DOI: 10.56511/JIPBS.2022.v9.i02.pp01-10

Journal of Innovations in Pharmaceutical and Biological Sciences (JIPBS)
ISSN: 2349-2759
Available online at www.jipbs.com

Review article

Alzheimer's disease and attempts to find an effective treatment (Review)

Yasmin Maher Helmy[1], Ahmed M. A. Akabawy[2], Laila A. Rashed[3], Sahar A. Ali[2]*

[1]*Biological products registration department- Egyptian Drug Authority.*
[2]*Biochemistry and molecular biology department, Faculty of Pharmacy-Helwan University.*
[3]*Biochemistry department, Faculty of Medicine - Cairo University.*

***Corresponding Author : Sahar A. Ali**, Biochemistry and molecular biology department, Faculty of Pharmacy-Helwan University.
Email id: ganah_nour@yahoo.com

Copyright © 2022 **:** Sahar A. Ali *et al.* This is an open access article distributed under the terms of the Creative Commons Attribution Non Commercial-Share Alike 4.0 International License which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Keywords: Alzheimer disease, pathology, Diagnosis, treatment.

Vol. 9 (2): 01-10, Apr-Jun, 2022.

Received on: 27-12-2021
Revised on: 03-03-2022
Accepted on: 07-03-2022
Published on: 10-04-2022

Abstract

The most common neurodegenerative disease is Alzheimer's disease (AD) and according to the World Health Organization, there are about 10 million new cases are recorded every year. It seems likely that damage to the brain starts a decade or more before memory and other cognitive problems appear. For most people with late-onset variety, symptoms of Alzheimer's first appear in their mid-60s. While those with early- onset, signs begin between a person's 30s and mid-60s. Whereas the exact etiology of the disease is unknown, observational research has suggested many hypotheses that describe the pathogenesis of the disease, as considerable advances in understanding the pathology have contributed to an early diagnosis, particularly the exact neuroanatomical setting of plaques. Accordingly, magnetic resonance imaging has been considered as the primarily adjunctive modality for the constant detection of abnormality. In addition, the analysis of cerebrospinal fluid contents has also been of interest for the diagnosis. These resulted in a broad variety of therapies that considerably control the activity and change the course and prognosis of the disease. In the present review, we evaluate the current state of knowledge on Alzheimer with emphasis on the pathology itself, the diagnosis and common therapeutical approaches accurately used.

Introduction

Alzheimer's disease (AD), the common cause of dementia and the most common neurodegenerative disease, in which cases suffering from dementia reached around 50 million people and it is estimated to increase more than threefold (~131 million) by 2050 [1], It becomes the 7th leading cause of global deaths, according to the World Health Organization (WHO) statistics [2]. In Egypt death cases related to dementia increased to become 3.23% of total deaths [3].

Based on symptoms, AD has been classified into three stages: preclinical, mild cognitive impairment (MCI) and dementia; in Preclinical AD stage people have detectable brain changes in biomarkers that considered the earliest signs of Alzheimer's disease, but with no symptoms. The biomarkers include abnormal levels of beta-amyloid as presented on positron emission tomography (PET) scans [1] in MCI due to Alzheimer's Disease; there is a biomarker evidence of Alzheimer's brain changes and slight problems with memory and thinking but this memory problems do not affect patients' everyday activities. The mild changes in thinking abilities occur when the brain can't compensate for the damage and death of nerve cells caused by Alzheimer's disease. The last stage is Alzheimer's dementia which is characterized by apparent memory, thinking or behavioral symptoms that interfere with a person's daily activities, combined with biomarkers deterioration of Alzheimer's-related brain changes. By progression of the disease, individuals commonly experience multiple types of symptoms that change with time. These symptoms reflect the degree of damage to nerve cells in different parts of the brain. This stage subdivided into three phases; the first is mild Alzheimer's Dementia, most people are able to function independently in several tasks like ability to drive, work but may need assistance with some activities to keep them safe, second is moderate Alzheimer's Dementia, it is

the longest stage, individuals may have problems communicating and performing routine tasks such as dressing; become incontinent at times; and start having personality and behavioral changes, including suspiciousness and agitation. The last one; severe Alzheimer's dementia; in this stage of Alzheimer's dementia, individuals need help with activities of daily living and are likely to require around-the-clock care, the effects of Alzheimer's disease on individuals' physical health become especially apparent in this stage. Because of damage to areas of the brain involved in movement, control swallowing that makes difficulty in eating and drinking [2].
There are several risk factors for AD include age, family history, apolipoprotein E ε4 genotype, diabetes, hypertension, obesity, hypercholesterolemia, traumatic brain injury, and low education level [3] [4] [5], Mutations in genes presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) are associated with early-onset autosomal-dominant AD [6].

Genetics of AD

Alzheimer genetics is traditionally subdivided into early onset (EOAD) and late onset (LOAD). EOAD has an onset before age 60–65 years and accounts for 1–5% of all cases. [7] LOAD has an onset after age 60–65 years and is the predominant form of AD. Additionally, family history may be consistent with autosomal dominant, familial, or sporadic AD.

Autosomal dominant

Autosomal dominant AD, which represents <5% of cases, is seen almost exclusively in EOAD families [7]. It is important to note, however, that not all EOAD is inherited in an autosomal dominant pattern. Mutations in known causative genes in such families are identified approximately 40–80% of the time with variability likely due to inconsistency in criteria used to define autosomal dominant AD [7–9].

Familial

Familial clustering represents approximately 15–25% of AD cases. Most often these are families with LOAD (15–25% of all LOAD cases), but familial clustering can be seen in approximately 47% of EOAD cases [7][10]. These familial EOAD cases may represent hidden autosomal dominant AD due to small family size or cases of premature death.

Sporadic

Sporadic AD is characterized by an isolated case in the family or cases separated by more than three degrees of relationship. Sporadic AD represents approximately 75% of all cases. Typically, sporadic cases are LOAD, but approximately 40% of EOAD cases may be classified as sporadic possibly representing hidden familial or autosomal dominant disease, particularly if the family size is small and/or there are case(s) of premature death [7-11].

The use of genetic testing for diagnostic purposes in early-onset autosomal dominant AD has long been debated by clinicians in the dementia field [12]–[14]. Although mutations are rare and testing may reveal variants of unknown significance, genetic testing may result in definitive diagnosis, improve understanding for the family, and allow at-risk relatives to have the option of predictive testing [15].

Pathology

There are several hypotheses discuss Alzheimer's Disease, the first hypothesis is the Cholinergic Hypothesis (Figure 2). which proposed that reduction in synthesis of acetylcholine in neurons is the cause of cognitive decline happened in AD patients [17][18]. The second one is the Mitochondrial Cascade Hypothesis assumed that mitochondrial dysfunction is the initial causative factor of Amyloid beta ($A\beta$) deposition, neurofibrillary tangle (NFT) formation, and synaptic degeneration in AD [19], there are mainly three mitochondrial enzymes that are found to be defective; α-ketoglutarate dehydrogenase complex, cytochrome oxidase, and pyruvate dehydrogenase complex [20] mitochondrial abnormalities associated with enhanced oxidative stress play a major role in the cell degeneration and death, during AD development alteration in mitochondria lead to reduced generation of adenosine triphosphate (ATP) and enhanced production of reactive oxygen species. Mitochondria also lose their Ca^{2+} buffering capacity, which result in deleterious cascade within the cell. Impaired mitochondria also release several pro-apoptotic factors upon induction of apoptosis. Finally, some mitochondrial, pro-apoptotic proteins translocate into the nucleus lead to DNA fragmentation, these mitochondrial alterations contribute to cell degeneration and death (Figure 3) [21]. The third hypothesis is tau hypothesis of Alzheimer's Disease; Tau phosphorylation plays both physiological and pathological roles in the cell. When the phosphorylation state of tau is appropriately coordinated, it plays a role in regulating neurite outgrowth, axonal transport and microtubule stability and dynamics. However, in pathological conditions in which there is an imbalance in the phosphorylation/ dephosphorylation of tau, aberrant tau phosphorylation can cause tau filament formation, disrupt microtubule-based processes owing to decreased microtubule binding and perhaps even increase cell death (Figure 4) [22][23][24][25]. Tau propagation hypothesis was introduced in 2009 [26]. The pathology of tau first appears in certain areas and later spreads to more regions of the brain. Aggregates of fibrillar and misfolded tau may propagate through cells, eventually spreading through the brains of AD patients. Another hypothsis is inflammatory hypothesis; the inflammatory responses of microglia and astrocytes in the central nervous system (CNS) also play important roles in the development of AD [27]. Microglial cells are brain-specific macrophages in the CNS, and they make up 10–15% all brain cells [28]. The infiltration and activation of microglial cells lead to

release of proinflammatory cytokines, including IL-1b, TNF-a, and IFN-g, which stimulate the nearby astrocyte–neuron to produce further amounts of Aβ42 oligomers, thus activating more Aβ42 production [29]. The last one is Amyloid Cascade Hypothesis, the most studied and considered the best accepted, the presence of amyloid plaques is considered to be the main characteristic of AD pathology, the main constituent of senile plaques is Aβ peptide, which is produced from proteolytic process of the amyloid-β protein precursor (AβPP) by β- and γ-secretases enzymes. Amyloid Precursor Protein (APP) has function in cell survival, growth, and motility by releasing soluble ectodomains upon normal cleavage of APP [30].

APP is cleaved either through a non-amyloidogenic pathway (normal condition) or through an amyloidogenic pathway (diseased condition) (Figure 5) [31].

On the other hand, there are several neurotrophic factors called also growth factors play an essential role for the survival of neurons, have the ability to regulate differentiation and to support growth during development of nervous system, alterations in their regulation occurred in the neurodegeneration [32], the family of neurotrophins consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4 (NT4). To raise a survival response, each bind to a specific member of the tyrosine receptor kinase (Trk) family: NGF binds to TrkA, BDNF and NT4 bind to TrkB, and NT3 binds to TrkC., downregulation of BDNF and proBDNF are thought to be an underlying mechanism related to early AD [33]. Patterson found that BDNF play a major role in CNS; helps to protect neurons from damage caused by infection or injury [34].

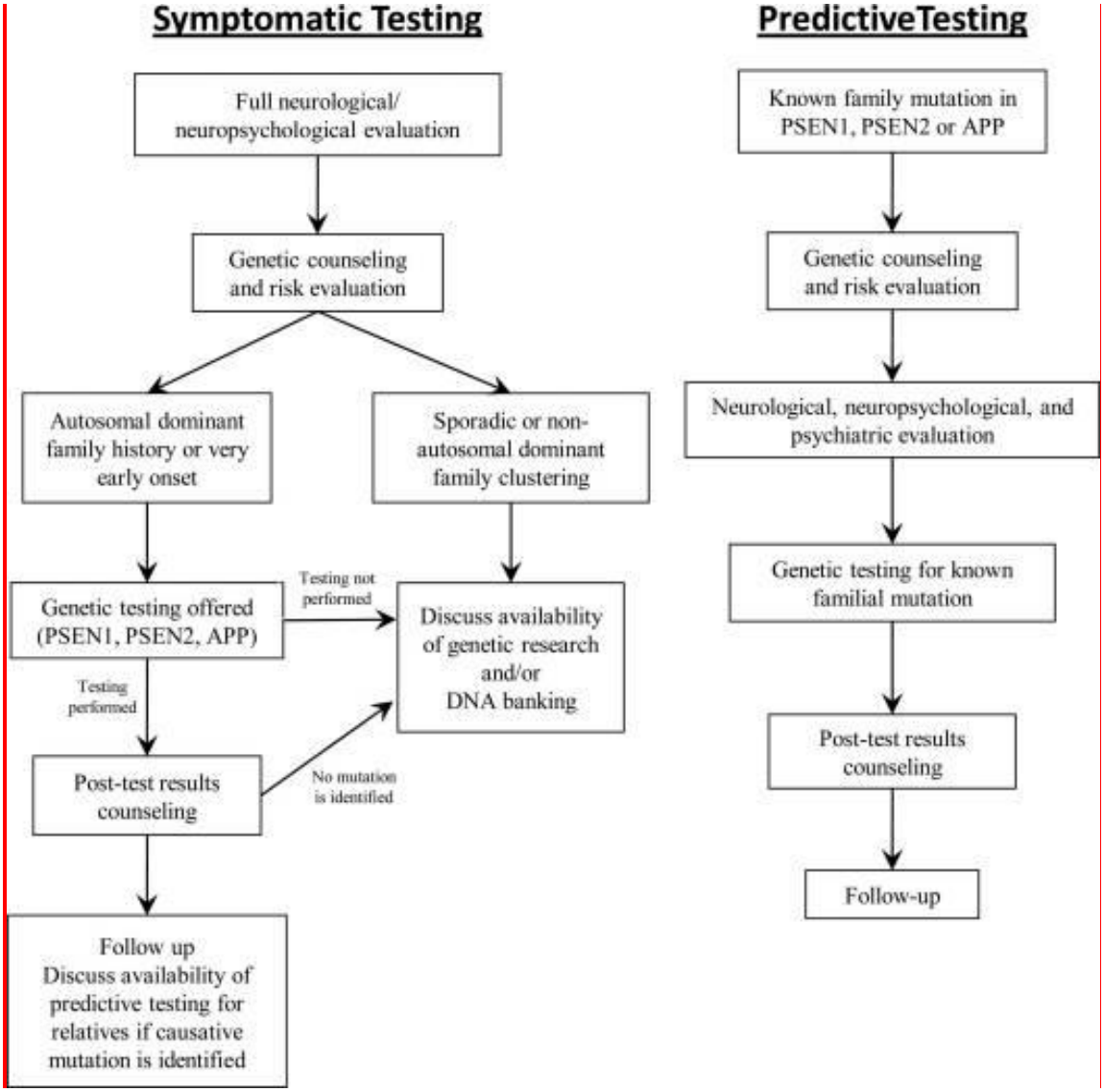


Figure 1. Protocols for genetic testing for AD [19].

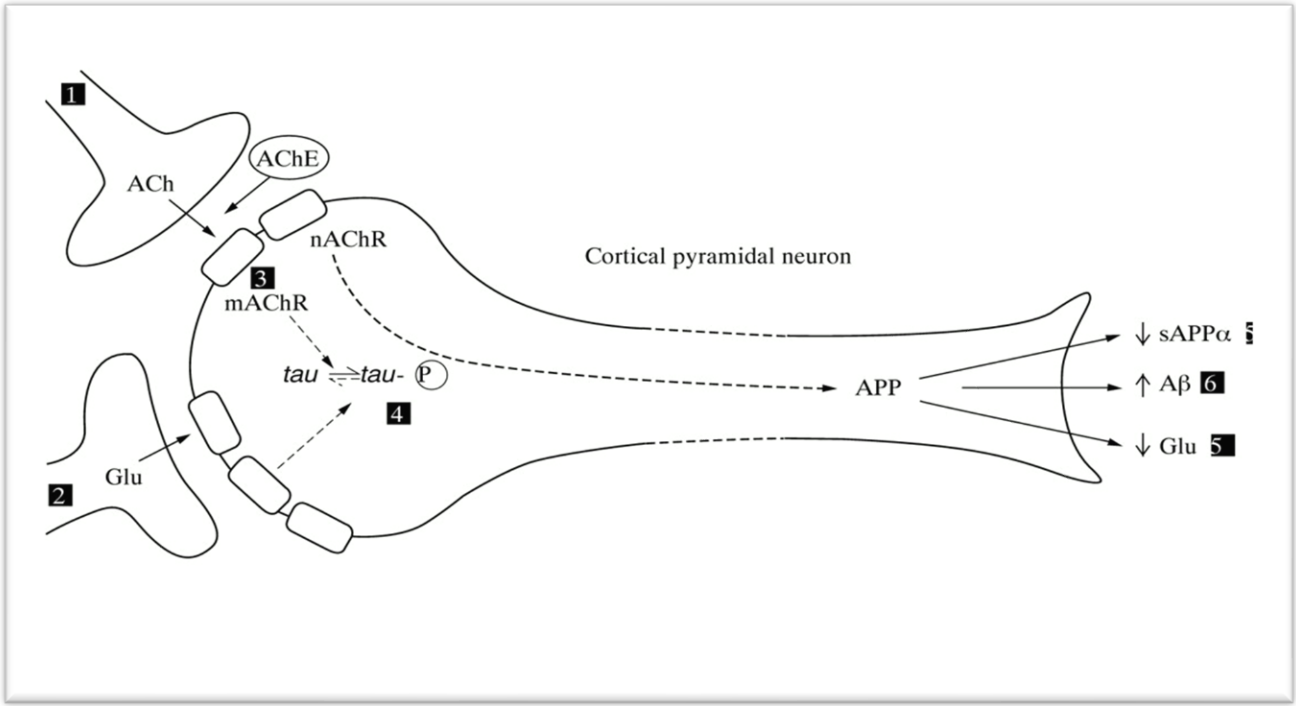


Figure 2. Steps Describing the Cholinergic Hypothesis [20].

Ach: Acetylcholine; AChE: Acetyl cholinesterase; mAChR- nAChR: muscarinic and nicotinic receptors Glu: glutamate; APP: Amyloid precursor protein (1) reduced cortical cholinergic innervation; (2) reduced corticocortical glutamatergic neurotransmission due to neuron or synapse loss; (3) reduced coupling of muscarinic M1 receptors to second messenger system; (4) shift of tau to the hyperphosphoryalted state—precursor of neurofibrillary tangles; (5) reduced secretion of soluble APP; (6) increased production of â-amyloid protein.

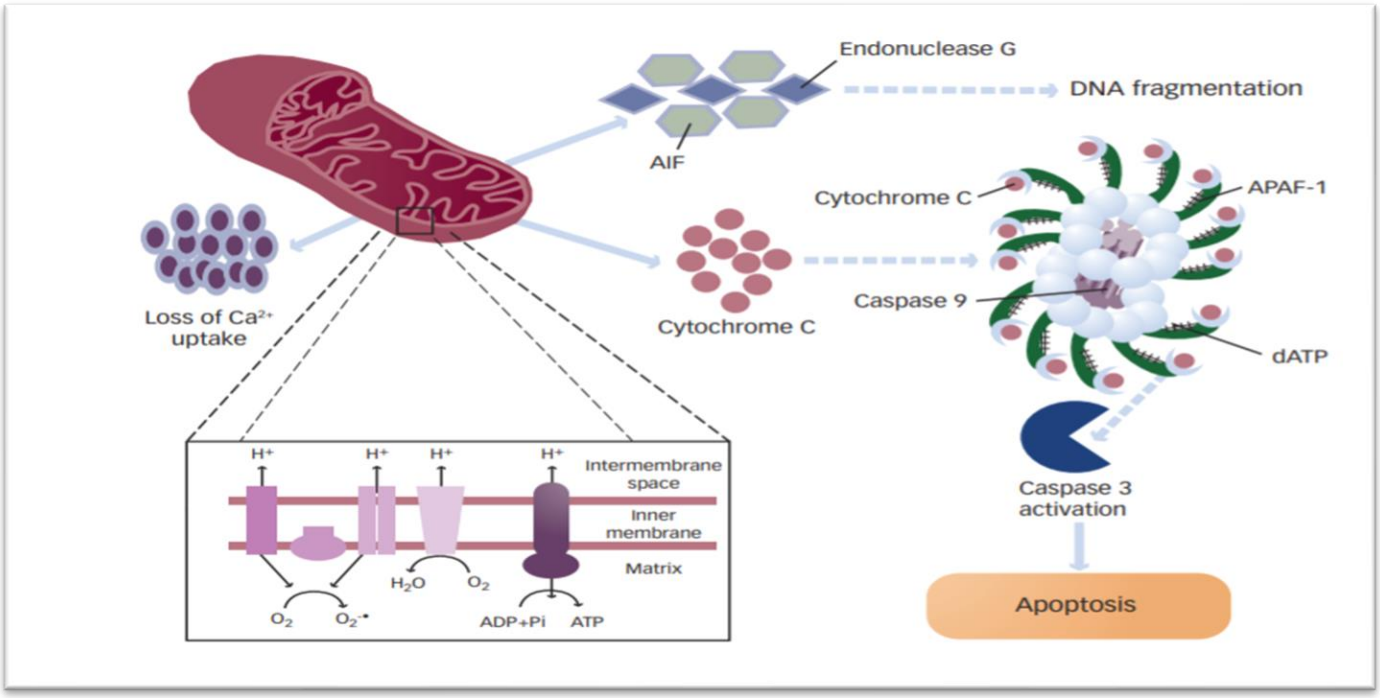


Figure 3. Mitochondrial Cascade Hypothesis adapted from [24].

AIF = apoptosis-inducing factor; APAF-1 = protease-activating factor 1; Ca2+= calcium; dATP = 2′-deoxyadenosine 5′-triphosphate; O2 -•= superoxide.

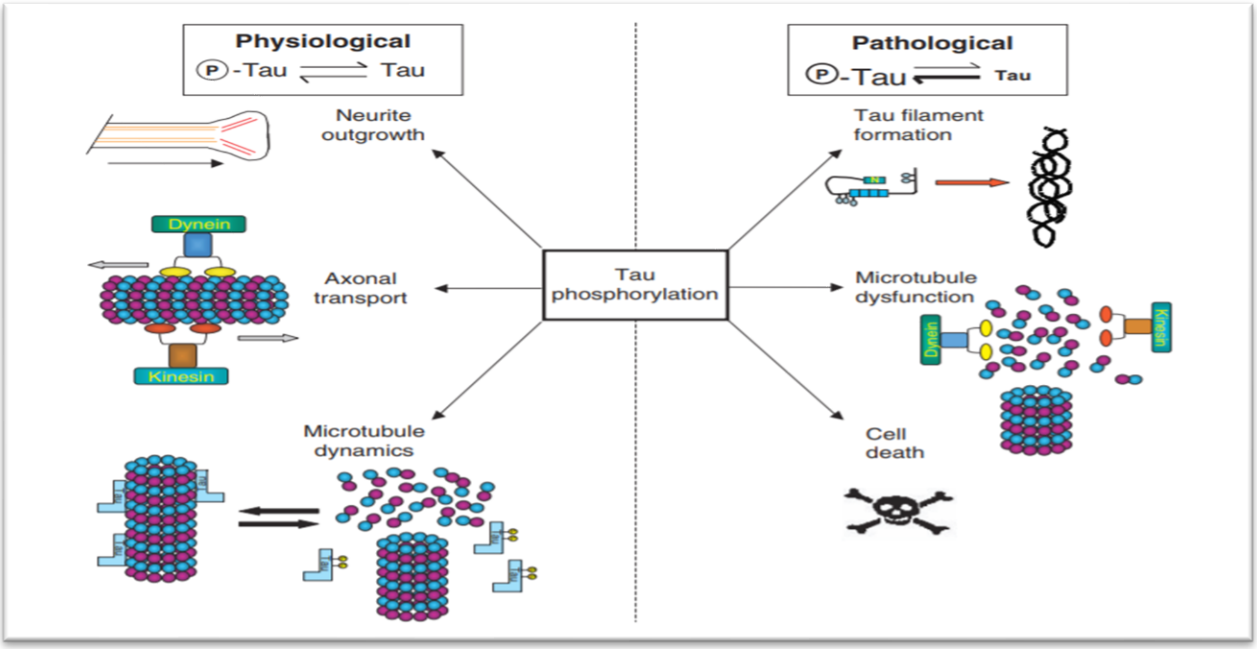


Figure 4. Tau phosphorylation adapted from [28].

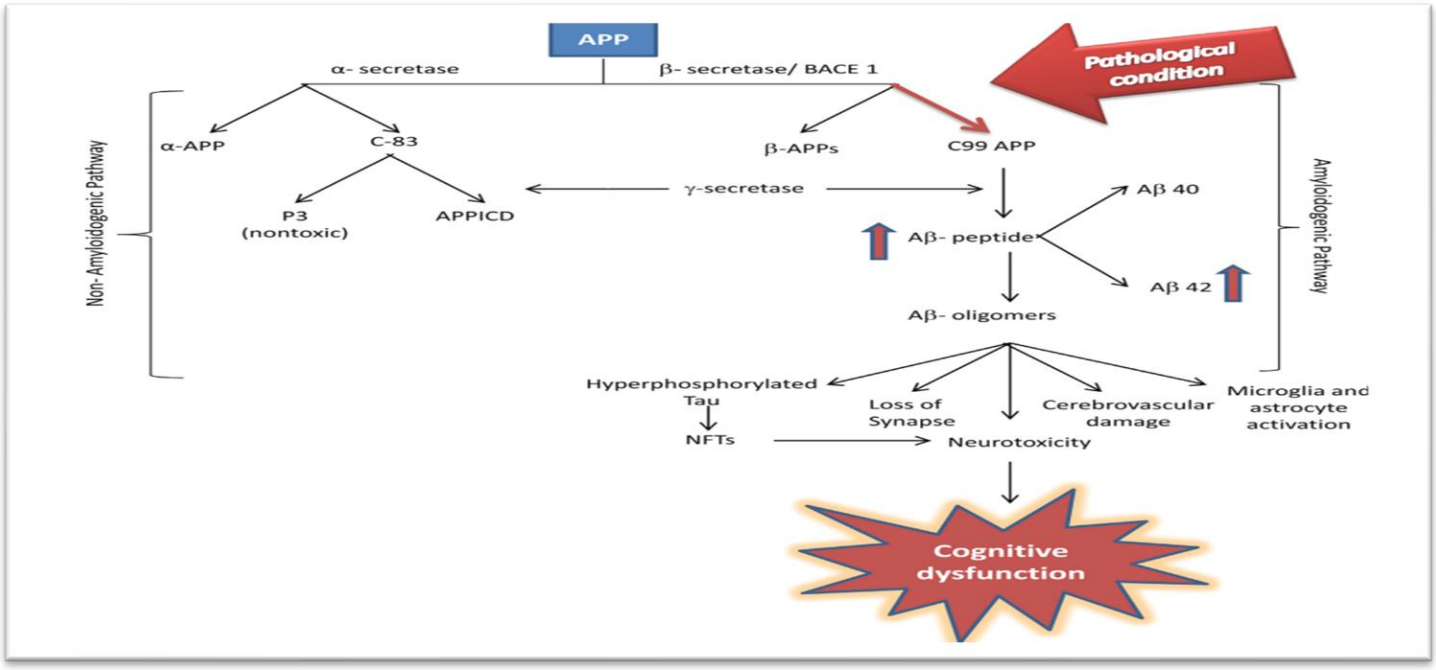


Figure 5. Amyloid Cascade Hypothesis adapted from [34].

Diagnosis

It is important to understand that cognitive and family history, mental status and neurological examinations is very important [35], testing advances have been take place in the last decade

Volumetric Data

Volume changes in specific brain regions can expect the state of disease and progression from mild cognitive impairment (MCI) to AD. These volume assessments may be performed by radiologists or with the help of FDA-approved MRI volumetric data software packages such as Neuroquant and Neuoreader. Especially Hippocampal volume changes are an important AD biomarker [36] but MRI studies are not sufficient in themselves for determining a diagnosis [37].

Diffusion Tensor Imaging (DTI) is an advanced neuroimaging technique that based on the diffusion properties of water molecules to generate magnetic resonance images that correspond to changes in macroscopic axonal organization. It is used to evaluate the structure of vertical cellular micro-circuits, termed "minicolumns". Previous studies have demonstrated that minicolumns are

altered in progressive manner during aging, MCI, and AD [38]. Additionally, pathologic changes of cortex columnar architecture are associated with increased plaque load and cognitive decline [39] With the aid of suitable software, DTI can be measured and used as a marker of neurodegeneration.

Positron emission tomography (PET Scan)

In 2014, the International Working Group (IWG) issued a revised diagnostic criteria IWG-2, which further categorized the biomarkers into diagnostic and progression biomarkers, among which tau and amyloid-β positron emission tomography (tau-PET and Aβ-PET) are used for diagnosis and served as a reliable biomarker [40].

PET scans have ability to assess both proteins amyloid-β (Aβ) and hyperphosphorylated tau and Amyloid accumulation precedes clinically significant cognitive changes and tau accumulation progresses in step with cognitive decline, reflecting the value of PET scans for diagnosis and measurement of disease progression [41].

Cerebrospinal fluid (CSF) and Blood Tests, CSF done through lumbar puncture, surrounds the brain. Changes in the levels of Aβ and tau proteins in the CSF develop decades before the onset of clinically significant AD[42]. The most prominent are CSF Aβ42:Aβ40 ratio and the CSF tau phosphorylated at threonine 181 (P-tau181), CSF Ptau217, can be measured in the peripheral circulation, is predicted to provide a biomarker with very high sensitivity and specificity [43] Additionally, research on plasma Aβ42: Aβ40 ratio and P-tau181 suggests potential value[44] [45].

Treatment

AD is a complex disease; however there is a great increase in number of patients suffering from AD, only few drugs were approved for symptoms treatment aimed at ameliorating cognitive function through two different modes of action: agonism of the cholinergic system and antagonism of the N-methyl-D-aspartate receptor (NMDA-R); agonism of the cholinergic system through increasing levels of acetylcholine by inhibition acetylcholinesterase, the enzyme which catalyzes its degradation, so result in increased level of acetylcholine;There are currently three FDA-approved cholinesterase (ChE) inhibitors: The Acetylcholinesterase inhibitors (AChEIs) donepezil, galantamine, rivastigmine. According to the mechanism of AChEI, overstimulation of central and peripheral muscarinic and nicotinic receptors may contribute to diarrhea, nausea, vomiting, vagotonic effects (bradycardia, heart block, syncope), tremor, insomnia, urinary incontinence, and seizure [46]–[49] Common ADRs induced by AChEIs are principally neuropsychiatric (17%), gastrointestinal (16.2%). The forth approved therapy with different mechanism of action is memantine which is NMDAR antagonist, is a symptomatological and neuroprotective treatment for AD [50]. NMDAR activation has been implicated in AD related to synaptic dysfunction [51]. Synaptic dysfunction may be due to perturbed synaptic Ca^{2+} handling in response to over activation of glutamate receptors [52], excessive stimulation of glutamatergic signaling results in excitotoxicity [53] Clinical trials of memantine for use in moderate to severe AD have shown positive effects on patient cognition and function, as well as associated societal benefits [54]. reported side-effects included diarrhea, dizziness, headache, hallucinations, agitation, insomnia and urinary incontinence [55]. Since December 2014, the FDA approved a once-daily fixed-dose combination (FDC) of memantine ER and donepezil (Namzaric™, Allergan, Inc., Irvine, CA, USA) for the treatment of moderate-to-severe AD in patients already stabilized on memantine and donepezil [56].

Also the core symptoms of different dementia subtypes are the behavioral and psychological symptoms of dementia (BPSD) and its neuropsychiatric symptoms (NPS) [57]. BPSD symptoms may occur at any stage in the case of dementia due to Alzheimer's disease (AD), BPSD treatment consists of non-pharmacological as well as pharmacological interventions, with non-pharmacological interactions being suggested as first-line treatment; Non-pharmacological approaches comprise various types of intervention: sensory stimulation (acupressure, aromatherapy, massage, touch therapy, light therapy, garden activities), cognitive and emotion-oriented approaches (cognitive stimulation, reminiscence therapy, validation therapy, and simulated presence therapy), behavior management techniques, multicomponent interventions, and other therapies (education of patients and caregivers, exercise, and animal-assisted therapy involving real or robotic animals) [58]. Agitation, psychotic features, apathy, depression, and anxiety may not respond to acetylcholinesterase inhibitors or memantine in AD cases; therefore, antipsychotics, antidepressants, sedative drugs or anxiolytics, and antiepileptic drugs are typically prescribed [59].

Many trials to target different pathways involved in AD were performed ; many of them failed to treat AD for example; Drugs targeting β-secretase (BACE 1) enzyme which is involved in amyloidogenic cleavage of APP [60] .One BACE 1 inhibitor; verubecestat was investigated in patients with mild to moderate AD, but it was terminated due to a lack of positive effect in an interim analysis of the trial[61] this lack of efficacy suggest that use of a BACE 1 inhibitor in patients who have accumulated Aβ deposition to have dementia is with no clinical outcome.

Several Aβ mAb passive immunization studies have not been successful; placebo-controlled phase III trials with solanezumab and bapineuzumab, both of which demonstrated promise in early studies, failed to show clinical benefit as add-on therapy to standard-of-care agents and resulted in termination of their development programs [62], [63].

Also the receptor for advanced glycation end-products (RAGE); is expressed by various brain cells and binds and transports Aβ from blood to brain, however it is play

multiple roles in the pathogenesis of AD and has emerged as a potential target for the treatment of the disease , a phase III clinical trial for the RAGE inhibitor, azeliragon; study to evaluate the efficacy and safety of azeliragon for patients with mild AD, were discontinued because those trials failed to achieve their primary endpoints in June 2018 [64] [65].

The most popular and accepted explanations for the multiple failures of clinical trials of DMT agents for AD include the too late starting of therapies in disease development, the inappropriate drug doses, the wrong main target of the treatment, and mainly an inadequate understanding of the pathophysiology of AD [66].

Another strategy under development is treatment with Erythropoietin (EPO) it was found that EPO has a role through its expression in the central nervous system [67] in the development of the brain and vascular system, EPO was found to enhance and stimulate neurogenesis [68]. Recombinant human EPO (rhEPO) is indicated in the treatment of anemic patients and diseases associated with low concentrations of EPO in plasma [69] It was found that these patients show significant cognitive improvements, that result in researches directed toward EPO and its usage for the treatment of neurodegenerative diseases [70].

EPO reduces hippocampal Aβ accumulation in an intracerebroventricular streptozotocin-induced AD rat model [71] and intranasal administration of EPO also decreases Aβ deposits in an APP/PS1 transgenic AD mouse model [72] .

Therapies directed at neuronal regeneration are relative newcomers to the AD pipeline and currently focused on the use of human mesenchymal stem cells (hMSC) derived from adipose tissue, placental tissue or bone marrow [73]. A study done by Shin *et al* [74] demonstrated that human MSCs can enhance autophagy in Aβ-treated neuronal cells and mice, thus promoting Aβ clearance and increasing neuronal survival against Aβ toxicity, a new stem cell product is currently assessed in a phase 2 study (NCT03117738), human mesenchymal stem cells (hMSCs) treatment is assessed in a phase 1 study (NCT02600130) [75].

Exosomes are microvesicles of 30–100 nm in diameter, and small lipid vesicles secreted by all cell types [76]. They can cross the blood–brain barrier (BBB), especially under pathological conditions such as AD and other neurodegenerative diseases [77] and serve as vesicular carriers for intercellular communication [78]. An evidence showed that infusion of neuronal exosomes into the brain of APP transgenic mice decreased Aβ generation and deposition [11] Administration of MSC-exosomes can enhance neurogenesis in different mice models of disease including AD and augment neuroprotection against inflammation and oxidative stress [79].

Also, Tau aggregation inhibitors (TAIs) have the potential to prevent or reverse tau aggregation and consequently reduce tau pathology and associated behavioral deficits in patients with AD [80] [81].

Another strategy in treatment is targeting the amyloid cascade through the use of humanized or fully human monoclonal antibodies (mAbs) that bind and mount an immunologic response against the Aβ peptide, leading to increased amyloid clearance [82].

Based on promising results in phase I/II trials [83][84][85] three Aβ mAbs (aducanumab, gantenerumab, and crenezumab) are being investigated in placebo-controlled phase III trials as add-on therapy in patients with early or mild AD.

On June 7, 2021; FDA approved aducanumab fully human IgG1 monoclonal antibody against a conformational epitope found on Aβ. binds aggregated forms of Aβ, not monomer. The product name is Aduhelm; the first new treatment approved for Alzheimer's since 2003 and is the first therapy that targets the fundamental pathophysiology of the disease, it was found that Aduhelm includes a warning for amyloid-related imaging abnormalities (ARIA), which most commonly presents as temporary swelling in areas of the brain that usually resolves over time and does not cause symptoms (FDA), as the drug breaks up amyloid plaques, the fragments move into the bloodstream. Also, some plaque is removed from the walls of the blood vessels in the brain, and can lead to some leakiness of fluid. If this occurs, it usually happens early in the treatment and without symptoms. This process is reversible and can be monitored with MRI until it resolve [86].

Conclusion

Combined therapies is the new strategy in the treatment of several diseases such as cancer and human immunodeficiency virus-1 (HIV) and have succeeded in several diseases from this new direction. Due to complexity of the AD and upon the failure of different strategies with mono therapies; it is expected that targeting more than one pathway at the same time with the appropriate dose will result in successful treatment which not only relieve the symptoms that patients suffer from but also lead to cessation of the progression of AD and improve patient's life.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this review article.

Authors Contribution

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

References

1. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: Pathogenesis, diagnostics, and therapeutics. International Journal of Nanomedicine. 2019; 14:5541-5554. doi:10.2147/IJN.S200490.

2. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
3. https://www.worldlifeexpectancy.com/egypt-alzheimers-dementia.
4. Sperling RA, Donohue MC, Raman R, *et al*. Association of Factors with Elevated Amyloid Burden in Clinically Normal Older Individuals. JAMA Neurology. 2020; 77(6):735-745. doi:10.1001/jamaneurol.2020.0387.
5. 2021 Alzheimer's disease facts and figures. Alzheimer's and Dementia 2021; 17(3):327-406. doi:10.1002/alz.12328.
6. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's Disease 368; 2006. http://www.alzgene.org
7. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nature Reviews Neurology. 2011; 7(3):137-152. doi:10.1038/nrneurol.2011.2
8. Gaugler J, James B, Johnson T, Scholz K, Weuve J. 2016 Alzheimer's disease facts and figures. Alzheimer's and Dementia. 2016; 12(4):459-509. doi:10.1016/j.jalz.2016.03.001
9. Ringman JM, Goate A, Masters CL, *et al*. Genetic Heterogeneity in Alzheimer Disease and Implications for Treatment Strategies. Current Neurology and Neuroscience Reports 2014; 14(11). doi:10.1007/s11910-014-0499-8
10. Bertram L, Tanzi RE. The genetic epidemiology of neurodegenerative disease. Journal of Clinical Investigation. 2005; 115(6):1449-1457. doi:10.1172/JCI24761
11. Tedde A, Forleo P, Nacmias B, *et al*. A presenilin-1 mutation (Leu392Pro) in a familial AD kindred with psychiatric symptoms at onset. Neurology 2000; 55(10):1590-1591. doi:10.1212/WNL.55.10.1590
12. Janssen JC, Beck JA, Campbell TA, *et al*. Early Onset Familial Alzheimer's Disease Mutation Frequency in 31 Families. 2003. http://molgen-www.
13. Brickell KL, Steinbart EJ, Rumbaugh M, *et al*. Early-Ons*et al*zheimer Disease in Families With Late-Ons*et al*zheimer Disease A Potential Important Subtype of Familial Alzheimer Disease. 2006; 63:1307-1311.
14. Yuyama K, Sun H, Usuki S, *et al*. A potential function for neuronal exosomes: Sequestering intracerebral amyloid-β peptide. FEBS Letters. 2015; 589(1):84-88. doi:10.1016/j.febslet.2014.11.027
15. Letters to the Editor Genetic Testing Should Not Be Advocated as a Diagnostic Tool in Familial Forms of Dementia 2000; 67:1033–1035
16. Finckh U, Alberici; A, Antoniazzi; M, *et al*. Variable Expression of Familial Alzheimer Disease Associated with Presenilin 2 Mutation M239I.2000; 54:2006–2008.
17. Van der Cammen TJM, Croes EA, Dermaut B, *et al*. Ethics, public policy, and medical economics Genetic Testing Has No Place as a Routine Diagnostic Test in Sporadic and Familial Cases of Alzheimer's Disease. 2004; 52:2110–2113.
18. Williamson J, Larusse S. Genetics and Genetic Counseling: Recommendations for Alzheimer's Disease, Frontotemporal Dementia, and Creutzfeldt-Jakob Disease. Current Neurology and Neuroscience Reports. 2004; 4:351-357.
19. Goldman JS, Hahn SE, Catania JW, *et al*. Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genetics in Medicine*. 2011; 13(6):597-605. doi:10.1097/GIM.0b013e31821d69b8
20. Francis PT, Palmer AM, Snape M, Wilcock GK. The Cholinergic Hypothesis of Alzheimer's Disease: A Review of Progress. 1999; 66.
21. Terry A v., Buccafusco JJ. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: Recent challenges and their implications for novel drug development. Journal of Pharmacology and Experimental Therapeutics. 2003; 306(3):821-827. doi:10.1124/jpet.102.041616
22. Terry A v., Buccafusco JJ. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: Recent challenges and their implications for novel drug development. *Journal* of Pharmacology and Experimental Therapeutics. 2003;306(3):821-827. doi:10.1124/jpet.102.041616
23. Hirai K, Aliev G, Nunomura A, *et al*. Mitochondrial Abnormalities in Alzheimer's Disease. J Neurosci 2001; 21(9):3017–3023.
24. Moreira PI. Mitochondrial dysfunction and oxidative stress in Alzheimer's disease. European Neurological Review. 2010; 5(1):17-21. doi:10.17925/ENR.2010.05.01.17
25. Biernat J, Wu YZ, Timm T, *et al*. Protein kinase MARK/PAR-1 is required for neurite outgrowth and establishment of neuronal polarity. Molecular Biology of the Cell. 2002; 13(11):4013-4028. doi:10.1091/mbc.02-03-0046
26. Fath T, Eidenmü J, Brandt R. Tau-Mediated Cytotoxicity in a Pseudohyperphosphorylation Model of Alzheimer's Disease. J Neurosci. 2002; 22(22):9733–9741
27. Tatebayashi Y, Haque N, Tung YC, Iqbal K, Grundke-Iqbal I. Role of tau phosphorylation by glycogen synthase kinase-3β in the regulation of organelle transport. Journal of Cell Science. 2004; 117(9):1653-1663. doi:10.1242/jcs.01018
28. Johnson GVW, Stoothoff WH. Tau phosphorylation in neuronal cell function and dysfunction. Journal of Cell Science. 2004; 117(24):5721-5729. doi:10.1242/jcs.01558
29. Frost B, Jacks RL, Diamond MI. Propagation of Tau misfolding from the outside to the inside of a cell. Journal of Biological Chemistry. 2009; 284(19):12845-12852. doi:10.1074/jbc.M808759200
30. Bagyinszky E, Giau V van, Shim K, Suk K, An SSA, Kim SY. Role of inflammatory molecules in the Alzheimer's disease progression and diagnosis. Journal of the Neurological Sciences. 2017; 376:242-254. doi:10.1016/j.jns.2017.03.031
31. Santos LE, Beckman D, Ferreira ST. Microglial dysfunction connects depression and Alzheimer's disease. Brain, Behavior, and Immunity. 2016; 55:151-165. doi:10.1016/j.bbi.2015.11.011
32. Dal Prà I, Chiarini A, Gui L, *et al*. Do astrocytes collaborate with neurons in spreading the "infectious" Aβ and Tau drivers of Alzheimer's disease? Neuroscientist. 2015; 21(1):9-29. doi:10.1177/1073858414529828
33. Oh ES, Savonenko A v., King JF, *et al*. Amyloid precursor protein increases cortical neuron size in transgenic mice. Neurobiology of Aging. 2009; 30(8):1238-1244. doi:10.1016/j.neurobiolaging.2007.12.024
34. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: An update. Pharmacological Reports. 2015; 67(2):195-203. doi:10.1016/j.pharep.2014.09.004
35. Bothwell M. Recent advances in understanding neurotrophin signaling [version 1; referees: 2 approved]. F1000Research. 2016; 5. doi:10.12688/F1000RESEARCH.8434.1
36. Peng S, Wuu J, Mufson EJ, Fahnestock M. Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. Journal of Neurochemistry. 2005; 93(6):1412-1421. doi:10.1111/j.1471-4159.2005.03135.x
37. Patterson SL. Immune dysregulation and cognitive vulnerability in the aging brain: Interactions of microglia, IL-1β, BDNF and synaptic plasticity. Neuropharmacology. 2015; 96(PA):11-18. doi:10.1016/j.neuropharm.2014.12.020

38. Mendez MF. The accurate diagnosis of early-onset dementia. Int J Psychiatry Med 2006; 36.
39. Tanpitukpongse TP, Mazurowski MA, Ikhena J, Petrella JR. Predictive utility of marketed volumetric software tools in subjects at risk for Alzheimer disease: Do regions outside the hippocampus matter? American Journal of Neuroradiology. 2017; 38(3):546-552. doi:10.3174/ajnr.A5061.
40. Lombardi G, Crescioli G, Cavedo E, *et al.* Structural magnetic resonance imaging for the early diagnosis of dementia due to Alzheimer's disease in people with mild cognitive impairment. Cochrane Database of Systematic Reviews. 2020; 2020(3). doi:10.1002/14651858.CD009628.pub2
41. Chance SA, Clover L, Cousijn H, Currah L, Pettingill R, Esiri MM. Microanatomical correlates of cognitive ability and decline: Normal ageing, MCI, and Alzheimer's disease. Cerebral Cortex. 2011; 21(8):1870-1878. doi:10.1093/cercor/bhq264.
42. Van Veluw SJ, Sawyer EK, Clover L, *et al.* Prefrontal cortex cytoarchitecture in normal aging and Alzheimer's disease: A relationship with IQ. Brain Structure and Function. 2012; 217(4):797-808. doi:10.1007/s00429-012-0381-x
43. Dubois B, Feldman HH, Jacova C, *et al.* Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. The Lancet Neurology. 2014; 13(6):614-629. doi:10.1016/S1474-4422(14)70090-0
44. Hanseeuw BJ, Betensky RA, Jacobs HIL, *et al.* Association of Amyloid and Tau with Cognition in Preclinical Alzheimer Disease: A Longitudinal Study. JAMA Neurology. 2019; 76(8):915-924. doi:10.1001/jamaneurol.2019.1424
45. Jansen WJ, Ossenkoppele R, Knol DL, *et al.* Prevalence of cerebral amyloid pathology in persons without dementia: A meta-analysis. JAMA - Journal of the American Medical Association. 2015; 313(19):1924-1938. doi:10.1001/jama.2015.4668
46. Palmqvist S, Janelidze S, Quiroz YT, *et al.* Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA - Journal of the American Medical Association. 2020; 324(8):772-781. doi:10.1001/jama.2020.12134
47. Fandos N, Pérez-Grijalba V, Pesini P, *et al.* Plasma amyloid β 42/40 ratios as biomarkers for amyloid β cerebral deposition in cognitively normal individuals. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring. 2017; 8:179-187. doi:10.1016/j.dadm.2017.07.004
48. Janelidze S, Mattsson N, Palmqvist S, *et al.* Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nature Medicine. 2020; 26(3):379-386. doi:10.1038/s41591-020-0755-1
49. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Effi Cacy and Safety of Donepezil, Galantamine, and Rivastigmine for the Treatment of Alzheimer's Disease: A Systematic Review and Meta-Analysis. 2008; 3.
50. Kroger E, van Marum R, Souverein P, Carmichael PH, Egberts T. Treatment with rivastigmine or galantamine and risk of urinary incontinence: Results from a Dutch database study. Pharmacoepidemiology and Drug Safety. 2015; 24(3):276-285. doi:10.1002/pds.3741
51. Olovi MB, Krsti DZ, Lazarevi-Pati TD, Bondi AM, Vasi VM. Send Orders of Reprints at Reprints@ benthamscience.Net Acetylcholinesterase Inhibitors: Pharmacology and Toxicology. 2013; 11, 315-335
52. Lockhart IA, Mitchell SA, Kelly S. Safety and tolerability of donepezil, rivastigmine and galantamine for patients with alzheimer's disease: Systematic review of the "real-world" evidence. Dementia and Geriatric Cognitive Disorders. 2009; 28(5):389-403. doi:10.1159/000255578
53. Parsons CG, Danysz W, Dekundy A, Pulte I. Memantine and cholinesterase inhibitors: Complementary mechanisms in the treatment of Alzheimer's disease. Neurotoxicity Research. 2013; 24(3):358-369. doi:10.1007/s12640-013-9398-z
54. Stroebel D, Carvalho S, Grand T, Zhu S, Paoletti P. Controlling NMDA receptor subunit composition using ectopic retention signals. Journal of Neuroscience. 2014; 34(50):16630-16636. doi:10.1523/JNEUROSCI.2736-14.2014
55. Mota SI, Ferreira IL, Rego AC. Dysfunctional synapse in Alzheimer's disease - A focus on NMDA receptors. Neuropharmacology. 2014; 76(PART A):16-26. doi:10.1016/j.neuropharm.2013.08.013
56. Rothman SM, Olney JW. NEUROLOGICAL PROGRESS Glutamate and the Pathophysiology of Hypoxic-Ischemic Brain Damage. 1986; 19:105-111
57. Wilkinson D. A review of the effects of memantine on clinical progression in Alzheimer's disease. International Journal of Geriatric Psychiatry. 2012; 27(8):769-776. doi:10.1002/gps.2788
58. Pariente A, Joseph-Reinette Sanctussy D, Miremont-Salamé G, Moore N, Haramburuoise, Fourrier-Réglat A. Factors Associated with Serious Adverse Reactions to Cholinesterase Inhibitors A Study of Spontaneous Reporting. 2010; 24 (1): 55-63
59. Namzaric (memantine hydrochloride extended-release/donepezil hydrochloride) Capsules. Accessed November 3, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206439Orig1s000TOC.cfm
60. Zhao QF, Tan L, Wang HF, *et al.* Erratum: Corrigendum to: "The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis" (J. Affect. Disord. (2016) 190 (264–271)). Journal of Affective Disorders. 2016; 206:8. doi:10.1016/j.jad.2016.04.054
61. Abraha I, Rimland JM, Trotta FM, *et al.* Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. BMJ Open. 2017; 7:12759. doi:10.1136/bmjopen-2016
62. Magierski R, Sobow T, Schwertner E, Religa D. Pharmacotherapy of Behavioral and Psychological Symptoms of Dementia: State of the Art and Future Progress. Frontiers in Pharmacology. 2020; 11. doi:10.3389/fphar.2020.01168
63. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine. 2016; 8(6):595-608. doi:10.15252/emmm.201606210
64. Egan MF, Kost J, Voss T, *et al.* Randomized Trial of Verubecestat for Prodromal Alzheimer's Disease. *New* England Journal of Medicine. 2019; 380(15):1408-1420. doi:10.1056/nejmoa1812840
65. Salloway S, Sperling R, Fox NC, *et al.* Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease. New England Journal of Medicine. 2014; 370(4):322-333. doi:10.1056/nejmoa1304839
66. Doody RS, Thomas RG, Farlow M, *et al.* Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease. New England Journal of Medicine. 2014; 370(4):311-321. doi:10.1056/nejmoa1312889
67. Huang LK, Chao SP, Hu CJ. Clinical trials of new drugs for Alzheimer disease. Journal of Biomedical Science. 2020; 27(1). doi:10.1186/s12929-019-0609-7
68. Azeliragon | ALZFORUM. Accessed November 3, 2021. https://www.alzforum.org/therapeutics/azeliragon

69. Gauthier S, Albert M, Fox N, *et al.* Why has therapy development for dementia failed in the last two decades? *Alzheimer's and Dementia*. 2016; 12(1):60-64. doi:10.1016/j.jalz.2015.12.003
70. Marti HH, Wenger RH, Rivas LA, *et al.* Erythropoietin Gene Expression in Human, Monkey and Murine Brain. 1996; Vol 8.
71. Lombardero M, Kovacs K, Scheithauer BW. Erythropoietin: A hormone with multiple functions. Pathobiology. 2011; 78(1):41-56. doi:10.1159/000322975
72. Ng T, Marx G, Littlewood T. Recombinant Erythropoietin in Clinical Practice. 2003; 79.
73. Rey F, Balsari A, Giallongo T, *et al.* Erythropoietin as a Neuroprotective Molecule: An Overview of Its Therapeutic Potential in Neurodegenerative Diseases. ASN Neuro. 2019; 11. doi:10.1177/1759091419871420
74. Samy DM, Ismail CA, Nassra RA, Zeitoun TM, Nomair AM. Downstream modulation of extrinsic apoptotic pathway in streptozotocin-induced Alzheimer's dementia in rats: Erythropoietin versus curcumin. European Journal of Pharmacology. 2016; 770:52-60. doi:10.1016/j.ejphar.2015.11.046
75. Cruz YR, Strehaiano M, Rodríguez Obaya T, Rodríguez JCG, Maurice T. An intranasal formulation of erythropoietin (Neuro-EPO) prevents memory deficits and amyloid toxicity in the APPSwe transgenic mouse model of Alzheimer's disease. Journal of Alzheimer's Disease 2016; 55(1):231-248. doi:10.3233/JAD-160500
76. Bali P, Lahiri DK, Banik A, *et al.* Potential for Stem Cells Therapy in Alzheimer's Disease: Do Neurotrophic Factors Play Critical Role? HHS Public Access Author Manuscript. 2017; 14.
77. Shin JY, Park HJ, Kim HN, *et al.* Mesenchymal stem cells enhance autophagy and increase β-amyloid clearance in Alzheimer disease models. Autophagy. 2014; 10(1):32-44. doi:10.4161/auto.26508
78. Yiannopoulou KG, Papageorgiou SG. Current and Future Treatments in Alzheimer Disease: An Update. Journal of Central Nervous System Disease. 2020; 12: 117957352090739. doi:10.1177/1179573520907397
79. Sluijter JPG, Verhage V, Deddens J, van den Akker F, Doevendans PAF. Microvesicles and Exosomes for Intracardiac Communication Downloaded From. 2014; Vol 26. http://cardiovascres.oxfordjournals.org/
80. Chen CC, Liu L, Ma F, *et al.* Elucidation of Exosome Migration Across the Blood–Brain Barrier Model In Vitro. Cellular and Molecular Bioengineering. 2016; 9(4):509-529. doi:10.1007/s12195-016-0458-3
81. Schneider A, Simons M. Exosomes: Vesicular carriers for intercellular communication in neurodegenerative disorders. Cell and Tissue Research. 2013; 352(1):33-47. doi:10.1007/s00441-012-1428-2
82. Reza-Zaldivar EE, Hernández-Sapiéns MA, Gutiérrez-Mercado YK, *et al.* Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease. Neural Regeneration Research. 2019; 14(9):1626-1634. doi:10.4103/1673-5374.255978
83. Wischik CM, Harrington CR, Storey JMD. Tau-aggregation inhibitor therapy for Alzheimer's disease. Biochemical Pharmacology. 2014; 88(4):529-539. doi:10.1016/j.bcp.2013.12.008
84. Panza F, Solfrizzi V, Seripa D, *et al.* Tau-Centric Targets and Drugs in Clinical Development for the Treatment of Alzheimer's Disease. BioMed Research International. 2016; 2016. Article ID 3245935, doi:10.1155/2016/3245935
85. Schenk D, Basi GS, Pangalos MN. Treatment strategies targeting amyloid β-protein. Cold Spring Harbor Perspectives in Medicine. 2012; 2(9). doi:10.1101/cshperspect.a006387
86. Sevigny J, Chiao P, Bussière T, *et al.* The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016; 537(7618):50-56. doi:10.1038/nature19323
87. Novakovic D, Feligioni M, Scaccianoce S, *et al.* Profile of gantenerumab and its potential in the treatment of Alzheimer's disease. Drug Design, Development and Therapy. 2013; 7:1359-1364. doi:10.2147/DDDT.S53401
88. Mackey H, Cho W, Ward M, *et al.* P2-006: Exploratory Analyses of Cognitive Effects of Crenezumab in a Mild Alzheimer's Disease Subpopulation of a Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 2 Study (ABBY). Alzheimer's & Dementia. 2016; 12(7S_Part_12). doi:10.1016/j.jalz.2016.06.1210.
89. After the FDA's approval, what to know about the new Alzheimer's drug Available from https://www.brown.edu/news/2021-06-11/aducanumab.