated dementias are receiving care at home. Over 16 million Americans donate over 17 billion hours of unpaid care to friends and family who suffer from Alzheimer's and associated dementias annually. It is projected that these caregivers will deliver 18.5 billion hours of care in 2019. nearly 25% of dementia caregivers are "sandwich generation" caregivers, meaning they look after both younger children and elderly parents. Women make up nearly two-thirds of dementia caregivers, and 34% of caregivers are 65 years of age or older.

Compared to caregivers of other types of conditions, those with Alzheimer's and related dementias provide care for a longer period of time (79% versus 66%). For four years or longer, more than half (57%) of family caregivers for individuals with Alzheimer's and related dementias do so. Compared to less than half of caregivers of people without dementia (49%), more than six in ten (63%) Alzheimer's caregivers anticipate continuing to provide care for their patients for the next five years.

The demands of caregiving can limit a caregiver's ability to take care of themselves. Family caregivers of people with Alzheimer's and related dementias are at greater risk for anxiety, depression, and poorer quality of life than caregivers of people with other conditions (36).

The Effects Of Alzheimer's on Family Caregivers :

Alzheimer's disease progresses gradually, but consistent behavioral and functional changes need more attention, time, and effort from the caregiver. There are many different ways that Alzheimer's affects family members and caregivers. Among them are:

- **Increased Risk of Physical Illness:** Compared to non-caregivers, caregivers report more physical health issues and poorer general health. Caretakers are more likely to experience cardiovascular issues, weakened immune systems,

irregular sleep habits, delayed wound healing, and higher rates of chronic illnesses like diabetes, rheumatoid arthritis, ulcers, and anemia.

- **Diminished Emotional Well-Being:** Compared to other caregiver types and non-caregivers, dementia caregivers experience significantly higher levels of psychological distress. Stress among caregivers can lead to major psychological issues, such as depression and anxiety, which need to be treated right away.
- **Increasing Social Isolation:** Caregivers frequently face social isolation due to a lack of social interaction and support. In order to spend more time with their loved one, they often give up or scale back on their jobs, sacrifice their own hobbies and leisure activities, and spend less time with friends and family.
- **Raising Financial Difficulties:** Taking care of a loved one who has Alzheimer's is expensive. Medical care, diagnostic testing, prescription drugs, and personal nursing care are examples of direct costs. The loss of income incurred by family caregivers who choose to forgo or cut back on paid work and hours is an example of an indirect cost(37).

CURRENT DIAGNOSTIC APPROACHES:

Alzheimer's disease can be diagnosed in a number of ways. Alzheimer's is frequently identified through a medical examination. They will assess symptoms and perform a number of tests. To learn more about symptoms and behavior, they might consult with friends and family. The most prevalent kind of dementia, Alzheimer's, requires a precise diagnosis. Accurate diagnosis is a crucial first step in receiving the right care, treatment, family education, and future planning.

A specialist in brain disorders (neurologist), or a geriatrician, who specializes in treating older adults, will examine patient medical history, and symptoms. They will also speak with a close friend or relative to get a more thorough diagnosis of Alzheimer's disease. In addition, doctor will run a number of tests and do a physical examination(38).

Significant study has been done to find earlier and more accurate ways to diagnose AD, and in the past ten years, testing has advanced. Neuropsychological testing, laboratory testing (blood and other biologic fluids), brain neuroimaging, and genetic testing are some of the procedures used to diagnose dementia after a medical history and physical examination, which includes a neurologic and psychiatric assessment. Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) (39) are techniques that can identify alterations in brain physiology and function. These techniques have been used in conjunction with blood biomarkers in certain clinical trials. Computed Tomography (CT) and structural and functional Magnetic Resonance Imaging (MRI) may also be used in certain situations, however less frequently.

Emerging Diagnostics:

Here is a high-level summary of recently invented diagnostic techniques :

- **Volumetric Data:**

In simple terms, the probability that mild cognitive impairment (MCI) will progress to Alzheimer's disease (AD) can be predicted by changes in volume in particular brain regions. Radiologists or FDA-approved MRI volumetric data software programs like Neuroquant and Neuoreader can assist with these volume assessments. Changes in hippocampal volume in particular are thought to be a significant AD biomarker (40). However, due to the measure's low sensitivity in AD diagnosis, MRIs are considered a useful tool in the diagnostic process, rather than being adequate on their own to establish a diagnosis (41).

- **Diffusion Tensor Imaging:**

Diffusion Tensor Imaging (DTI) is a sophisticated neuroimaging method that produces magnetic resonance images corresponding to changes in macroscopic axonal organization by utilizing the diffusion properties of water molecules. This method can be applied to assess the structure of "minicolumns," which are vertical cellular micro-circuits. Minicolumns are known to change during aging, MCI, and AD in a somewhat predictable and progressive manner, as previous research has shown (42). Additionally, a higher plaque load and cognitive decline are linked to pathologic alterations in the cortex columnar architecture(43). It is possible to measure DTI and use it as a neurodegenerative marker with the help of proprietary software.

- **PET Scan:**

Amyloid-β (Aβ) and hyperphosphorylated tau are two pathologic species that build up in the brains of AD patients. PET scans are a trustworthy biomarker that candetect both proteins. Tau accumulation increases in tandem with cognitive decline, and amyloid accumulation occurs prior to clinically significant cognitive changes, indicating the utility of PET scans for both diagnosis and tracking disease progression(44).

- **CSF and Blood Tests:**

The brain is surrounded by cerebrospinal fluid (CSF), which is accessible via lumbar puncture. Decades before clinically significant AD manifests, changes in the CSF's levels of the tau and Aβ proteins occur (45). The two most well-known CSF tests that have been developed in recent decades are the CSF tau phosphorylated at threonine 181 (P-tau181) and the CSF Aβ42:Aβ40 ratio. It is hoped that CSF P-tau217, which is detectable in the peripheral circulation, will offer a biomarker with exceptionally high sensitivity and specificity (46).

- **Biomarkers :**

The primary objective of data accumulation was originally intended to identify, assess, and validate biomarkers for use in clinical research. In many situations, proving earlier diagnostic and predictive capacity is the primary objective.
Additionally, biomarkers are used to validate and enhance dementia diagnosis precision. The primary focus of biomarker development and validation in Alzheimer's disease (AD) has been on cerebrospinal fluid (CSF) -omics, which includes proteomics, and PET ligands to identify CNS tau/tangles or amyloid beta (Aβ), the two pathological hallmarks of AD (47) (48)(49). However, the invasiveness and expense of CSF and PET biomarkers, respectively, restrict their use. Biomarker discovery and validation also face challenges related to sample storage, assay standardization within and between laboratories, collection techniques, and processing protocols.

The validation of blood-based biomarkers for dementia comes with difficulties. Just 19 of the 196 potential blood-based biomarkers were given priority by the Alzheimer's Precision Medicine Initiative for further review. However, it was determined that none of the 19 blood-based biomarkers match the intended product profile. Lack of confirmation in other participants limited the majority of biomarker candidates. Insufficient external validation could result in biased reporting and exaggerated forecast accuracy (50). Academia, industry, and regulators must work closely together to expedite the development of blood-based biomarkers for clinical application. Academic research frequently identifies biomarkers, and industry carries out their commercialization. Collaborations between academic institutions and business would enable access to clinical data, product testing, and clinical definitive areas.

- **Transcranial magnetic stimulation (TMS):**

A non-invasive therapeutic method called transcranial magnetic stimulation (TMS) stimulates underlying nerve cells by altering the magnetic field. Treatments for various neurological disorders, including dementia, are being researched with TMS. According to research by Benussi et al., paired-pulse TMS can differentiate AD from FTD and healthy controls (HC) (51).

- **Electroencephalographic (EEG) :**

Assessments of electroencephalographic (EEG) recordings have also been made for dementia diagnosis. Since EEG captures cortical neurons' electrical activity, it can be used to determine general brain function. Abnormalities in EEG recording are observed in subcortical dementias. EEG is a non-invasive technique that aims to achieve an earlier diagnosis, much like other methods. On the other hand, EEG recordings are more widely

accessible and reasonably priced at clinical centers than PET or MRI scanning. There are two general approaches to EEG methods.
The first is carried out in the absence of any stimuli while the subject is in the resting state, or awake at rest. Patients find it more comfortable and less stressful as they are not expected to complete a behavioral task (52).

Multiple investigations using EEG in the resting state have documented four effects of AD (53). In AD patients, the power spectrum slows down from high frequency (alpha, beta, and gamma) to low frequency (54). The progression of AD is correlated with the frequency shift from higher to lower. Patients with AD have a reduction in the complexity of their EEG signals, which is most likely due to neuronal death (55). Patients with AD show decreased synchronization, which is the outcome of reduced brain area connectivity (56, 57). Although the exact cause of desynchronization is unknown, atrophy of neural networks may be the root cause. Patients with AD have neuromodulatory deficits related to their cross- frequency interaction (58). For example, theta-rate modulated beta rhythms are more prominent in controls than in AD patients.**PROMISING TREATMENT OPTIONS:**

Multiple mechanisms have been proposed to explain the pathology of AD, and the treatments available today work against these mechanisms. The tau hypothesis, cholinergic hypothesis, excitotoxicity hypothesis, and amyloid cascade hypothesis are the most commonly recognized disease models.

The cholinergic deficiency that arises early in AD is the reason our current AD medications were created. Acetylcholine, a neurotransmitter that affects learning and memory neural circuitry, is profoundly reduced when cholinergic neurons are selectively lost, an early pathologic finding in AD. Therefore, an early approach to treating AD involved facilitating cholinergic transmission, which led to the continued use of several palliative medications. Digestive symptoms, vertigo, fatigue, insomnia, hallucinations, bradycardia, syncope, and cramping in the muscles are some of the significant side effects (59)(60)(61).

Present-day Treatment Approaches and Choices :

- **Cholinesterase Inhibitors :**

The main function of cholinesterase inhibitors is to reversibly inhibit cholinesterase, the enzyme that degrades acetylcholine in brain synapses, so extending the effects of the reduced acetylcholine levels in the brain(62)(63). There are currently three cholinesterase inhibitors in use: galantamine, rivastigmine, and donepezil.

Acetylcholinesterase and butyrylcholinesterase are pseudo-irreversibly inhibited by Rivastigmine, which works by attaching to two of the enzyme's active sites. Due to its slower dissociation than acetylcholinesterase, it is referred to as pseudo- irreversible. The

reversible, non-competitive acetylcholinesterase inhibitor Donepezil has been shown to have an impact on daily living activities, cognitive function, and overall clinical status. Benefits appear to be slightly greater for the 10 mg dosage than the 5 mg dosage. There is a larger dose form available, 23 mg, which has suspicious clinical benefits. According to meta-analyses, these medications can postpone, on average, the onset of adverse behaviors and the decline in activities of daily living (ADL) by six to twelve months. They can also slow the decline in global clinical rating and the decline in cognitive function(64)(65).

Galantamine is a nicotinic acetylcholine receptor modulator and reversible competitive acetylcholinesterase inhibitor. Theoretically, regions of the brain with low acetylcholine levels will be more affected by this agent. Its effects resemble those of the other inhibitors of cholinesterase(66).

- **N-methyl-D-aspartate (NMDA) Receptor Antagonist :**

Through N-methyl-D-aspartate (NMDA) receptor ion channels, an excitotoxic overload of calcium flux into neurons is caused by overstimulation of glutamatergic activity in the brain(67)(68). Excitotoxicity causes a progressive loss of synaptic function and ultimately neurodegeneration, which is consistent with the pathological anatomy of AD and the progressive decline in cognition(69). The synaptic plasticity that is assumed to underpin learning and memory, as well as glutamate synaptic transmission, are both significantly influenced by the NMDA receptor. Memantine, a low-affinity NMDA receptor antagonist, is believed to mitigate the cognitive decline linked to AD by modulating NMDA receptors to lessen glutamate-induced excitotoxicity(70)(71). The FDA has approved memantine for moderate to severe AD(72). It has been demonstrated to improve scores on the activities of daily living, the global function assessment, and the dementia stage assessment(73)(74). Additionally, it has been proposed that it may be effective in decreasing anxiety, agitation/aggression, delusions, and disruptions of the circadian rhythm(75). The benefit is readily apparent but it is not very great. It comes in both immediate- and extended-release forms, as well as combined with donepezil to form a pill. Memantine and cholinesterase inhibitors together seem to have synergistic effects, which is why treating moderate-to-severe AD with this combination is standard procedure(76).

Combination treatments:

Randomized controlled trials on parallel groups of patients with moderate to severe AD demonstrated that combination memantine and donepezil use significantly improved global state, language, ADL, behavior, and cognitive function compared to the placebo group (memantine and placebo)(77). However, in patients with mild to moderate AD, this benefit was not shown(78).

Emerging Treatments Options:

The development of drugs that specifically target the pathologic forms of tau and amyloid beta (Aβ) proteins linked to AD has emerged from the search for disease-

modifying therapies. According to the amyloid cascade theory, toxic variations of the Aβ protein cause synaptic dysfunction and neuronal death. One of the disease's early findings is Aβ pathology(79)(80). Research has demonstrated a more precise correlation between the tau pathology and the advancement of cognitive impairment(81)(82).

- **Targeting Amyloid Pathology :**

Although more recent theories suggest other possibilities, beta amyloid and hyperphosphorylated tau are partially responsible for the neurodegenerative effects of AD. For a pathological diagnosis of AD, tau-containing neurofibrillary tangles and amyloid plaques remains needed(83). Genetic alterations that change the production of amyloid have been connected to multiple familial forms of Alzheimer's disease. Studies using CSF biomarkers have additionally demonstrated that Aβ42 peptides decrease one to two decades before AD symptoms appear(84). While both soluble and insoluble amyloid dimers have been shown to produce synaptic toxicity, it is thought that the soluble aggregates have a stronger correlation with AD symptoms and disease severity(85).

Therapeutic agents have been developed to increase Aβ clearance from the central nervous system, reduce various forms of pathologic Aβ, or stop Aβ aggregation.
However, a number of tested drugs have not shown to be effective, and some have even make cognitive or physical symptoms worse, creating doubt on the amyloid hypothesis(86). By making sure that the right subjects are chosen to participate in clinical trials and that appropriate measures are taken, newer research techniques aim to enhance drug evaluation(87).

- **Passive Immunotherapeutics :**

Therapeutic agents have been developed to increase Aβ clearance from the central nervous system, reduce various forms of pathologic Aβ, or stop Aβ aggregation.
However, a number of tested drugs have not shown to be effective, and some have even make cognitive or physical symptoms worse, creating doubt on the amyloid hypothesis. By making sure that the right subjects are chosen to participate in clinical trials and that appropriate measures are taken, newer research techniques aim to enhance drug evaluatiAfter an early-stage vaccine meant to stimulate a protective immune response in AD patients failed, scientists created passive immunotherapeutic agents, which are monoclonal antibody solutions produced in biological systems and infused into human subjects(88). Reducing Aβ42's central and peripheral effects is the goal(89). While some passive immunotherapeutic agents are still being tested, others have failed clinical trials.

Human anti-Aβ monoclonal antibody Aducanumab (BIIB037) specifically targets aggregated forms of Aβ, such as soluble oligomers and insoluble fibrils.
Aducanumab, when administered as an infusion, acts in a dose- and time- dependent manner to reduce Aβ in prodromal or mild AD with Aβ PET-confirmed pathology. It does this by entering the central nervous system. Considerable evidence of plaque reduction has been provided. The

most significant safety finding has been the increased frequency of dose-related amyloid-related imaging abnormalities, specifically edema/effusion (ARIA-E), in Apo-E4 carriers. A notable reduction in the advancement of cognitive impairment was noted by the researchers in subjects who were administered the maximum dose of 10 mg/kg (based on the CDR-Sum of Boxes)(90). The FDA approved aducanumab in June 2021 to treat AD, subject to a phase IV trial that carefully evaluates the drug's safety and efficacy. Subsequently, the FDA changed the medication's indication to focus on mild cognitive impairment or mild dementia related to AD, amid some controversy regarding the accelerated approval process that was carried out despite scant evidence of treatment benefit.

Lecanemab (BAN2401), Lecanemab (BAN2401), Donanemab (LY3002813), Gantenerumab, Crenezumab are other passive immunotherapeutic agents used in the treatment of alzheimer's disease(91).

- **Inhibition of Tau Aggregation :**

Since it promotes mitochondrial activity and reduces neuroinflammation, Methylene Blue (MB) is a well-known drug with a wide range of applications(92). MB has been studied in animal models to lower Aβ levels and enhance memory and learning, which is thought to be mediated by raising Aβ clearance(93). It has been found to induce autophagy(94), which helps to promote the removal of tau filaments and reverse tau aggregation(95). While some animal studies reported some efficacy in improving cognition and reducing tau pathology, human trials have not shown clear benefits. This has been ascribed to MB's ability to decrease tau fibrils while increasing granular tau oligomers, which are believed to be crucial for the death of neurons(96).

Turmeric root is the natural source of curcumin, a plant compound having anti- inflammatory and antioxidant qualities. It binds directly to protein sheets that haveβ pleated patterns, which stops aggregation(97). Similar to MB, it has also been demonstrated to lessen cognitive impairments and reduce tau and Aβ pathology in animal studies. There haven't been any notable cognitive effects from earlier
trials(98). Only moderate results were seen in a recent trial with a small population. Concerns regarding curcumin's poor water solubility at neutral or acidic pH, instability at basic pH, and rapid intestinal and first pass glucuronidation have limited the drug's clinical development as a therapeutic agent.

Treatment of behavioral and psychological symptoms of dementia in Alzheimer's disease :

Even in amnestic mild cognitive impairment (MCI), the predementia stage of AD, noncognitive neuropsychiatric symptoms, also known as behavioral and psychological symptoms of dementia (BPSD), are prevalent throughout all clinical stages of AD and become more common as the

disease advances. They are the primary causes of patients being institutionalized and an increased caregiver load. Four major symptom clusters with high prevalence can be identified in BPSD, according to a large observational study: psychosis (38% of patients, e.g., delusions), affective symptoms (59%, anxiety and depression), hyperactivity (64%, e.g., aggression, disinhibition), and apathy (65%).For treating comorbid depression in AD dementia, serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, paroxetine, citalopram, and fluvoxamine are widely regarded as some of the most effective antidepressants. SSRIs may also be taken into account in the treatment of AD dementia agitation and psychosis(99).

In these individuals, other commonly used antidepressants include Bupropion, Venlafaxine, Duloxetine, and selective noradrenalin and serotonin inhibitors (SNRIs). Their effectiveness in treating depression in AD dementia is supported by meta-analyses and a few randomized controlled trials with small patient populations(100).

It is clear that medications currently used to treat AD either only slightly improve cognitive function or provide some Behavioral and Psychological Symptoms of Dementia (BPSD) relief. One might claim that the development of novel medications that function in the early stages of AD represents a "medical need"
(101). Since a delay in treatment is linked to irreversible symptom progression, prompt treatment is essential.

Conclusion:

Alzheimer's disease presents a formidable challenge to individuals, families, and healthcare systems globally. While the devastating effects of the disease are profound, the ongoing research and promising treatment options provide hope for a future where effective interventions can mitigate its impact. Continued efforts in understanding the disease's mechanisms and advancing innovative therapies are crucial in the quest to unravel the mysteries of Alzheimer's and ultimately find a cure.

Reference:

1. Anand A, Patience AA, Sharma N and Khurana N: The present and future of pharmacotherapy of Alzheimer's disease: A comprehensive review. European Journal of Pharmacology 2017; 815: 364-365.
2. Gustavsson A, Green C, Jones RW, Förstl H, Simsek D, de Vulpillieres FDR, Luthman S, Adlard N, Bhattacharyya S and Wimo A: Current issues and future research priorities for health economic modeling across the full continuum of Alzheimer's disease. Alzheimer's & Dementia: the Journal of the Alzheimer's Association 2017; 13(3): 312- 321.
3. Alzheimer's Association: Alzheimer's disease facts and figures. Alzheimer's & Dementia 2018; 14(3): 367-429.
4. https://chat.openai.com/
5. Masters, C., Bateman, R., Blennow, K. *et al.* Alzheimer's disease. *Nat Rev Dis Primers* **1**, 15056 (2015). https://doi.org/10.1038/nrdp.2015.56
6. Alzheimer's disease international dementia statistics https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/
7. Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, Waters C, Jimison P, Shepherd E, Sevush S, et

al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the state of Florida brain Bank. Alzheimer Dis Assoc Disord. 2002;16:203–12.

8. Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, Waters C, Jimison P, Shepherd E, Sevush S, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the state of Florida brain Bank. Alzheimer Dis Assoc Disord. 2002;16:203–12.
9. World Alzheimer Report 2016. http://www.alz.co.uk/research/ WorldAlzheimerReport2016.pdf. 2016
10. World Alzheimer Report 2015. http://www.alz.co.uk/research/ WorldAlzheimerReport2015.pdf. 2015.
11. Schultz C., Del Tredici K.H.B: Neuropathology of Alzheimer's Disease. In Alzheimer's Disease Current Clinical Neurology. Edited by R. R, B. R. Totowa, NJ: Humana Press; 2004.

12. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. Alzheimer's Dement. 2019 Mar;15(3):321–87.
13. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: Results of the cognitive function and ageing study I and
II. Lancet. 2013;382(9902):1405–12.
14. Schrijvers EMC, Verhaaren BFJ, Koudstaal PJ, Hofman A, Ikram MA, Breteler MMB. Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam study. Neurology. 2012;78(19):1456–63.
15. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL.
Alzheimer's disease. Nat Rev Dis Prim. 2015 Dec 15;1(1):15056. [PubMed] [CrossRef]
16. Talwar P, Sinha J, Grover S, Rawat C, Kushwaha S, Agarwal R, et al. Dissecting complex and multifactorial nature of Alzheimer's disease pathogenesis: A clinical, genomic, and systems biology perspective. Mol Neurobiol. 2016;53(7):4833–
64. [PubMed] [CrossRef]
17. Cuyvers E, Sleegers K. Genetic variations underlying Alzheimer's disease: Evidence from genome-wide association studies and beyond. Lancet Neurol. 2016;15(8):857–
68. [PubMed] [CrossRef]

18. Huang X, Moir RD, Tanzi, RE, Bush AI and Rogers JT: Redox-active metals, oxidative stress, and Alzheimer's disease pathology. Annals of the New York Academy of Sciences 2004; 1012(1): 153-163.
19. Godyń J, Jończyk J, Panek D and Malawska B: Therapeutic strategies for Alzheimer's disease in clinical trials. Pharmacological Reports 2016; 68(1): 127-38.
20. Anand A, Patience AA, Sharma N and Khurana N: The present and future of
pharmacotherapy of Alzheimer's disease: A comprehensive review. European Journal of Pharmacology 2017; 815: 364-365.
21. Kumar A and Singh A: A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacological Reports 2015; 67(2): 195-203.
22. Kumar A, Nisha C, Silakari C, Sharma I, Anusha K, Gupta N, Nair P, Tripathi T and Kumar A: Current and novel therapeutic molecules and targets in Alzheimer's disease. Journal of the Formosan Medical Association 2016; 115(1): 3-10.
23. Mecocci P, Boccardi V, Cecchetti R, Bastiani P, Scamosci M, Ruggiero C and Baroni M: A Long journey into aging, brain aging, and alzheimer's disease following the oxidative stress tracks. Journal of Alzheimer's Disease 2018; 62(3): 1319-1335.
24. Ferreira-Vieira HT, Guimaraes MI, Silva RF and Ribeiro MF: Alzheimer's disease: targeting the cholinergic system. Current Neuropharmacology 2016; 14(1): 101-115.
25. Blokland A: Acetylcholine: A neurotransmitter for learning and memory?. Brain Research Reviews 1995; 21(3): 285-300.
26. Arendt T, Brückner MK, Morawski M, Jäger C and Gertz HJ: Early neuron loss in Alzheimer's disease: cortical or subcortical?. Acta Neuropathological Communications 2015; 3(1): 10.
27. Kihara T and Shimohama S: Alzheimer's disease and acetylcholine receptors. Acta Neurobiologiae Experi-mentalis 2004; 64(1): 99-106.
28. Muir JL: Acetylcholine, aging, and Alzheimer's disease. Pharmacology Biochemistry and Behavior 1997; 56(4): 687-696.
29. Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT,
Khachaturian AS, Vergallo A, Cavedo E, Snyder PJ and Khachaturian ZS: The
cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain 2018; 141(7): 1917-1933.
30. Perl DP. Neuropathology of Alzheimer's disease. Mt Sinai J Med. 2010;77:32–42.

31. Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD,Kramer JH, Weiner M, Miller BL, Seeley WW. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer'sdisease. Brain. 2010;133:1352–67.
32. Piguet O, Double KL, Kril JJ, Harasty J, Macdonald V, McRitchie DA, Halliday GM. White matter loss in healthy ageing: a postmortem analysis. Neurobiol Aging. 2009;30:1288–95.
33. Apostolova LG, Green AE, Babakchanian S, Hwang KS, Chou YY, Toga AW, Thompson PM. Hippocampal atrophy and ventricular enlargement in normal aging, mild cognitive impairment (MCI), and Alzheimer disease.
Alzheimer Dis Assoc Disord. 2012;26:17–27
34. .Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med. 2011;1:a006189.
35. Fact sheet March 2023, The Impact of Alzheimer's on Families , portal.alzimpact.org was first indexed by Google in September 2022.
36. Centers for Disease Control and Prevention, https://www.cdc.gov/aging/caregiving/alzheimer.htm
37. The Effects Alzheimer's Disease Has On Family Members And Caregivers By Unicity Healthcare / August 17, 2018
38. Diagnosing Alzheimer's: How Alzheimer's is diagnosed, Mayo Clinic ; https://www.mayoclinic.org › in-depth › art-20048075
39. Pietrzak K, Czarnecka K, Mikiciuk-Olasik E, Szymanski P. New perspectives of alzheimer disease diagnosis—the most popular and future methods. Med Chem. (2018) 14:34–43. doi: 10.2174/1573406413666171002120847.
40. Tanpitukpongse, T. P., Mazurowski, M. A., Ikhena, J., & Petrella, J. R., & the Alzheimer's Disease Neuroimaging Initiative. (2017, March). Predictive utility of
marketed volumetric software tools in subjects at risk for Alzheimer disease: Do regions outside the hippocampus matter? *AJNR. American Journal of Neuroradiology*, *38*(3), 546–552. https://doi.org/10.3174/ajnr.A5061

41. Filippini, G. (2020, March 2). Structural magnetic resonance imaging for the early diagnosis of dementia due to Alzheimer's disease in people with mild cognitive impairment. *Cochrane Database Syst Rev*, *3*(3), CD009628. https://doi.org/10.1002/14651858.CD009628.

42. Chance, S. A., Clover, L., Cousijn, H., Currah, L., Pettingill, R., & Esiri, M. M. (2011, August). Microanatomical correlates of cognitive ability and decline: Normal ageing, MCI, and Alzheimer's disease. *Cereb Cortex*, *21*(8), 1870–1878. https://doi.org/10.1093/cercor/bhq264

43. van Veluw, S. J., Sawyer, E. K., Clover, L., Cousijn, H., De Jager, C., Esiri, M. M., & Chance, S. A. (2012, October). Prefrontal cortex cytoarchitecture in normal aging and Alzheimer's disease: A relationship with IQ. *Brain Structure & Function*, *217*(4), 797– 808 https://doi.org/10.1007/s00429-012-0381-x

44. Hanseeuw, B. J., Betensky, R. A., Jacobs, H. I. L., Schultz, A. P., Sepulcre, J., Becker, J. A., . . . Johnson, K. (2019, August 1). Association of amyloid and tau with cognition in

preclinical Alzheimer disease: A longitudinal study. *JAMA Neurology*, *76*(8), 915–924. PubMed https://doi.org/10.1001/jamaneurol.2019.1424

45. Jansen, W. J., Ossenkoppele, R., Knol, D. L., Tijms, B. M., Scheltens, P., Verhey, F. R. J., Zetterberg, H., & the Amyloid Biomarker Study Group. (2015, May 19).
Prevalence of cerebral amyloid pathology in persons without dementia: A meta-analysis.
JAMA, 313(19), 1924–1938.

46. Palmqvist, S., Janelidze, S., Quiroz, Y. T., Zetterberg, H., Lopera, F., Stomrud, E., . . . Hansson, O. (2020, August 25). Discriminative accuracy of plasma phospho-tau217 for Alzheimer Disease vs other neurodegenerative disorders. *JAMA*, *324*(8), 772–781. PubMed https://doi.org/10.1001/jama.2020.12134

47. Hampel H, O'Bryant SE, Molinuevo JL, Zetterberg H, Masters CL, Lista S, et al. Blood- based biomarkers for Alzheimer disease: mapping the road to the clinic. Nat Rev Neurol. (2018) 14:639–52. doi: 10.1038/s41582-018-0079-7

48. Chertkow H, Black S. Imaging biomarkers and their role in dementia clinical trials. Can J Neurol Sci. (2007) 34(Suppl. 1):S77–83. doi: 10.1017/s031716710000562x

49. Blennow K, Zetterberg H. Use of CSF biomarkers in Alzheimer's disease clinical trials. J Nutr Health Aging. (2009) 13:358– 61. doi: 10.1007/s12603-009-0043-8

50. Kerr NL. HARKing: hypothesizing after the results are known. Pers Soc Psychol Rev. (1998) 2:196–217. doi: 10.1207/s15327957pspr0203_4

51. . Benussi A, Di Lorenzo F, Dell'Era V, Cosseddu M, Alberici A, Caratozzolo S, et al. Transcranial magnetic stimulation distinguishes Alzheimer disease from frontotemporal dementia. Neurology. (2017) 89:665–72. doi: 10.1212/WNL.0000000000004232

52. Vecchio F, Babiloni C, Lizio R, Fallani FDV, Blinowska K, Verrienti G, et al. Resting state cortical EEG rhythms in Alzheimer's disease: toward EEG markers for clinical applications: a review. Suppl Clin Neurophysiol. (2013) 62:223–36. doi: 10.1016/b978- 0-7020-5307-8.00015-6

53. Cassani R, Estarellas M, San-Martin R, Fraga FJ, Falk TH. Systematic review on resting-state EEG for alzheimer's disease diagnosis and progression assessment. Dis Markers. (2018) 2018:5174815. doi: 10.1155/2018/ 5174815

54. Jeong J. EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol. (2004) 115:1490–505. doi: 10.1016/j.clinph.2004.01.001

55. Jeong J, Kim SY, Han SH. Non-linear dynamical analysis of the EEG in Alzheimer's disease with optimal embedding dimension. Electroencephalogr Clin Neurophysiol. (1998) 106:220–8. doi: 10.1016/s0013-4694(97)00079-5

56. Dunkin JJ, Leuchter AF, Newton TF, Cook IA. Reduced EEG coherence in dementia: state or trait marker? Biol Psychiatry. (1994) 35:870– 9. doi: 10.1016/0006- 3223(94)90023-x

57. Wen D, Zhou Y, Li X. A critical review: coupling and synchronization analysis methods of EEG signal with mild cognitive impairment. Front Aging Neurosci. (2015) 7:54. doi: 10.3389/fnagi.2015.00054

58. Falk TH, Fraga FJ, Trambaiolli L, Anghinah R. EEG amplitude modulation analysis for semi-automated diagnosis of Alzheimer's disease. EURASIP J Adv Signal Proc. (2012) 2012:192. doi: 10.1186/1687-6180-2012-192

59. Joe, E., & Ringman, J. M. (2019, December 6). Cognitive symptoms of Alzheimer's disease: Clinical management and prevention. BMJ (Clinical Research Ed.), 367, l6217. PubMed https://doi.org/10.1136/bmj.l6217 16.

60. Masterman, D. (2004, February). Cholinesterase inhibitors in the treatment of Alzheimer's disease and related dementias. Clinics in Geriatric Medicine, 20(1), 59–68. PubMed https://doi.org/10.1016/j.cger.2003.11.002

61. Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011, May). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 7(3), 270–279. PubMed https://doi.org/10.1016/j.jalz.2011.03.008

62. Ritchie, C. W., & Zhinchin, G. (2013, April). Low dose, high dose, or no dose: Better prescribing of cholinesterase inhibitors for Alzheimer's disease. International Psychogeriatrics, 25(4), 511–515. PubMed https://doi.org/10.1017/S1041610212002414

63. Chu, L. W. (2012, June). Alzheimer's disease: Early diagnosis and treatment. Hong Kong Med J, 18(3), 228–237. PubMed

64. 0. Birks, J. S., & Harvey, R. J. (2018, June 18). Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev, 6(6), CD001190. PubMed https://doi.org/10.1002/14651858.CD001190.pub3

65. . Hansen, R. A., Gartlehner, G., Webb, A. P., Morgan, L. C., Moore, C. G., & Jonas, D. E. (2008). Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: A systematic review and meta-analysis. Clinical Interventions in Aging, 3(2), 211–225. PubMed

66. Loy, C., & Schneider, L. (2006, January 25). Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Systemat Rev, (1): CD001747. PubMed https://doi.org/10.1002/14651858.CD001747.pub3

67. Sucher, N. J., Awobuluyi, M., Choi, Y. B., & Lipton, S. A. (1996, October). NMDA receptors: From genes to channels. Trends in Pharmacological Sciences, 17(10), 348–355. PubMed https://doi.org/10.1016/S0165-6147(96)80008-3

68. Johnson, J. W., & Kotermanski, S. E. (2006, February). Mechanism of action of memantine. Current Opinion in Pharmacology, 6(1), 61–67. PubMed https://doi.org/10.1016/j.coph.2005.09.007

69. Wang, R., & Reddy, P. H. (2017). Role of glutamate and NMDA receptors in Alzheimer's Disease. J Alzheimers Dis, 57(4), 1041–1048. PubMed https://doi.org/10.3233/JAD-160763

70. . Liu, J., Chang, L., Song, Y., Li, H., & Wu, Y. (2019, February 8). The role of NMDA receptors in Alzheimer's Disease. Frontiers in Neuroscience, 13, 43. PubMed https://doi.org/10.3389/fnins.2019.00043

71. Reisberg, B., Doody, R., Stöffler, A., Schmitt, F., Ferris, S., & Möbius, H. J., & the Memantine Study Group. (2003, April 3). Memantine in moderate-to-severe Alzheimer's disease. The New England Journal of Medicine, 348(14), 1333–1341. PubMed https://doi.org/10.1056/NEJMoa013128

72. Matsunaga, S., Kishi, T., & Iwata, N. (2015, April 10). Memantine monotherapy for Alzheimer's disease: A systematic review and meta-analysis. PLoS One, 10(4), e0123289. PubMed https://doi.org/10.1371/journal.pone.0123289

73. Matsunaga, S., Kishi, T., & Iwata, N. (2015, April 10). Memantine monotherapy for Alzheimer's disease: A systematic review and meta-analysis. PLoS One, 10(4), e0123289. PubMed https://doi.org/10.1371/journal.pone.0123289

74. McShane, R., Westby, M. J., Roberts, E., Minakaran, N., Schneider, L., Farrimond, L. E., . . . Debarros, J. (2019, March 20). Memantine for dementia. Cochrane Database Syst Rev, 3(3), CD003154. PubMed

75. Kishi, T., Matsunaga, S., & Iwata, N. (2017, July 20). The effects of memantine on behavioral disturbances in patients with Alzheimer's disease: A meta-analysis. Neuropsychiatric Disease and Treatment, 13, 1909–1928. PubMed https://doi.org/10.2147/NDT.S142839

76. Atri, A., Hendrix, S. B., Pejović, V., Hofbauer, R. K., Edwards, J., Molinuevo, J. L., & Graham, S. M. (2015, May 18). Cumulative, additive benefits of memantine-donepezil combination over component monotherapies in moderate to severe Alzheimer's dementia: A pooled area under the curve analysis. Alzheimer's Research & Therapy, 7(1), 28. PubMed https://doi.org/10.1186/s13195-015-0109-2

77. Howard R., McShane R., Lindesay J., Ritchie C., Baldwin A., Barber R., et al. (2012) Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med* 366: 893–903 [PubMed] [Google Scholar] [Ref list]

78. Farlow M., Alva G., Meng X., Olin J. (2010) A 25-week, open label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis. *Curr Med Res Opin* 26: 263–269
[PubMed] [Google Scholar] [Ref list]

79. Bakota, L., & Brandt, R. (2016, March). Tau biology and tau-directed therapies for Alzheimer's Disease. Drugs, 76(3), 301–313. PubMed https://doi.org/10.1007/s40265- 015- 0529-0 35.

80. Jia, Q., Deng, Y., & Qing, H. (2014). Potential therapeutic strategies for Alzheimer's disease targeting or beyond β-amyloid: Insights from clinical trials. BioMed Research International, 2014, 1. PubMed.

81. Nelson, P. T., Alafuzoff, I., Bigio, E. H., Bouras, C., Braak, H., Cairns, N. J., . . . Beach,
T. G. (2012, May). Correlation of Alzheimer disease neuropathologic changes with cognitive status: A review of the literature. Journal of Neuropathology and Experimental Neurology, 71(5), 362–381. PubMed https://doi.org/10.1097/NEN.0b013e31825018f7

82. Bejanin, A., Schonhaut, D. R., La Joie, R., Kramer, J. H., Baker, S. L., Sosa, N., . . . Rabinovici, G. D. (2017, December 1). Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. Brain, 140(12), 3286–3300. PubMed https://doi.org/10.1093/brain/awx243

83. Gouras, G. K., Olsson, T. T., & Hansson, O. (2015, January). β-Amyloid peptides and amyloid plaques in Alzheimer's disease. Neurotherapeutics, 12(1), 3–11. PubMed https://doi.org/10.1007/s13311-014-0313-y

84. Buchhave, P., Minthon, L., Zetterberg, H., Wallin, A. K., Blennow, K., & Hansson, O. (2012, January). Cerebrospinal fluid levels of β-amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Archives of General Psychiatry, 69(1), 98–106. PubMed https://doi.org/10.1001/archgenpsychiatry.2011.155

85. Ricciarelli, R., & Fedele, E. (2017). The amyloid cascade hypothesis in Alzheimer's Disease: It's time to change our mind. Current Neuropharmacology, 15(6), 926–935. PubMed https://doi.org/10.2174/1570159X15666170116143743

86. Panza, F., Lozupone, M., Solfrizzi, V., Sardone, R., Piccininni, C., Dibello, V., . . . Imbimbo, B. P. (2018, November). BACE inhibitors in clinical development for the treatment of Alzheimer's disease. Expert Review of Neurotherapeutics, 18(11), 847– 857. PubMed https://doi.org/10.1080/14737175.2018.1531706

87. Panza, F., Lozupone, M., Seripa, D., & Imbimbo, B. P. (2019, March). Amyloid-β immunotherapy for alzheimer disease: Is it now a long shot? Annals of Neurology, 85(3), 303–315. PubMed https://doi.org/10.1002/ana.25410

88. Lozupone, M., Solfrizzi, V., D'Urso, F., Di Gioia, I., Sardone, R., Dibello, V., . . . Panza, F. (2020, September). Anti-amyloid-β protein agents for the treatment of
Alzheimer's disease: An update on emerging drugs. Expert Opinion on Emerging Drugs, 25(3), 319–335. PubMed https://doi.org/10.1080/14728214.2020.1808621

89. Selkoe, D. J., & Hardy, J. (2016, June 1). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine, 8(6), 595–608. PubMed https://doi.org/10.15252/emmm.201606210

90. Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., . . . Sandrock, A. (2016, September 1). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature, 537(7618), 50–56. PubMed https://doi.org/10.1038/nature19323

91. Diagnosis and Treatment of Alzheimer's Disease ; An Update, Emily Bomasang-Layno, M.D., M.Sc. and Rachel Bronsther, M.D. Department of Psychiatry, ChristianaCare Doi: 10.32481/djph.2021.09.009

92. Tucker, D., Lu, Y., & Zhang, Q. (2018, June). From mitochondrial function to neuroprotection-an emerging role for methylene blue. Molecular Neurobiology, 55(6), 5137–5153. PubMed https://doi.org/10.1007/s12035-017-0712-2

93. Medina, D. X., Caccamo, A., & Oddo, S. (2011, March). Methylene blue reduces aβ levels and rescues early cognitive deficit by increasing proteasome activity. Brain Pathology (Zurich, Switzerland), 21(2), 140–149. PubMed https://doi.org/10.1111/j.1750- 3639.2010.00430.x

94. Congdon, E. E., Wu, J. W., Myeku, N., Figueroa, Y. H., Herman, M., Marinec, P. S., . .
. Duff, K. E. (2012, April). Methylthioninium chloride (methylene blue) induces autophagy and attenuates tauopathy in vitro and in vivo. Autophagy, 8(4), 609–622. PubMed https://doi.org/10.4161/auto.19048

95. Wischik, C. M., Edwards, P. C., Lai, R. Y., Roth, M., & Harrington, C. R. (1996, October 1). Selective inhibition of Alzheimer disease-like tau aggregation by phenothiazines. Proceedings of the National Academy of Sciences of the United States of America, 93(20), 11213–11218. PubMed https://doi.org/10.1073/pnas.93.20.11213

96. Soeda, Y., Saito, M., Maeda, S., Ishida, K., Nakamura, A., Kojima, S., & Takashima, A. (2019). Methylene blue inhibits formation of tau fibrils but not of granular tau
oligomers: A plausible key to understanding failure of a clinical trial for Alzheimer's disease. J Alzheimers Dis, 68(4), 1677–1686. PubMed https://doi.org/10.3233/JAD- 181001

97. Hu, S., Maiti, P., Ma, Q., Zuo, X., Jones, M. R., Cole, G. M., & Frautschy, S. A. (2015, June). Clinical development of curcumin in neurodegenerative disease. Expert Review of Neurotherapeutics, 15(6), 629–637. PubMed https://doi.org/10.1586/14737175.2015.1044981

98. Reddy, P. H., Manczak, M., Yin, X., Grady, M. C., Mitchell, A., Tonk, S., . . . Reddy, A. P. (2018). Protective effects of Indian spice curcumin against amyloid-β in Alzheimer's disease. J Alzheimers Dis, 61(3), 843–866. PubMed https://doi.org/10.3233/JAD-170512

99. Zec R., Burkett N. (2008) Non-pharmacological and pharmacological treatment of the cognitive and behavioral symptoms of Alzheimer disease. *NeuroRehabilitation* 23: 425–438 [PubMed] [Google Scholar] [Ref list]

100. Banerjee S., Hellier J., Dewey M., Romeo R., Ballard C., Baldwin R. (2011) Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet* 378: 403– 411 [PubMed] [Google Scholar] [Ref list]

101. Mancuso C., Siciliano R., Barone E., Butterfield D., Preziosi P. (2011) Pharmacologists and Alzheimer disease therapy: to boldly go where no scientist has gone before. *Expert Opin Investig Drugs* 20: 1243–1261 [PubMed] [Google Scholar] [Ref list]