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Review Article

Alzheimer's disease: newer modalities in treatment

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ABSTRACT

Alzheimer's disease (AD) remains insurmountable despite a long history of research and clinical development. It is projected to rise in the coming decades of public health due to the aging population worldwide. Understanding the basic tenets of the disease and targeting key steps remains a time-tested approach even for AD. Apart from the currently available treatment options namely NMDA blockers, and acetylcholinesterase inhibitors, recently monoclonal antibodies that target Aβ amyloid protein are approved. This review highlights the key features of currently approved drugs along with promising drugs in clinical development.

Keywords: AD, Monoclonal antibody, Degenerative brain disease, Clinical development for AD

INTRODUCTION

Alzheimer's disease (AD) is one of the most common forms of dementia affecting an estimated 24.3 million people worldwide, with 40% of that population living in less developed countries.[1] The prevalence of dementia in Western Europe is around 4.5 million, and its total annual costs amount of 55 billion euros in treatment and developmental research.[2]

It is characterized as a chronic degenerative disease of the central nervous system, with characteristics of cognitive dysfunction, and behavioural disability. The pathological differences include the formation of senile plaques-containing beta-amyloid (Aβ), neurofibrillary tangles (NFTs), loss of neurons, and synapses. So far, the pathogenesis of AD is still not well studied.[1] AD is classified into two regardless of the family history, familial AD and sporadic AD. Familial AD is usually caused by a mutation in the autosomal dominant gene that codes for amyloid precursor protein (APP), presenilin 1 and 2. Furthermore, amyloid precursor protein (APP) and presenilin (PS) are the definitive virulence genes that are mainly responsible for this disease occurring in the first place. A recent study conducted concluded that patients who had been diagnosed with down syndrome or any other aneuploidy had a consequently higher risk of developing AD as they had an extra pair of amyloid precursor protein (APP) in that chromosome that in turn lead to an increase in the beta-amyloid (Aβ) peptide in the brain that significantly increases the risk of having AD. The other pathological abnormalities contributing towards the neurodegeneration in AD are gliosis which is characterised by reactive astrocytes and activated microglia, chronic inflammation, excitotoxic damage accompanied by altered ion homeostasis, altered energy metabolism, oxidative stress and altered antioxidant defence systems. Early sign of AD is brain atrophy of hippocampus specifically located inside the presubiculum, this indicates that there is an early accumulation of Aβ.[3]

Diagnosing AD in patients usually involves analysing mild cognitive impairment in the patient which usually starts off with a detailed history from the patient to obtain and rule out other pathologies like substance dependence and etc. The next step in reaching to a final conclusion on the

diagnosis can be sparked by carrying out a complete neuro physical examination to identify any acute or chronic ongoing illnesses and focality. A mini-mental state examination (MMSE) used to be used in the past but due to its low specificity for MCI and early AD it has now been replaced by montreal cognitive assessment (MoCA) which has been proven to be more effective in reaching the diagnosis for moderate to severe dementia.[4] Both the scores usually are done on a scale of 30 with ≤26 hinting towards cognitive impairment. The following step usually involves obtaining an MRI, a brain CT and a PET scan to rule out other pathologies that can hint the diagnosis of Alzheimer's if negative for all.[5] Lastly, invasive procedure of extracting the cerebrospinal fluid is used and tested further to check the levels of amyloid β-protein (Aβ) usually decreased in this condition and phosphorylated tau and total tau which is usually increased in this condition.[6]

The treatment for this disease is usually palliative and drugs are given to treat the symptoms more than the cure, only 4 drugs were FDA-approved for the treatment which include, AChEIs donepezil, galantamine, rivastigmine, and the NMDA antagonist memantine.[7] Some new drugs have also surfaced in the field of treatment of the AD that are discussed in this article.

CURRENT MANAGEMENT OF AD

The current treatment plan usually endorsed for patients with Alzheimer's usually consists of a multifactorial approach that includes physician-patient communication, behavioural approach, caregiver support and pharmacological intervention. Physician-patient communication consists of a good relationship between the physician and the patient to successfully conveying the symptoms and the feelings. Secondly, behavioural therapy comprises of simplifying the environment of the patient, establishing a simple yet effective routine for the patient to follow, and initiating behavioural and exercise therapy for the patients physical and mental wellbeing. Thirdly, caregiver's support including small sessions of rest for the caregiver in charge, psychoeducation that consists of mentally preparing the patient for the after effect of dementia and symptoms.[3] The pharmacological intervention consists of medications for improvement of symptoms.

Acetylcholinesterase inhibitors

These class of drugs usually work by inhibiting the enzyme acetylcholinesterase which is responsible for breaking down Acetylcholine which gets saturated in the neural synapse. This group of drugs exhibit a dose-dependent enhancement of treating the symptoms caused by AD. the most commonly used acetylcholinesterase inhibitor are donepezil and galantine, and the use of a drug with dual action of butyrylcholinesterase inhibitor and acetylcholinesterase inhibitor called rivastigmine.[8] A previously used drug named tacrine has recently stopped being prescribed for AD due to its steep probability in developing hepatotoxicity when used under the therapeutic dose.[9] Although all these drugs do have similar mode of action on the human body they all differ in their pharmacokinetics drastically. The main mode of neurotransmission is by the use of acetylcholine which is usually released from the presynaptic neuron which can either formulate and lead to action with nicotinic or muscarinic receptors. Once the transmission is conveyed forward this acetylcholine is usually hydrolyzed by the help of either acetylcholine esterase which is located centrally in the synaptic cleft or butyrylcholinesterase which is predominantly associated and present in the glial cells of the body.[10-11] A recent research conducted has concluded with the help of sensitive histochemical techniques that the enzymes that are responsible for the hydrolysis of acetylcholine is now of high importance due to its role in the activity.[12] A study also conferred that in AD as the disease follows through its course and worsens the activity of the hydrolyzing enzyme acetylcholine esterase reduces to about 45% and the activity of the other hydrolyzing enzyme butyrylcholinesterase increases to about 40% to 90%.[12,13]

Donepezil

Donepezil is prescribed for the symptomatic management of mild to moderate AD. Acting as a specific and reversible inhibitor of acetylcholinesterase (AChE), it effectively slows down the hydrolysis of acetylcholine. This mechanism aims to sustain acetylcholine levels, potentially compensating for the decline in functioning cholinergic neurons observed in AD.[14] Among the available acetylcholinesterase inhibitors (AChEIs), only tacrine has been in circulation longer than donepezil; tacrine received approval in 1993 but is infrequently prescribed nowadays due to associated risks of liver damage. Donepezil gained approval in 1996/1997, followed by rivastigmine in 2000 and galantamine in 2001.[15] Considering side effects, donepezil primarily induces gastrointestinal discomfort including nausea, diarrhea, and alterations in appetite. Additionally, it may trigger insomnia, headaches, and muscle cramps. Severe adverse reactions attributed to donepezil are infrequent.[16]

Galantamine

Galantamine functions as both an acetylcholinesterase inhibitor and an allosteric modulator of nicotinic receptors.[17] Its consistent efficacy in improving cognition, overall functioning, and performance in daily activities among individuals with mild to moderate AD has been well-documented with neuroprotective properties with the use of galantamine. These effects seem to operate independently of its cholinesterase inhibition function and may involve mechanisms related to alpha-7 nicotinic receptors and the phosphatidylinositide 3-kinase–Akt pathway. Given that previous research has indicated an increased risk of AD progression and higher rates of brain and hippocampal atrophy in individuals with mild cognitive impairment (MCI) who carry the apolipoprotein

E (APOE) e4 allele, any evaluation of galantamine's impact on atrophy in MCI should consider the APOE genotype.[18] Regardless of Galantamine importance and effectiveness when combined in the treatment of Alzheimer disease, it does cause some real side effects in gastrointestinal disturbances such as nausea, vomiting, diarrhoea, and abdominal pain also loss of appetite or weight loss. Galantamine cannot be given in combination with any heart rate control drug, like beta blockers, and non-dihydropyridine CCBs, calcium channel blockers, for its risk of causing cardiovascular events by slowing the rate and leading to syncope.[19,20]

Rivastigmine

Rivastigmine, a cholinesterase inhibitor, functions through the inhibition of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), enzymes responsible for the breakdown of acetylcholine (ACh). By impeding the degradation of ACh, rivastigmine elevates the levels of this neurotransmitter in the synaptic cleft, thereby enhancing cholinergic neurotransmission. This augmentation of cholinergic activity is particularly beneficial in the treatment of mild to moderate stage of Alzheimer disease.[21] Rivastigmine also should efficacy in patients complaining of Parkinson's disease.[22] The predominant adverse reactions linked with rivastigmine administration typically manifest within the gastrointestinal system. Predominantly, individuals may experience symptoms such as nausea and vomiting as the primary indicators of these side effects.[23] Rare adverse reactions may be extrapyramidal symptoms, disruptions in sleep patterns, muscular cramping, and diminished strength.[24]

Memantine

Memantine serves as a valuable pharmaceutical agent across various neurological conditions, prominently severe form AD. Its primary mode of action entails the inhibition of current flow within the channels of N-methyl-D-aspartate (NMDA) receptor, a low-affinity voltage-dependent uncompetitive antagonist, a subset of glutamate receptors involved in brain functionality.[25] Intriguingly, while other substances targeting NMDA receptor channels, such as ketamine, manifest severe adverse effects.[26] In clinical settings, memantine administration has been associated with a spectrum of potential side effects. These effects may vary in severity and occurrence among individuals. Common adverse reactions reported include dizziness, headache, confusion, and fatigue. Gastrointestinal disturbances such as constipation and vomiting have also been documented. Additionally, some patients may experience hallucinations, agitation, or mood changes. Less frequently, memantine use has been linked to cardiovascular effects such as hypertension or hypotension. Rare but serious side effects may include seizures, urinary retention, or allergic reactions presenting as rash or swelling.

NEWER AGENTS WITH THE POTENTIAL FOR USE IN AD

Tideglusib

This drug is a GSK-3 inhibitor, it exhibited promising results in preclinical studies by mitigating neuronal loss, gliosis, tau protein phosphorylation, and ameliorating spatial memory deficits in transgenic mice models of AD. Human trials, including a placebo-controlled phase IIa escalating dose trial conducted on 30 AD patients over a 5-month period, demonstrated overall positive cognitive trends with tideglusib treatment, affirming its safety profile.[27-30] The clinical trials were halted due to lack of efficacy.

Saracatinib

Another kinase gaining attention as a potential therapeutic target is Fyn tyrosine kinase, which phosphorylates tau protein at the N-terminal domain and influences the amyloid signalling pathway.[31] Saracatinib, a Fyn inhibitor, has shown memory improvement in transgenic mice and demonstrated safety and tolerability in a phase I clinical trial. Currently, a multicenter phase IIa study involving 159 AD patients treated with Saracatinib is underway, aiming to further explore its therapeutic potential.[32-36] Saracatinib elicited gastrointestinal adverse effects, notably diarrhea, prompting premature cessation of treatment in a quarter of enrolled subjects prior to trial completion. These findings were documented in a peer-reviewed scientific publication.[37]

Aducanumab

This drug is a complete human immunoglobulin gamma 1 (IgG1) monoclonal antibody that ultimately combines to the Aβ fibrils N-terminal blocking the collection of amyloid protein.[38] It is usually administered to patients suffering from mild to moderate AD. In the month of August of 2015, two researches were initiated in the phase 2 clinical trial named EMERGE and ENGAGE. This research aimed to find out the influence between the dementia rate and different infusion doses of aducanumab which was assessed using the clinical dementia rating (CDR). The research revealed that when the analysis was done the subgroup that was initiated with a high dose of Aducanumab showed a slow progression decline in cognitive function. This research prompted the speedy approval of FDA in the month of June of the year 2021.[39] A research conducted in 2022 revealed that the most evident side effect seen in 30% of them when administering high doses aducanumab on AD patients was ARIA (Amyloid-related imaging abnormalities)-edema.[40]

Lecanemab

Lecanemab, a humanized IgG1 monoclonal antibody that targets soluble aggregated Aβ species (protofibrils) that was approved by the FDA at 6th of January 2023. A clinical

trial was conducted for 18 months with 1795 patients from the ages of (50-70 years) 898 assigned to receive lecanemab and 897 to receive placebo. The results show that lecanemab showed promising outcomes in reducing early AD symptoms by lowering markers of amyloid. Over 18 months, it led to somewhat slower decline in cognitive and functional abilities compared to placebo. However, there were also some negative side effects reported.[41]

Donanemab

Donanemab is a humanized IgG1 monoclonal antibody has been developed from the mouse mE8-IgG2a. This biologic medication specifically targets Aβ (p3-42), which is a pyroglutamate form of Aβ found aggregated within amyloid plaques. A randomized clinical trial was conducted on 1736 randomized participants with a mean age of 73, participants were randomly assigned in equal numbers to receive either donanemab (n=860) or a placebo (n=876) via intravenous administration every 4 weeks for 72 weeks. If participants in the donanemab group met dose completion criteria they were switched to receive the placebo in a blinded manner the results were among participants with early symptomatic AD and amyloid pathology donanemab significantly slowed clinical progression at 76 week.[42] The drug was approved by the FDA in the 11th of March 2024 (Table 1).

Cyclo-oxygenase 2 inhibitors

Research into AD has provided more understanding into its underlying pathological mechanisms.[43] Evidence of inflammation is apparent through the presence of inflammatory markers, such as the complement attack complex, which is found at levels akin to those observed in ischaemic heart disease.[44] This understanding, combined with the observation that individuals with rheumatoid arthritis exhibit a lower incidence of AD, has prompted investigations into the potential of anti-inflammatory drugs for treatment.[45] While trials involving prednisolone have yielded unsuccessful results, ongoing research involving cyclo-oxygenase inhibitors, specifically Cox-2, in both animal and human clinical trials may offer promising results. However, caution is warranted due to the long-term side effects associated with these medications, leading to the current practice of refraining from routine recommendation of their use. Moreover, there's speculation that this intervention could extend benefits to other forms of dementia and neurodegenerative conditions.[46,47]

Table 1: The summary of recently approved drugs for AD.

Medication	MOA	Indications	Side effects	FDA approval
Aducanumab	(IgG1) monoclonal antibody	Used in patients with mild cognitive impairment.	Blurred or changes in vision confusion, confusion as to time, place, or person dizziness.	Approved in the year 2021
Lecanemab	(IgG1) monoclonal antibody	Used in patients with early signs of dementia	Dizziness. headache visual changes worsening confusion swelling or bleeding in the brain brain shrinkage rarely, death	Approved in the year 2023
Donanemab	(IgG1) monoclonal antibody	Used in patients with mild cognitive impairment.	nausea, urinary tract infection, diarrhea, cerebral microhemorrhage, infusion-related reaction, vomiting, and anxiety.	Approved in the year 2024

OTHER TREATMENT MODALITIES FOR AD

Hormone replacement therapy

Furthermore, an observational study has indicated a decreased risk of AD among women taking hormone replacement therapy (HRT). The documented neuroprotective effects of oestrogen on the nervous system and vasculature have prompted clinical trials to evaluate the efficacy of oestrogen therapy, particularly with 17α-oestradiol. However, initial results from early treatment studies have not been promising. Consequently, in the absence of positive published studies, HRT cannot be prescribed for AD treatment until now. Nonetheless, its utilisation appears to be rising in AD prevention, particularly in the United States. Neuroendocrine investigations indicate the pivotal role of the cholinergic system in memory and learning processes, notably within the septo-hippocampal cholinergic pathway. In AD, there is a decline in the cholinergic system, characterised by reduced acetylcholine levels and choline-acetyltransferase activity. Long-term trials of oestrogen therapy (ET) in postmenopausal women have shown improvements in cholinergic function. Additionally, these trials have observed heightened responsiveness to dopaminergic and serotonergic neurotransmitters. Nonetheless, these studies possess inherent limitations, as they do not directly assess oestrogen's impact on receptor response within the hypothalamic-pituitary axis and are primarily observational and cross-sectional in nature.[48]

Antioxidants

Antioxidants have demonstrated efficacy in various aspects of chronic health conditions, including AD, as evidenced by a study investigating the impact of selegiline and vitamin E on disease progression. The findings revealed a favourable positive impact on the rate of dependency escalation and postponed institutionalisation. However, replication of these results is still pending.

Notably, vitamin E, being cost-effective and relatively safe, was administered at a high dosage (2000 IU) during the trial. Given the substantial costs associated with institutionalisation, there exists potential for considerable returns from this treatment, albeit without rigorous confirmation. Consequently, many medical facilities are now recommending the use of vitamin E, typically at a dosage of around 1000 IU, for patients with AD.[49]

Oxidative stress (OS) is a significant contributor to the pathology of AD, characterised by an imbalance between reactive oxygen/nitrogen species and antioxidant defence mechanisms. This imbalance can lead to the accumulation of oxidatively damaged molecules. Despite this understanding, there remains a paucity of scientific literature identifying specific OS markers for early detection of AD. The primary objective of this review is to delineate potential OS markers in brain tissue, cerebrospinal fluid (CSF), blood, and/or urine that may facilitate early diagnosis of AD in humans. The rationale behind investigating OS markers lies in the ineffectiveness of antioxidant therapies when initiated at later stages of AD progression. Secondly, we aim to assess the efficacy of natural antioxidants in preventing or mitigating AD symptoms. Our evaluation, based on human studies, underscores lipid peroxidation as a promising non-invasive OS marker for detecting mild cognitive impairment (MCI) and early-stage AD with heightened specificity and sensitivity. However, a comprehensive diagnostic approach integrating OS markers, familial history, and biochemical assays is imperative for early AD detection. Additionally, we highlight the potential benefits of long-term supplementation with vitamins (such as vitamin E found in almonds) and consumption of polyphenol-rich foods (e.g., curcumin from turmeric, ginkgo biloba, and epigallocatechin-3-gallate from green tea) in ameliorating AD symptoms. Further human studies are warranted to substantiate the therapeutic potential of natural antioxidants in AD management.

The close association between tau protein phosphorylation and its impact on the progression of pathological processes has spurred the quest for tau protein kinase inhibitors as promising therapeutic interventions in AD. Among these, the forefront approach to kinase inhibition in clinical settings presently targets glycogen synthase kinase-3 (GSK-3). Initial investigations focused on the clinical effects of lithium in AD patients, aiming to inhibit GSK-3; however, the outcomes were inconsistent, possibly due to limited sample size, low susceptibility, and the narrow therapeutic window of lithium.[50]

CONCLUSION

In conclusion, this degenerative condition, characterised by cognitive impairment and behavioural disabilities, requires a comprehensive approach to management and treatment. Diagnosis involves a multifaceted process, including cognitive assessment, neuroimaging, and cerebrospinal fluid analysis. While no cure exists, current pharmacological interventions primarily focus on symptom management, with FDA-approved drugs such as acetylcholinesterase inhibitors and the NMDA antagonist memantine.

Multifactorial approach to managing Alzheimer's encompasses effective physician-patient communication, behavioural strategies, caregiver support, and pharmacological interventions. Acetylcholinesterase inhibitors, including donepezil, galantamine, and rivastigmine, aim to alleviate symptoms by modulating acetylcholine levels. Additionally, NMDA antagonist memantine serves as a valuable option in managing severe Alzheimer's symptoms.

Emerging research indicates potential new avenues for Alzheimer's treatment, such as cyclo-oxygenase 2 inhibitors, nootropic drugs, hormone replacement therapy, and antioxidants, although definitive recommendations are pending clinical validation. Furthermore, promising advancements in drug development, particularly targeting tau protein and amyloid plaques, including aducanumab, lecanemab, and donanemab, have garnered attention and offer potential therapeutic benefits.

Efforts to advance Alzheimer's research and treatment will require ongoing collaboration among healthcare professionals, researchers, pharmaceutical companies, and policymakers. With growing understanding of disease's underlying mechanisms, potential for personalised, targeted interventions offers hope for improved outcomes for individuals affected by Alzheimer's and their families. Concerted, multidisciplinary approach is essential in addressing the complex challenges posed by this pervasive neurodegenerative condition.

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