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Alzheimer's disease: Pathological changes, recent treatment and future perspectives

Susheel Kumar*

IIMT College of Medical Sciences IIMT university, Meerut, Uttar Pradesh, India

*Corresponding author

Dr. Mojahid Hasan,

IIMT College of Medical Sciences IIMT university, Meerut, Uttar Pradesh, India

Dr. Sachin Singhal,

IIMT College of Medical Sciences IIMT university, Meerut, Uttar Pradesh, India

Anupam

IIMT College of Medical Sciences IIMT university, Meerut, Uttar Pradesh, India

Abstract---Alzheimer's disease (AD) is the most common cause of dementia associated with a progressive neurodegenerative disorder, with a prevalence of 44 million people throughout the world in 2015, and this figure is estimated to double by 2050. This disease is characterized by blood-brain barrier disruption, oxidative stress, mitochondrial impairment, neuroinflammation, and hypometabolism; it is related to amyloid- β peptide accumulation and tau hyperphosphorylation as well as a decrease in acetylcholine levels and a reduction of cerebral blood flow. Studies of potential disease-modifying therapy have generally been undertaken in patients with clinically detectable disease, yet evidence suggests that the pathological changes associated with AD begin several years before this. It is possible that pharmacological therapy may be beneficial in this pre-clinical stage before the neurodegenerative process is established. Techniques providing earlier diagnosis, such as cerebrospinal fluid biomarkers and amyloid positron emission tomography neuroimaging, are key to testing this theory in clinical trials. Recent results from trials of agents such as aducanumab are encouraging but must also be interpreted with caution. Such medicines could potentially delay the onset of dementia and would therefore markedly reduce its prevalence. Strategies for prevention of AD through nonpharmacological treatments are associated with lifestyle interventions such as exercise, mental challenges, and socialization as well as caloric restriction and a healthy diet. AD is an important health issue on which all people should be informed so that

prevention strategies that minimize the risk of its development may be implemented.

Keywords---Alzheimer, anti-Alzheimer, cholinesterase inhibitors, amyloid binders.

Introduction

Alzheimer disease (AD) is characterized by progressive deficits in memory, and cognitive and behavioural impairments that ultimately lead to dementia. It affects more than 5.4 million individuals in the USA. The prevalence, cost of care, impact on individuals and caregivers, and lack of mechanism-based treatments make AD one of the most challenging diseases. The syndrome of AD results from dysfunction and death of neurons in specific regions and circuits, particularly those populations of nerve cells subserving memory and cognition (Whitehouse et al., 1982). Characteristics of AD neuropathology include accumulations of intracellular and extracellular protein aggregates. Abnormally phosphorylated tau assembles into paired helical filaments (PHFs) that aggregate into neurofibrillary tangles (NFTs) in the neuronal perikarya and dystrophic neurites. The second pathological hallmark is the extracellular deposition of β -pleated assemblies of A β peptide, forming diffuse and neuritic senile plaques (Braak & Braak, 1991). In the 1970s and 1980s, neurochemical examination of brain samples from cases of AD led to the demonstration of a dramatic loss of cortical cholinergic innervations, and subsequent neuropathological studies found degeneration of basal forebrain magnocellular neurons and cholinergic deficits in the cortex and hippocampus. These observations led to the introduction of cholinesterase inhibitors as a first treatment for AD. Evidence of the involvement of glutamatergic systems in hippocampal and cortical circuits in AD, coupled with information about glutamate excitotoxicity [mediated, in part, by N-methyl-D-aspartate receptors (NMDA-R)], led to a second therapy being approved by the US Food and Drug Administration, NMDA-R antagonists. Both of these therapeutic strategies have given modest and transient symptomatic benefit in some patient. Observations of autosomal dominant inheritance in families with early-onset, familial Alzheimer disease (fAD) in concert with the work of geneticists resulted in the discovery of mutations in genes encoding the amyloid precursor protein (APP) and the presenilins (PS1 and PS2). Although the exact mechanisms affected by each mutation differ, the general outcome of fAD-associated mutations is an increase in production of A β _{1–40} and/or A β _{1–42} peptides or the A β _{1–40}/A β _{1–42} ratio. The presence of specific alleles of other genes such as apolipoprotein E (ApoE) has been found to be a risk factor for late-onset disease (Chung et al., 2021). The mechanisms affected by the risk factors associated with late-onset AD are likely to include alterations in A β metabolism, A β aggregation and clearance, or cholesterol homeostasis. Intensive study of the mechanisms of generation of A β peptides resulted in the discovery of sequential endoproteolytic cleavages of APP by two membrane-bound enzymes, termed β -site APP cleaving enzyme-1 (BACE1) and γ -secretase. Using mouse models with genetically altered activities of BACE1 or γ -secretase, both of these enzymes have been experimentally validated as high priority therapeutic targets for AD therapy.^{6–8} Based on preclinical studies, pharmacological inhibition of these activities has been predicted to decrease the

generation of $A\beta$ and to ameliorate cognitive decline in AD (Kim et al., 2011). However, when these novel mechanism-based experimental therapies were moved into clinical trials, they showed lower than expected efficacies in ameliorating functional deficits, and prominent adverse effects. These discrepancies between the outcomes of preclinical and clinical trials are forcing a re-evaluation of views of the disease, its models, and ways to resolve this translational dilemma (Cai et al., 2001).

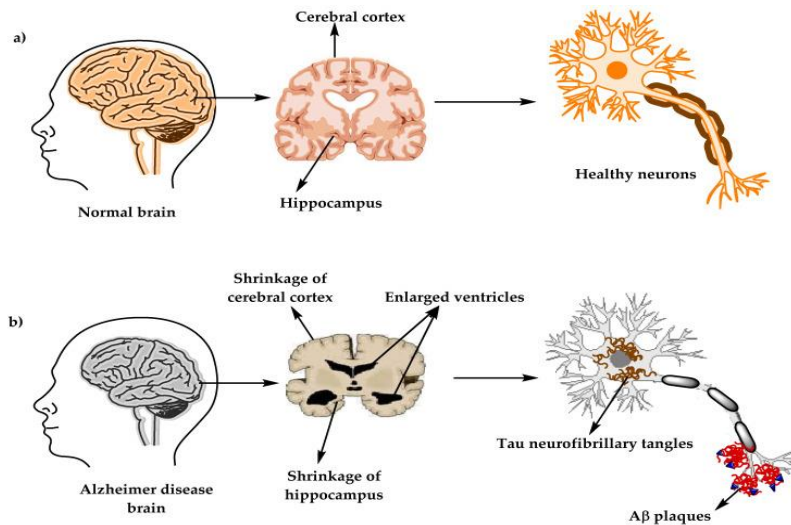


Fig.1 The physiological structure of the brain and neurons in (a) healthy brain and (b) Alzheimer's disease (AD) brain (Breijyeh & Karaman, 2020)

Alzheimer's Disease Diagnostic Criteria

A patient suspected to have AD should undergo several tests, including neurological examination, magnetic resonance imaging (MRI) for neurons, laboratory examinations such as vitamin B12, and other tests besides the medical and family history of the patients (Hampel et al., 2019). Vitamin (vit.) B12 deficiency has been long known for its association with neurologic problems and increasing risks of AD, according to some studies. A special marker of vit. B12 deficiency is elevated homocysteine levels, which can cause brain damage by oxidative stress, increasing calcium influx and apoptosis. Diagnoses of vit. B12 deficiency can be done by measuring serum vit. B12 level alongside complete blood count and serum homocysteine levels tests (Jatoi et al., 2020).

In 1984, The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) formed a work group (NINCDS-ADRDA) to establish a clinical diagnostic's criteria for Alzheimer's disease. This criterion includes: (1) probable Alzheimer's disease, which can be diagnosed by dementia that is confirmed by neuropsychological tests, progressive memory loss, impaired daily-life activity, and other symptoms like aphasia (impairment of a language), apraxia (a motor skills disorder), and agnosia (a loss of perception). All of these symptoms can start from age 40–90, with the absence of any systemic or brain diseases, (2) possible

Alzheimer's disease can be applied in the absence of neurologic, psychiatric disorders, and the presence of another illness like systemic or brain disorder, but they are not the primary cause of dementia, and (3) definite Alzheimer's disease, that is confirmed by histopathologic confirmation obtained from a biopsy or autopsy (McKhann et al., 1984).

In 2011, The National Institute on Aging-Alzheimer's Association made several changes and updated the 1984 NINCDS-ADRDA criteria for higher specificity and sensitivity in the diagnosis of Alzheimer's disease. The newly proposed criteria include probable and possible AD dementia for the use in clinical settings and probable or possible AD dementia with pathophysiological evidence for research purposes, in addition to clinical biomarkers. There are two categories of Alzheimer's disease biomarkers: (a) markers of brain amyloid such as positron emission tomography (PET) and cerebrospinal fluid (CSF), and (b) markers of neuronal injury like cerebrospinal fluid tau, fluorodeoxyglucose (FDG) for metabolic activity, and magnetic resonance imaging (MRI) for atrophy measurement (G. M. McKhann et al., 2011).

Recent advancement in Treatment of Alzheimer's disease

Currently, Alzheimer's disease cases worldwide are reported to be around 24 million, and in 2050, the total number of people with dementia is estimated to increase 4 times. Even though AD is a public health issue, as of now, there is only two classes of drugs approved to treat AD, including inhibitors to cholinesterase enzyme (naturally derived, synthetic and hybrid analogues) and antagonists to *N*-methyl D-aspartate (NMDA) (Pankaj, 2021). Several physiological processes in AD destroy Ach-producing cells which reduce cholinergic transmission through the brain. Acetylcholinesterase inhibitors (AChEIs), which are classified as reversible, irreversible, and pseudo-reversible, act by blocking cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)) from breaking down ACh, which results in increasing ACh levels in the synaptic cleft (Singh & Sadiq, 2022). On the other hand, overactivation of NMDAR leads to increasing levels of influxed Ca^{2+} , which promotes cell death and synaptic dysfunction. NMDAR antagonist prevents overactivation of NMDAR glutamate receptor and hence, Ca^{2+} influx, and restores its normal activity. Despite the therapeutic effect of these two classes, they are effective only in treating the symptoms of AD, but do not cure or prevent the disease (Wang & Reddy, 2017). Unfortunately, only a few clinical trials on AD have been launched in the last decade and their outcome was a big failure (Pankaj, 2021). Several mechanisms have been proposed to understand AD pathology in order to modify its pathway and develop successful treatments, which include abnormal tau protein metabolism, β -amyloid, inflammatory response, and cholinergic and free radical damage (Kumar et al., 2021). On the other hand, most AD modifiable risk factors such as cardiovascular or lifestyle habits can be prevented without medical intervention. Studies showed that physical activity can improve the brain health and reduce AD by activating the brain vascularization, plasticity, neurogenesis, and reducing inflammation by decreasing $A\beta$ production, which all result in improving cognitive function in older people (Bhatt et al., 2021). Moreover, the Mediterranean diet (MD), intellectual activity, and higher education all may reduce the progression of AD and memory loss and increase the brain capacity and cognitive functions. Several studies

revealed that multi-domain intervention which includes lifestyle (diet, exercise, and cognitive training), depression of AD symptoms, and controlling cardiovascular risk factors, can increase or maintain cognitive function and prevent new cases of AD in older people (Crous-Bou et al., 2017). Herein, we summarize the currently available drugs and theories for the development of new therapies for AD.

Anti-Amyloid Beta Monoclonal Antibodies (Bapineuzumab and Solanezumab)

Passive immunization with the humanized monoclonal antibodies, bapineuzumab and solanezumab, has been evaluated in several, large-scale phase three clinical trials in AD patients (Panza et al., 2011). However, many of these trials have failed to achieve their projected endpoints (Tayeb et al., 2013). Bapineuzumab is the humanized monoclonal antibody, directed against the N-terminus of amyloid beta that recognizes the amyloid beta 1–5 region. In a phase 2 clinical trial, the occurrence of amyloid-related imaging abnormalities (ARIA) detected by magnetic resonance imaging (MRI) of the brain, in particular, vasogenic edema among bapineuzumab-treated mild to moderate AD patients (which was increased in apolipoprotein E epsilon 4 [APOE e4] carriers) was an important adverse effect of this therapeutic (Rinne et al., 2010). Simultaneously, in another phase 2 double-blind, placebo-controlled, ascending dose study conducted in mild-to-moderate AD patients, bapineuzumab was shown to lower the brain amyloid beta burden assessed by ¹¹C Pittsburgh compound B positron emission tomography (PET) amyloid imaging (which is a marker of cortical fibrillar amyloid-beta load). In *post hoc* analysis of two phase 2 trials on bapineuzumab, evaluating cerebrospinal fluid (CSF) biomarker (amyloid beta, and tau protein) levels in mild-to-moderate AD patients, the main study outcomes were slightly different for CSF tau protein (tau protein was lower in the treatment group). However, there was no difference in the CSF amyloid beta level between the treatment and placebo groups (Rinne et al., 2010). Similarly, no significant clinical benefits have been reported in two large phase three trials, leading in consequence to the discontinuation of all phase 3 clinical trials on bapineuzumab, in mild-to-moderate AD patients, in 2012. In addition, it was reported that bapineuzumab failed to meet primary study endpoints, including changes in cognitive scores and functional performance, compared with placebo, in AD patients who were both APOE e4 carriers and noncarriers (Rinne et al., 2010). Although all phase 3 trials on bapineuzumab have ended, two phase 1 clinical trials in mild-to-moderate AD patients (ClinicalTrials.gov Identifiers: NCT01193608 and NCT01369225) are still ongoing, to test the safety and tolerability of the re-engineered version of bapineuzumab (AAB-003), aimed at reducing the risk of ARIAs (Lemere, 2013).

Solanezumab is an anti-amyloid beta monoclonal antibody, directed against the amyloid beta 13–28 region, and able to recognize various N-terminal truncated species (e.g., amyloid beta 3–42), which are often present in AD senile plaques. Solanezumab has demonstrated preferential binding to soluble amyloid beta, but not to fibrillar amyloid beta. Two large randomized, double-blind, controlled phase 3 trials of solanezumab: EXPEDITION1 (Expanding Alzheimer's Disease Investigations 1) and EXPEDITION2 (ClinicalTrials.gov Identifiers: NCT00905372 and NCT00904683) have involved over 2050 patients with mild-to-moderate AD, and as a follow-up of these trials, an open-label

extension, EXPEDITION-EXIT trial (ClinicalTrials.gov Identifier: NCT01127633) has been conducted to determine the long-term safety of solanezumab (Tayeb et al., 2013). In 2012, it was reported that the cognitive and functional study outcomes were not met in either of the two EXPEDITION trials. In particular, the EXPEDITION1 trial did not meet primary cognitive and functional endpoints in the overall mild-to-moderate AD patient population. However, the prespecified secondary subgroup analyses of pooled data, across both studies (EXPEDITION1 and EXPEDITION2), showed a statistically significant 34% reduction in cognitive decline, in patients with mild AD (Mini-Mental Status Examination [MMSE] score of 20–26), but not in the ones with moderate AD (MMSE of 16–19) (Tayeb et al., 2013). Simultaneously, an independent analysis by the Alzheimer's Disease Cooperative Study (ADCS) confirmed these beneficial findings (Tayeb et al., 2013). Furthermore, the biomarker analysis has shown an increase in plasma amyloid beta levels of AD patients suggesting that this toxic protein was removed from the brain. There were no significant changes in other AD biomarkers. Adverse events that occurred more often in the solanezumab group than in the placebo group included lethargy, rash, and malaise in EXPEDITION1 and angina in EXPEDITION2. Two ongoing phase 3 trials on solanezumab: The open-label extension study EXPEDITION-EXT (ClinicalTrials.gov Identifier: NCT01127633) and the EXPEDITION3 (ClinicalTrials.gov Identifier: NCT01900665) in mild AD patients will hopefully provide new data, on cognitive performance in the early stage of AD (Tayeb et al., 2013).

Cholinesterase Inhibitors

According to the cholinergic hypothesis, AD is due to the reduction in acetylcholine (ACh) biosynthesis. Increasing cholinergic levels by inhibiting acetylcholinesterase (AChE) is considered one of the therapeutic strategies that increases cognitive and neural cell function. AChEIs are used to inhibit acetylcholine degradation in the synapses, which results in continuous accumulation of ACh and activation of cholinergic receptors. Tacrine (tetrahydroaminoacridine) (**1**, Figure 2) was the first FDA (Food and Drug Administration)-approved cholinesterase inhibitor drug for the treatment of AD, which acts by increasing ACh in muscarinic neurons, but it exited the market immediately after its introduction due to a high incidence of side effects like hepatotoxicity and a lack of benefits, which was observed in several trials. Later on, several AChEIs were introduced, such as donepezil (**2**, Figure 2), rivastigmine (**3**, Figure 2), and galantamine (**4**, Figure 2), and are currently in use for the symptomatic treatment of AD (Larner, 2010; Sharma, 2019). Another strategy that may help in the treatment of AD is increasing choline reuptake and as a result, increasing acetylcholine synthesis at the presynaptic terminals. This can be achieved by targeting choline transporter (CHT1) which is responsible for supplying choline for the synthesis of ACh. Developing drugs that are capable of increasing CHT1 at the plasma membrane may become the future therapy of AD (Ferreira-Vieira et al., 2016).

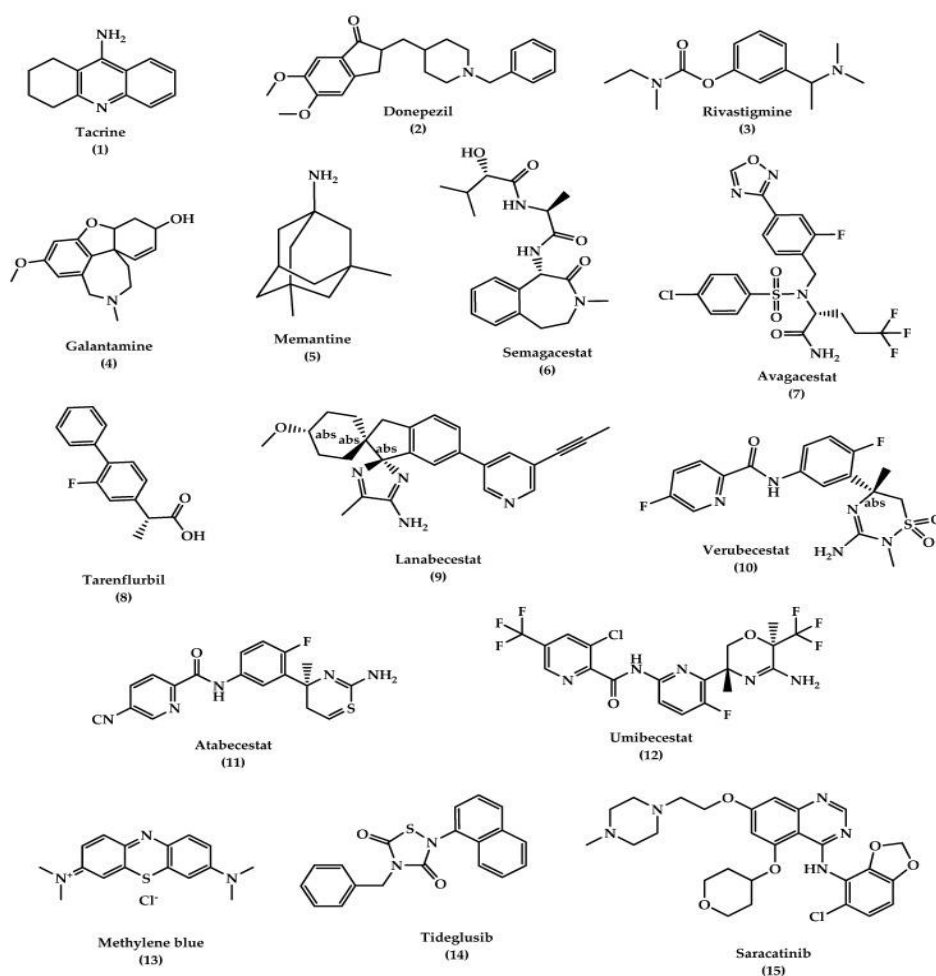


Fig. 2 The chemical structures of approved drugs for symptomatic treatment of AD (tacrine 1, donepezil 2, rivastigmine 3, galantamine 4, and memantine 5) and disease-modifying compounds that entered clinical trials (semagacestat 6, avagacestat 7, tarenflurbil 8, lanabecestat 9, verubecestat 10, atabecestat 11, umibecestat 12, methylene blue 13, tideglusib 14, and saracatinib 15) (Breijyeh & Karaman, 2020).

N-Methyl-D-aspartate Receptor (NMDA) Antagonist

Glutamate-mediated excitotoxicity is known to result in calcium overload and mitochondrial dysfunction, with increased nitric oxide generation, which can be detrimental to cells, forming high levels of oxidants and eliciting neuronal apoptosis. This overstimulation can be blocked by NMDA receptor antagonists such as memantine, which was approved in 2003 by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe AD, with a marginal beneficial effect on cognition in mild-to-moderate AD (Guest et al., 2020).

Memantine can protect neurons by attenuating tau phosphorylation through a decrease in glycogen synthase kinase 3 β (GSK-3 β) activity. This noncompetitive glutamatergic NMDA receptor antagonist can be administered alone or in combination with an acetylcholinesterase inhibitor, although there may be few significant favorable changes in the combination therapy (Leung et al., 2017).

Other Neurotransmitter Systems

Muscarinic and nicotinic ACh receptors are also considered targets for AD treatment, although selectivity of the agonists has been a problem outcome in clinical trials. EVP-6124 is currently in phase II trial. Based on the cholinergic hypothesis and NMDA glutamate participation in AD, it is natural to consider the different neurotransmitter networks, particularly of the hippocampus. Serotonin receptors are expressed in areas of the CNS involved in learning and memory. The inhibition of 5-HT₆ serotonin receptors was shown to promote acetylcholine release, and some compounds are in various stages of clinical research, considered as possible treatments for mild-to-moderate AD (Folch et al., 2016). Histamine receptors, particularly H₃ receptors, are also present in large amounts in memory- and cognition-related structures in the brain. It seems that H₃ receptor antagonists may improve cholinergic neurotransmission. Phase I and II studies with H₃ antagonists are currently being conducted (Godyń et al., 2016).

Amyloid Binders

The deposition of A β in AD is concentration-dependent; increased amyloidogenic processing of APP and inefficient removal of peptides may be involved in the pathology. There is reduced activity of A β -degrading enzymes, such as neprilysin, an insulin-degrading enzyme, as well as the ApoE determinant, which correlates well with the proposal of AD as a metabolic disorder (Folch et al., 2016).

Preventing the formation of A β extracellular neuritic (senile) plaques is one of the targets for disease-modifying treatment in AD, although there is evidence of correlation with A β biomarkers and cognitive deficits, previous to senile plaques. Inhibitors of A β aggregation have reached clinical trials (Folch et al., 2016). In addition, amyloid- β -directed immunotherapy includes several biological products involving probable sequestration of soluble monomeric A β (solanezumab) or microglia-mediated clearance (bapineuzumab, crenezumab, gantenerumab, aducanumab, and BAN2401) currently in clinical trials. However, active and passive immunization may involve side effects with neuroinflammation, which is considered in itself to explain the pathophysiology of AD, and anti-inflammatory agents for treatment of AD might be considered as well.

Other Therapies

As an age-related pathology, AD is correlated with other chronic-degenerative disorders, and coordinated therapies are needed. A type 3 diabetes hypothesis of AD has been developed, and intranasal insulin is included as a possible treatment for the disease, due to its ability to penetrate the brain-blood barrier (Godyń et al., 2016).

Elevated low-density lipoprotein (LDL) concentration increases the risk of developing AD but the use of statins as a protective treatment is controversial (Dias et al., 2015). Dyslipidemia and obesity are considered causative factors in relation to other pathologies such as metabolic syndrome, which includes atherogenic dyslipidemia and central obesity, hyperglycemia and insulin resistance, hypertension, and a prothrombotic state and a proinflammatory state. Statins may prevent dementia due to their role in cholesterol reduction, although there is evidence that statins given in late life to people with a risk of vascular disease do not prevent cognitive decline or dementia. There is a reduction in cholesterol levels in the diabetic brain, as well as in neuron-derived cholesterol content, which affects receptor signalling (Fukui et al., 2016), so the use of statins in AD treatment should be with consideration to the early management of the disease.

In addition, drugs used in the treatment of type II diabetes mellitus may have a neuroprotective effect in AD. Amylin and glucagon-like peptide-1 receptor agonist are also under study as AD treatments (Godyń et al., 2016). Finally, the mitochondrial cascade hypothesis includes oxidative stress, a state of lost balance with overproduction of oxidative free radicals as well as reactive oxygen species (ROS) and reactive nitrogen species (RNS). This imbalance also includes the participation of immune cells and NO signalling, and preventive treatment with antioxidants and anti-inflammatory drugs is considered. What is certain is that prevention is our best strategy for AD, with efforts to prevent obesity and chronic-degenerative disorders.

Tau-targeted therapy

Tau-targeted strategies that are currently in clinical trials include agents to prevent hyperphosphorylation, as well as those targeting microtubule stability and aggregation (Wischik et al., 2014). Both lithium and valproic acid may act to inhibit tau phosphorylation but randomised controlled trials of these agents were negative (Hampel et al., 2009). More recently, a phase II clinical trial of methylthioninium, a tau aggregation inhibitor, has demonstrated minor benefits in cognition in patients with both mild and moderate AD after 50 weeks therapy and there are plans to proceed to phase III trials (Wischik et al., 2015).

Future Perspective

Studies of potentially disease-modifying therapy up to now have generally been undertaken in patients with clinically detectable, established disease, while mounting evidence suggests that the pathological changes associated with dementia begin to occur several years before the emergence of the clinical syndrome (Silverman et al., 1997). It is possible then that pharmacological therapy may be more beneficial in this pre-clinical stage before the neurodegenerative process has been established. Techniques to provide earlier diagnosis are key to testing this theory in clinical trials, facilitating trials in pre-symptomatic phases.

Early diagnosis

Currently, earlier diagnosis of AD is primarily based on CSF and neuroimaging biomarkers, reflected in new research diagnostic criteria for AD.

Cerebrospinal fluid biomarkers

Reflecting the underlying neuropathology of AD, CSF markers of amyloid and tau are reliable diagnostic tools to detect dementia. CSF A β 42 is decreased in patients with AD, possibly because of deposition of the peptide in plaques (Ewers et al., 2015). However, a decreased ratio of A β 42/A β 40 appears to be a more reliable marker than A β 42 alone. Elevated total tau is a very sensitive marker for detection of AD but is also increased in other dementias, including VaD and frontotemporal dementia, while elevated phosphorylated tau, the major component of NFTs, is more specific than total tau. Combinations of these CSF markers have been used to improve diagnostic potential in early stages of AD, for example, MCI patients with both low A β 42 and high tau levels were shown to have a substantially increased risk of developing AD (Hertze et al., 2010). Despite this, the discriminatory power of CSF biomarkers in the differential diagnosis remains somewhat suboptimal as a lone diagnostic test and current strategies for pre-symptomatic evaluation involve combining results with neuroimaging findings.

Neuroimaging

Traditionally, structural neuroimaging in AD was used to rule out alternative diagnoses when presentations were atypical, eg. brain tumours. However, functional imaging modalities such as 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), are now able to detect loss of neuronal function in asymptomatic individuals by measuring cerebral metabolic rates of glucose metabolism (CMRglc), a surrogate marker for neuronal activity (Mosconi et al., 2010). Patients with early AD demonstrate reduced CMRglc in parietotemporal, frontal and posterior cingulate cortices. These changes have also been shown to precede the onset of symptoms in individuals genetically at risk for AD, as well as in patients with MCI. However, there is some overlap of the hypometabolic regions found in AD with those found in other dementia subtypes, and the additional use of amyloid PET, which can estimate amyloid plaque surface area, improves diagnostic accuracy (Vandenberghe et al., 2013).

Conclusion

Given the rising prevalence of dementia, and the relative inadequacy of current available pharmacological treatment, the need to develop and implement new therapies is pressing. Recent results from trials of agents in AD with potential disease-modifying effects are encouraging but must also be interpreted with caution. Such medicines could potentially delay the onset of dementia and would therefore markedly reduce its prevalence and impact; however, currently we remain a good distance away from clinically available disease-modifying therapy. One would hope, however, that with advancing neuroimaging techniques and biochemical biomarkers, and an enhanced understanding of the underlying

pathological processes involved, that this becomes a realistic goal in the near future. In addition, while focus on the development of new therapies is very welcome, we must also be mindful that dementia is a multifaceted, complex disease, which by its nature directs a need for a multidisciplinary approach to care. Our focus in managing patients with dementia must remain well rounded and holistic, concentrating not just on pharmacological therapy but also on the complex biopsychosocial aspects of caring for this group of patients.

Conflict of interest

None

References

- Birks, J. (2006). Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews*, 1, CD005593. <https://doi.org/10.1002/14651858.CD005593>
- Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica*, 82(4), 239–259. <https://doi.org/10.1007/bf00308809>
- Breijyeh, Z., & Karaman, R. (2020). Comprehensive review on Alzheimer's disease: Causes and treatment. *Molecules (Basel, Switzerland)*, 25(24), 5789. <https://doi.org/10.3390/molecules25245789>
- Cai, H., Wang, Y., McCarthy, D., Wen, H., Borchelt, D. R., Price, D. L., & Wong, P. C. (2001). BACE1 is the major beta-secretase for generation of Abeta peptides by neurons. *Nature Neuroscience*, 4(3), 233–234. <https://doi.org/10.1038/85064>
- Chung, J., Das, A., Mez, J., Sun, X., Chou, Y.-F., Leung, Y. Y., Thiagalingam, S., Zhang, X., Jun, G. R., Kunkle, B. W., Martin, E. R., Pericak-Vance, M. A., Mayeux, R., Haines, J. L., Schellenberg, G. D., Lunetta, K. L., Pinto, J. M., Wang, L.-S., Ober, C., & Farrer, L. A. (2021). Genome-wide association and multi-omics studies identify MGMT as a novel risk gene for Alzheimer disease among women. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 17 Suppl 3, e054483. <https://doi.org/10.1002/alz.054483>
- Crous-Bou, M., Minguillón, C., Gramunt, N., & Molinuevo, J. L. (2017). Alzheimer's disease prevention: from risk factors to early intervention. *Alzheimer's Research & Therapy*, 9(1). <https://doi.org/10.1186/s13195-017-0297-z>
- Dias, H. K. I., Brown, C. L. R., Polidori, M. C., Lip, G. Y. H., & Griffiths, H. R. (2015). LDL-lipids from patients with hypercholesterolaemia and Alzheimer's disease are inflammatory to microvascular endothelial cells: mitigation by statin intervention. *Clinical Science (London, England: 1979)*, 129(12), 1195–1206. <https://doi.org/10.1042/CS20150351>
- Ewers, M., Mattsson, N., Minthon, L., Molinuevo, J. L., Antonell, A., Popp, J., Jessen, F., Herukka, S.-K., Soininen, H., Maetzler, W., Leyhe, T., Bürger, K., Taniguchi, M., Urakami, K., Lista, S., Dubois, B., Blennow, K., & Hampel, H. (2015). CSF biomarkers for the differential diagnosis of Alzheimer's disease: A large-scale international multicenter study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 11(11), 1306–1315. <https://doi.org/10.1016/j.jalz.2014.12.006>

- Fattakhov, N., Normatova, S., Madaminov, S., Tilyakhodzhaeva, G., & Abdulkhakimov, A. (2021). Hirudotherapy as an effective method for treatment of migraine - a disease of unknown etiology. *International Journal of Health & Medical Sciences*, 4(2), 232-237. <https://doi.org/10.31295/ijhms.v4n2.1714>
- Ferreira-Vieira, T. H., Guimaraes, I. M., Silva, F. R., & Ribeiro, F. M. (2016). Alzheimer's disease: Targeting the cholinergic system. *Current Neuropharmacology*, 14(1), 101-115. <https://doi.org/10.2174/1570159x13666150716165726>
- Folch, J., Petrov, D., Ettcheto, M., Abad, S., Sánchez-López, E., García, M. L., Olloquequi, J., Beas-Zarate, C., Auladell, C., & Camins, A. (2016). Current research therapeutic strategies for Alzheimer's disease treatment. *Neural Plasticity*, 2016, 8501693. <https://doi.org/10.1155/2016/8501693>
- Fukui, K., Ferris, H. A., & Kahn, C. R. (2016). Effect of cholesterol reduction on receptor signaling in neurons. *The Journal of Biological Chemistry*, 291(30), 15910. <https://doi.org/10.1074/jbc.a115.664367>
- Godyń, J., Jończyk, J., Panek, D., & Malawska, B. (2016). Therapeutic strategies for Alzheimer's disease in clinical trials. *Pharmacological Reports: PR*, 68(1), 127-138. <https://doi.org/10.1016/j.pharep.2015.07.006>
- Guest, F. L., Rahmoune, H., & Guest, P. C. (2020). Early diagnosis and targeted treatment strategy for improved therapeutic outcomes in Alzheimer's disease. *Advances in Experimental Medicine and Biology*, 1260, 175-191. https://doi.org/10.1007/978-3-030-42667-5_8
- Hampel, H., Ewers, M., Bürger, K., Annas, P., Mörtberg, A., Bogstedt, A., Frölich, L., Schröder, J., Schönknecht, P., Riepe, M. W., Kraft, I., Gasser, T., Leyhe, T., Möller, H.-J., Kurz, A., & Basun, H. (2009). Lithium trial in Alzheimer's disease: A randomized, single-blind, placebo-controlled, multicenter 10-week study. *The Journal of Clinical Psychiatry*, 70(6), 922-931. <https://doi.org/10.4088/jcp.08m04606>
- Hampel, H., Vergallo, A., Afshar, M., Akman-Anderson, L., Arenas, J., Benda, N., Batrla, R., Broich, K., Caraci, F., Cuello, A. C., Emanuele, E., Haberkamp, M., Kiddle, S. J., Lucia, A., Mapstone, M., Verdooner, S. R., Woodcock, J., & Lista, S. (2019). Blood-based systems biology biomarkers for next-generation clinical trials in Alzheimer's disease. *Dialogues in Clinical Neuroscience*, 21(2), 177-191. <https://doi.org/10.31887/dcns.2019.21.2/hhampel>
- Hertze, J., Minthon, L., Zetterberg, H., Vanmechelen, E., Blennow, K., & Hansson, O. (2010). Evaluation of CSF biomarkers as predictors of Alzheimer's disease: a clinical follow-up study of 4.7 years. *Journal of Alzheimer's Disease: JAD*, 21(4), 1119-1128. <https://doi.org/10.3233/jad-2010-100207>
- Jatoi, S., Hafeez, A., Riaz, S. U., Ali, A., Ghauri, M. I., & Zehra, M. (2020). Low vitamin B12 levels: An underestimated cause of minimal cognitive impairment and dementia. *Cureus*, 12(2), e6976. <https://doi.org/10.7759/cureus.6976>
- Kim, S., Swaminathan, S., Shen, L., Risacher, S. L., Nho, K., Foroud, T., Shaw, L. M., Trojanowski, J. Q., Potkin, S. G., Huentelman, M. J., Craig, D. W., DeChairo, B. M., Aisen, P. S., Petersen, R. C., Weiner, M. W., Saykin, A. J., & Alzheimer's Disease Neuroimaging Initiative. (2011). Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort. *Neurology*, 76(1), 69-79. <https://doi.org/10.1212/WNL.0b013e318204a397>
- Kumar, A., Sidhu, J., Goyal, A., & Tsao, J. W. (2021). Alzheimer Disease. In *StatPearls [Internet]*. StatPearls Publishing.

- Larner, A. J. (2010). Cholinesterase inhibitors: beyond Alzheimer's disease. *Expert Review of Neurotherapeutics*, 10(11), 1699–1705. <https://doi.org/10.1586/ern.10.105>
- Lemere, C. A. (2013). Immunotherapy for Alzheimer's disease: hoops and hurdles. *Molecular Neurodegeneration*, 8(1), 36. <https://doi.org/10.1186/1750-1326-8-36>
- Leung, K.-C., Li, V., Ng, Y.-Z., Chan, T.-T., Chang, R. S., & Wong, R. Y. (2017). Systematic review of cholinesterase inhibitors on cognition and behavioral symptoms in patients of Chinese descent with Alzheimer's disease, vascular dementia, or mixed dementia. *Geriatrics (Basel, Switzerland)*, 2(3), 29. <https://doi.org/10.3390/geriatrics2030029>
- McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr, Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 7(3), 263–269. <https://doi.org/10.1016/j.jalz.2011.03.005>
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34(7), 939–944. <https://doi.org/10.1212/wnl.34.7.939>
- Mosconi, L., Berti, V., Glodzik, L., Pupi, A., De Santi, S., & de Leon, M. J. (2010). Pre-clinical detection of Alzheimer's disease using FDG-PET, with or without amyloid imaging. *Journal of Alzheimer's Disease: JAD*, 20(3), 843–854. <https://doi.org/10.3233/JAD-2010-091504>
- P. Bhatt, S. Singh, S. Kumar Sharma, and S. Rabiou, "Development and characterization of fast dissolving buccal strip of frovatriptan succinate monoydrate for buccal delivery," *Int. J. Pharm. Investig.*, vol. 11, no. 1, pp. 69–75, 2021.
- Pankaj, "Anti-cancer cyclodextrin nanocapsules based formulation development for lung chemotherapy," *J. Pharm. Res. Int.*, pp. 54–63, 2021.
- Pankaj, "Cyclodextrin modified block polymer for oral chemotherapy," *J. Pharm. Res. Int.*, pp. 21–29, 2021.
- Panza, F., Frisardi, V., Imbimbo, B. P., Seripa, D., Paris, F., Santamato, A., D'Onofrio, G., Logroscino, G., Pilotto, A., & Solfrizzi, V. (2011). Anti- β -amyloid immunotherapy for Alzheimer's disease: focus on bapineuzumab. *Current Alzheimer Research*, 8(8), 808–817. <https://doi.org/10.2174/156720511798192718>
- Rinne, J. O., Brooks, D. J., Rossor, M. N., Fox, N. C., Bullock, R., Klunk, W. E., Mathis, C. A., Blennow, K., Barakos, J., Okello, A. A., Rodriguez Martinez de Liano, S., Liu, E., Koller, M., Gregg, K. M., Schenk, D., Black, R., & Grundman, M. (2010). 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurology*, 9(4), 363–372. [https://doi.org/10.1016/S1474-4422\(10\)70043-0](https://doi.org/10.1016/S1474-4422(10)70043-0)

- Sharma, K. (2019). Cholinesterase inhibitors as Alzheimer's therapeutics (Review). *Molecular Medicine Reports*, 20(2), 1479–1487. <https://doi.org/10.3892/mmr.2019.10374>
- Silverman, W., Wisniewski, H. M., Bobinski, M., & Wegiel, J. (1997). Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiology of Aging*, 18(4), 377–379; discussion 389–92. [https://doi.org/10.1016/s0197-4580\(97\)00051-1](https://doi.org/10.1016/s0197-4580(97)00051-1)
- Singh, R., & Sadiq, N. M. (2022). Cholinesterase Inhibitors. In *StatPearls [Internet]*. StatPearls Publishing.
- Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). The COVID-19 pandemic. *International Journal of Health Sciences*, 5(2), vi-ix. <https://doi.org/10.53730/ijhs.v5n2.2937>
- Tayeb, H. O., Murray, E. D., Price, B. H., & Tarazi, F. I. (2013). Bapineuzumab and solanezumab for Alzheimer's disease: is the "amyloid cascade hypothesis" still alive? *Expert Opinion on Biological Therapy*, 13(7), 1075–1084. <https://doi.org/10.1517/14712598.2013.789856>
- Vandenbergh, R., Adamczuk, K., & Van Laere, K. (2013). The interest of amyloid PET imaging in the diagnosis of Alzheimer's disease. *Current Opinion in Neurology*, 26(6), 646–655. <https://doi.org/10.1097/WCO.0000000000000036>
- Wang, R., & Reddy, P. H. (2017). Role of glutamate and NMDA receptors in Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, 57(4), 1041–1048. <https://doi.org/10.3233/JAD-160763>
- Whitehouse, P. J., Price, D. L., Struble, R. G., Clark, A. W., Coyle, J. T., & Delon, M. R. (1982). Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science (New York, N.Y.)*, 215(4537), 1237–1239. <https://doi.org/10.1126/science.7058341>
- Wischnik, C. M., Harrington, C. R., & Storey, J. M. D. (2014). Tau-aggregation inhibitor therapy for Alzheimer's disease. *Biochemical Pharmacology*, 88(4), 529–539. <https://doi.org/10.1016/j.bcp.2013.12.008>
- Wischnik, C. M., Staff, R. T., Wischnik, D. J., Bentham, P., Murray, A. D., Storey, J. M. D., Kook, K. A., & Harrington, C. R. (2015). Tau aggregation inhibitor therapy: an exploratory phase 2 study in mild or moderate Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, 44(2), 705–720. <https://doi.org/10.3233/JAD-142874>