Review

Alzheimer's Disease and Related Dementia Drug Trials, Failures and Progress: Data Update 2024

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Review

Alzheimer's Disease and Related Dementia Drug Trials, Failures and Progress: Data Update 2024

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Abstract: According to latest report of 2024 by World Health Organization (WHO) based on global data of 2021, Alzheimer's disease (AD) and other forms of dementia is placed at seventh position among the leading cause of death, that accounts for killing of 1.8 million lives by the disease; and stroke causes highest number of deaths in the world ("World Health Organisation (WHO) The top 10 causes of death https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death ", 2024) Similarly, Centers for Disease Control and Prevention (CDC) National Center for Health Statistics in 2024 also reported AD to be seventh leading cause of death in the United States, based on data from 2021 to 2022 accounting 1.2 millions of deaths.("CDC's National Center for Health Statistics, Leading Causes of Death https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm," 2024). This alarming number of deaths due to AD is the call for the urgent need to find proper treatment or cure of the disease. AD also severely affects the global economy. However, there is no appropriate treatment or cure available. In the past two decades thousands of disease modifying drugs have been developed to treat dementia of AD, however most of the drugs could not pass phase I clinical trial and only a few could reach phase II and phase III stage. This review is determined to provide the status of various clinical trials, failures and progress of success of various drugs that have been designed to tread dementia of AD.

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Introduction

Alzheimer disease (AD) is a neurodegenerative disease, and it is the most common cause of dementia with 60% to 80% cases occurred among the elderly people; dementia is manifested by decline in memory, language, problem-solving, confusion with time/place and poor judgment etc. ("2023 Alzheimer's disease facts and figures," 2023; Kawas et al., 2015; Schneider et al., 2007; Schneider et al., 2009; Singh & Chanu, 2021). AD and other related dementias (ADRD) are the 7th most leading cause of death globally. Over the past three decades, number of deaths due to these diseases have increased from 0.56 million (1990) to 1.62 million (2019) (X. Li et al., 2022). Recent report revealed that 6.7 million Americans i.e., 1 out of 9 Americans with age 65 and older are affected by AD dementia (Rajan et al., 2021). AD and ADRD have direct impact on both health and economy. The 83% of caregivers are comprised of unpaid family members, friends or others (Friedman et al., 2015) that could cost about 339.5 billion USD if paid as of the year 2022. Because lifetime care cost of an individual with dementia is estimated to be 392874 USD as of 2022, of which 70% is covered by the unpaid family caregivers including food and medications ("2023 Alzheimer's disease facts and figures," 2023; Jutkowitz et al., 2017). Over the years, with the increased understanding of the regulatory mechanisms underlying pathophysiology of AD dementia, several drugs have been developed and clinical trials were carried out; however challenges remain in finding a cure or proper treatment due to complex pathogenesis of the disease (Dokholyan et al., 2022; Frozza et al., 2018;

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Tatulian, 2022). Currently available validated drugs for AD treatments modestly slow down progression of disease, but none can reverse it. Growing evidence on immunological mechanisms are revealed potential role of inflammatory pathway underlying the pathogenesis of AD/ADRD (Ahmad et al., 2022; Bettcher et al., 2021; Heneka et al., 2015; Katsel & Haroutunian, 2019; Lecca et al., 2022; Leng & Edison, 2021; Lopez-Rodriguez et al., 2021; Sobue et al., 2023). This review provides the summary of up-to-date available information on several drugs for treating dementia of AD patients, that have been used in clinical trial phase 1, phase II and phase III. As of now, only three drugs have reached the final stage of clinal trials, of which Lecanemab (Leqembi) has been aproved by the Food and Drug Administration (FDA), Aducanumab (Aduhelm) is on the process of aproval while for Donanemab the appllication for aproval by FDA is on the procress (Huang et al., 2023).

Pathophysiological Findings Linked to Dementia of AD/ADRD

The hallmark findings of AD pathphysiology are the accumulation of amyloid-β (Aβ) plaques that are mainly composed of the Aβ42 variant, and neurofibrillary tangles (NFTs) made up of hyperphosphorylated aggregates of the microtubule-associated protein tau, that associates with the loss of neurons and neurodegeneration in the brain of AD patients (Masters et al., 2015; Medeiros et al., 2011; Selkoe & Hardy, 2016; Singh & Chanu, 2021). Other pathological pathways that have been found to have significant role in the AD disease progression include apolipoprotein E (APOE) mediated cholesterol transportation and metabolism, neuroinflammatory responses, mitochondrial dysfunction and alteration in glucose metabolism etc. (Calsolaro & Edison, 2016; Cenini & Voos, 2019; Kinney et al., 2018; R, 2019; Tzioras et al., 2019; Wang et al., 2019).

Over the last several years, vast number of researses have evidenced presence of a prolonged immune response in the brain of AD patients and immune response have apperaed as a third core pathology in AD (Kinney et al., 2018). The prolong activation of resident macrophages (microglia) and other immune cells in brain aggravate both amyloid and tau pathology indicating its profound impact in the AD disease pathophysiology (Kinney et al., 2018). It may be noted that neuroinflammation has been well documented as a key player in most nervous system dysregulation diseases and continuously identified as a potential mediator of cognitive deficits. Neuroinflammation levels are increased with advancing of age and neurodegeneration, and the influence of age on neuroinflammation may contribute to accelerating cognitive impairment through glial activation, increased production of proinflammatory cytokines, abnormal neuronal signaling, magnifying deterioration of the central nervous system microenvironment etc.(Kumar, 2018; Y. W. Wang et al., 2020). Not only the AD, dementia is one of the clinical symptoms in several other neurological diseases that associates with neuroinflammation such as Vascular Dementia, Dementia Lewy Bodies, Parkinson´s Disease, Frontotemporal Dementia, Huntington´s Disease, Wernicke-Korsakoff Syndrome, Amyotrophic lateral sclerosis etc. (Amin et al., 2023; Bir et al., 2021; Chen et al., 2019; Cheng et al., 2015; Hosoki et al., 2023; Litke et al., 2021). Both the innate and adaptive immune system disregulation have been indidicated to have potential role in AD pathogenesis (Dani et al., 2019; Femminella et al., 2019; Hamelin et al., 2016; Kreisl et al., 2018; Kreisl et al., 2016; Tamburini et al., 2023; Wu et al., 2021). Microglia, astrocyes and oligodendrocytes have been accounted for innate immune system dysregulateion in AD. Whereas, the adaptive immune system dysregulation has been proposed from the detection of B and T lymphocytes in the post-mortem AD brain, cerebrospinal fluid (CSF) of mild cognitive impairment (MCI) individuals as well as AD patients (Lawson et al., 1990; Liu et al., 2018; Lueg et al., 2015; Rogers et al., 1988; Stowe et al., 2017; Tamburini et al., 2023), and the presence of higer frequency of T helper subsets (Saresella et al., 2011). These findings have directed to develelope several drugs that target these regulatory sites to reverse the demenia of AD and ADRD.

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Drug Trials and Failures

Over the past two decades, several diseases modifying drugs have been designed for treating dementia of AD and about 2700 clinical trials have been conducted so far since 2004; however only a few showed promising indications of success rate at phase II and III trials (Kim et al., 2022). The rate of failure is estimated to be at the rate of 99% (Cummings et al., 2014; Kim et al., 2022) which means only 1% is the success rate. The promising compounds are immunotherapy drugs, Aducanumab (brand name: Aduhelm), a monoclonal antibody designed to bind and eliminate aggregated Aβ plaques; Lecanemab (brand name: Leqembi) which functions in reduction of brain and CSF Aβ protofibril; Donanemab, a humanized monoclonal antibody developed from mouse mE8-IgG2a that recognizes Aβ (3–42) plaques; Oligomannate (GV-971), a seaweed-derived oligosaccharide that reduce bacterial metabolite–driven peripheral infiltration of immune cells into the brain, inhibit Aβ and Tau formation in animal studies (Huang et al., 2023; Kim et al., 2023; Lu et al., 2022; Murphy & LeVine, 2010). However, their effectiveness is yet to be available. So far and just recently only Lecanemab has been fully approved by Food and Drug Administration (FDA, United States) for AD treatment on July 6, 2023 (https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval) (Huang et al., 2023). There are several potential factors that contributed to the failures in clinical trials whether by the faulty drug development processes or the lack of clear understanding on the complex regulatory mechanisms underlying AD pathophysiology. The main reasons for failure are due to not having sufficient evidence to initiate the pivotal trials, shortcomings of the pivotal trial designs, lack of fulfilment of rational drug development principles for AD therapeutics development and less degree effectiveness (Kim et al., 2022). Even though the data from Phase II studies for compounds were not sufficient enough to convinced, there trials have been pushed into Phase III trials and ultimately failed (Gold, 2017). For example, publicly available data for bapineuzumab and solanezumab compound in the Phase II studies did not provide promising evidence that would justify for these drugs to take into the next decisive trials, but the sponsors ignoring the limitations had taken into Phase III trials, and ultimately failed to cross (Gold, 2017; Henley et al., 2019; Lilly, 2020). Subsequently, failure to acknowledge and apply the critical issues from the past clinical trials have also been a major source of recurrent challenges to the success and thereby resulting to negative outcomes (Cummings, 2018). Additionally, failing of timely treatment of symptomatic dementia, inappropriate therapeutic targets, imprecise or misinformation of clinical methodologies, can lead to the failure of clinical trials of AD (Mehta et al., 2017).

So far, most drugs have been designed to deal with Aβ, that would result in reducing Aβ production, inhibition of Aβ plaque formation, clearance of Aβ plaques and Aβ vaccine etc. (Kim et al., 2023; Masters et al., 2015; Selkoe & Hardy, 2016; Singh & Chanu, 2021). Several more drugs have also been designed attempting different target points that include mitigation of tau pathology (Kametani & Hasegawa, 2018), decrease inflammation (Kinney et al., 2018), reduction of cholesterol accumulation (Tzioras et al., 2019; Xue-Shan et al., 2016), improvement of brain energy utilization (Arvanitakis et al., 2020; Calsolaro & Edison, 2016; Ninomiya, 2019; Shieh et al., 2020), lower vascular burden (Gabin et al., 2017), neuroprotectant/antioxidant etc. (Nunomura & Perry, 2020; Palmer, 2011; Tonnies & Trushina, 2017), to increase neural growth/regeneration (Choi & Tanzi, 2019; Sampaio et al., 2017) and hormone balance(Pike, 2017). Among the 2695 clinical trials for AD (data available at ClinicalTrials.gov), after segmented by disease-modifying versus symptomatic, 41% failed in phase III, and 59% failed in phase II; of which 64% were disease-modifying and 36% were symptomatic agents respectively (Kim et al., 2022). This clearly shows drugs for proper treatment for dementia of AD/ADRD is yet to be available while hopes are still alive though. Extensive further research is required to overcome the challenges to find appropriate drugs for the treatment of AD/ADRD with better approaches. Several clinical trials that have been carried out have used included drugs for BACE1 inhibition, γ-Secretase inhibition, γ-Secretase modulation, Anti-ApoE, Aβ production inhibition, Aβ aggregation inhibition, Aβ dissociation, synaptic modulation, Aβ toxicity modulation, filament modulation, glutaminyl cyclase inhibition, active immunization, passive immunization,

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RAGE inhibition, mGluR5 modulation etc. for reversing or inhibiting amyloid pathology and cognitive deficit or dementia etc. Summary of the failed compounds/drugs which have been stop further clinical trials, promising the ones which are undergoing clinical as well as FDA approved drugs are briefly provided in the Table 1 and Table 2.

Table 1. List of drugs with approval status by FDA of the United States of America.

Drug name	Company	Mode of action and effect	Approval status
Aducanumab (Aduhelm)	Biogen, Neuroimmune	Eliminate aggregated Aβ plaques	Approval in progress (Green et al., 2009; Huang et al., 2023; Kim et al., 2023)
Lecanemab (Leqembi)	BioArctic AB, Biogen, Eisai	Reduce soluble Aβ protofibrils	Fully approved (Huang et al., 2023; Kim et al., 2023)
Donanemab	Eli Lilly & Co	Eliminate aggregated Aβ plaques	Application for full approval (Huang et al., 2023; Kim et al., 2023)

Table 2. List of drugs with clinical trial status ongoing, completed or discontinued.

Drug name	Mode of action and effect	Trial phase status	Side effects/outcome
Lenalidomide	BACE1 inhibition, inflammation reduction	Ongoing phase II	Yet to be available (Decourt et al., 2017; Valera et al., 2017)
CT1812	Aβ aggregation inhibition, Aβ oligomer reduction, behavioral improvement	Ongoing phase II	Yet to be available (Grundman et al., 2019; Rishton et al., 2021)
ALX-001	mGluR5 modulation, Synaptic function, and behavioral enhancement	Ongoing phase I	Yet to be available (Hamilton et al., 2016) (Haas et al., 2017)
Buntanetap	Aβ production inhibition, Aβ generation reduction	Ongoing phase III	Yet to be available (Fang et al., 2023; Lahiri et al., 2007)
GV-971	Aβ dissociation, Aβ, plaque burden reduction	Ongoing phase II	Yet to be available (Cumbo & Ligori, 2010; Vossel et al., 2021)

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Nasal insulin	Aβ toxicity modulation, Memory improvement	Ongoing (phase II/III	Yet to be available (Chapman et al., 2018; Craft et al., 2012; Reger et al., 2008)
Simufilam	Filament modulation, Amyloid, tau deposition, neuroinflammation reduction	Ongoing phase III	Yet to be available (Wang et al., 2017; H. Y. Wang et al., 2020)
Varoglutamstat	Glutaminyl cyclase inhibition, Amyloid pathology and pAβ reduction	Ongoing phase II	Yet to be available (Hoffmann et al., 2021; Vijverberg et al., 2021)
Aducanumab	Passive immunization, plaque clearance	Approved and ongoing phase III	Application for full approval (Green et al., 2009; Huang et al., 2023)
Lecanemab	Passive immunization, brain, and CSF Aβ protofibril reduction	Approved and ongoing phase III	Approved (Huang et al., 2023; Kim et al., 2023)
Donanemab	Passive immunization, plaque clearance	Approved and ongoing phase III	Approved (Ahn et al., 2020; Huang et al., 2023; Kim et al., 2023)
Thalidomide	BACE1 inhibition, Amyloid pathology, and gliosis reduction	Completed phase III	Adverse consequences (Decourt et al., 2017)
CHF5074	γ-Secretase modulation. Aβ reduction	Completed phase II	Decision unavailable (Imbimbo et al., 2013)
PBT2	RAGE inhibition, Spine density and synaptic protein level improvement	Completed phase II	Lack of effectiveness (Villemagne et al., 2017)
Contraloid	Aβ aggregation inhibition, Amyloid deposition reduction	Completed phase I	Yet to be available (Kutzsche et al., 2020)
Acitretin	Aβ production inhibition, Aβ reduction	Completed phase II	Yet to be available (Endres et al., 2014; Holthoewer et al., 2012)

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Bexarotene	Anti-ApoE, Aβ reduction, cognitive deficit improvement	Discontinued phase II	Adverse outcomes/ lack of efficiency (LaClair et al., 2013; O'Hare et al., 2016)
AN-1792	Active immunization, Amyloid plaque formation reduction	Discontinued phase II	Adverse events(Nicoll et al., 2003)
ACC-001	Active immunization, Amyloid plaque formation prevention	Discontinued phase II	Adverse incidents (Maia & Sousa, 2019)
CAD106	Active immunization, Amyloid accumulation in brain reduction	Discontinued phase II	No results available (May et al., 2015)
Ponezumab	Passive immunization, Cerebral blood vessel amyloid deposition reduction	Discontinued phase II	Lack of efficiency (Wessels et al., 2020)
Gammagard	Passive immunization, Aβ reduction	Discontinued phase II	Lack of efficiency (Bullich et al., 2022; Sudduth et al., 2013)
Bapineuzumab	Passive immunization, Plaque burden reduction	Discontinued phase II	Lack of efficiency (Henley et al., 2019)
Crenezumab	Passive immunization, Localized to Aβ oligomers	Discontinued phase II	Lack of efficiency (Doody et al., 2013)
Gantenerumab	Passive immunization,	Ongoing phase III	Yet to be available (Coric et al., 2015; Coric et al., 2012)
Atabecestat	BACE1 inhibition, reverse amyloid pathology and cognitive deficit	Discontinued phase II/III	Clinical worsening(Henley et al., 2019).(Thakker et al., 2015)
Elenbecestat	BACE1 inhibition, Brain, CSF, and plasma Aβ reduction	Discontinued phase III	Unfavorable risk-benefit ratio (Bullich et al., 2022)
LY2886721	BACE1 inhibition, Dose-dependent Aβ reduction	Discontinued phase II	Adverse consequence (May et al., 2015)
Lanabecestat	BACE1 inhibition, Aβ reduction	Discontinued phase III	Lack of effectiveness (Wessels et al., 2020)

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PF-06751979	BACE1 inhibition, CSF Aβ42 reduction	Discontinued phase I	Pfizer ended R&D in neurology (O'Neill et al., 2018; Qiu et al., 2019)
RG7129	BACE1 inhibition, Aβ reduction	Discontinued phase I	Adverse incidents (Jacobsen et al., 2014; Maia & Sousa, 2019)
Verubecestat	Dose dependent Aβ40,42 reduction	Discontinued phase III	Clinical worsening (Egan et al., 2018; Egan, Kost, et al., 2019; Egan, Mukai, et al., 2019)
Avagacestat	γ-Secretase inhibition, CSF Aβ reduction	Discontinued phase II	Clinical worsening/ adverse events (Coric et al., 2015; Coric et al., 2012)
PF-06648671	γ-Secretase inhibition, Brain Aβ42 reduction	Discontinued phase I	Pfizer ended. R&D in neurology(Ahn et al., 2020; Rynearson et al., 2021)
Semagacestat	γ-Secretase inhibition, Soluble Aβ and plaque reduction	Discontinued phase II	Clinical worsening/ adverse events (Doody et al., 2013)
Azeliragon	γ-Secretase modulation, Aβ load reduction, behavioral improvement	Discontinued phase III	Lack of effectiveness (Burstein et al., 2018)
Tarenflurbil	γ-Secretase modulation, Aβ reduction	Discontinued phase III	Lack of effectiveness (Green et al., 2009)
Ibuprofen	γ-Secretase modulation, Aβ reduction	Discontinued phase II	Lack of effectiveness (Pasqualetti et al., 2009)
Clioquinol	Aβ aggregation inhibition, Amyloid deposition reduction	Discontinued phase III	Toxic contaminant in manufacturing process

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			(Bareggi & Cornelli, 2012; Cherny et al., 2001)
ELND005	Aβ aggregation inhibition, Amyloid pathology reduction, learning deficit restored	Discontinued phase II	Lack of effectiveness (Salloway et al., 2011)
Tramiprosate	Aβ aggregation inhibition, Aβ40 reduction	Discontinued phase III	Lack of effectiveness (Abushakra et al., 2016; Manzano et al., 2020)

Drug Trial Progress and Hope

While most of the drugs have failed to demonstrate positive result, only three drugs demonstrated promising signs. The three FDA approved drugs Aducanumab, Lecanemab and Donanemab which target Aβ plaques/protofibrils, are still undergoing phase III clinical trial to further examine preventive effects and moreover comparing the therapeutic effects and data among these trials are believed to help in directing the next steps of AD drug development. Aducanumab is a human monoclonal antibody immunoglobulin gamma 1 (IgG1) from aged donors resistant to AD, which binds to N-terminus of Aβ fibrils and blocks amyloid aggregation, but not to Aβ monomers (Arndt et al., 2018; Sevigny et al., 2016). Earlier further clinical trials with Aducanumab were terminated because of not meeting the primary endpoint in CDR-SB scores (Clinical Dementia Rating scale Sum of Boxes) (Kim et al., 2023). In the recent subsequent two, phase III clinical trials conducted, namely ENGAGE and EMERGE studies, a significant slowing of cognitive decline at the highest dose was observed. However, only EMERGE trial reached statistical significance, whereas ENGAGE trial would not reach the primary endpoint(Huang et al., 2023). With this finding FDA approved Aducanumab through 'accelerated approval pathway' for MCI and mild dementia stage AD patients' treatment in June 2021 and is sold as Aduhelm by Biogen (Tampi et al., 2021). In both the trials an intermediate effect of the drug on biomarkers was evidence, showing amyloid removal, that may result to clinical benefit of aducanumab, and the phase IIIb/4 ENVISION trial (Govt identifier: NCT05310071) is currently on progress(Huang et al., 2023; Kim et al., 2023). Donanemab is also humanized IgG1 monoclonal antibody developed from mouse mE8-IgG2a and it recognizes Aβ (3–42), a pyroglutamate form of Aβ which is richly present in the brain of AD patients (Bayer, 2022; Irizarry MC et al., 2016). Interestingly, Donanemab can bind about one-third of Aβ plaques in postmortem brains AD or Down syndrome patients and moreover strongly reacted with the plaque core (Bouter et al., 2022). In the phase 2 TRAILBLAZER-ALZ study, combination therapy using Donanemab and Beta-Secretase 1 (BACE1) inhibitor LY3202626 was carried to target pyroglutamate form Aβ and examined the safety, tolerability, and effectiveness of the treatment. The outcome met primary endpoint of delaying cognitive decline as determined by Integrated Alzheimer's Disease Rating Scale (iADRS) (Huang et al., 2023; Kim et al., 2023). The reduction of Aβ burden was correlated with improvement in iADRS scores but only in APOE4 carriers (Shcherbinin et al., 2022). Donanemab also reduced the tau aggregation in temporal, parietal, and frontal lobes, and plasma pTau217 also significantly decreased (Pontecorvo et al., 2022). It may be noted that phase I trials of Donanemab was found to sustained reduction in cortical amyloid load and the treatment was well tolerated (Mintun et al., 2021). While phase II trials of Donanemab replicated phase I results in reduction of Aβ plaque levels with no adverse effects, patients received the treatment were more likely to exhibit amyloid-related imaging abnormalities ARIA-E and ARIA-H (Doggrell, 2021). On the other hand, LY3202626 as well as most BACE1 inhibiting candidates was excluded from the further trials due to

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a lack of evidence regarding the safety and effectiveness except Lenalidomide (Kim et al., 2023). Phase III clinical trials for Donanemab currently on progress. United States FDA granted traditional approval for Lecanemab with the brand name Leqembi in July 2023, for the treatment of AD patients ("FDA Converts Novel Alzheimer's Disease Treatment to Traditional

Approval-Action Follows Confrmatory Trial to Verify Clinical Benefit," 2023). Lecanemab a humanized IgG1 antibody which is derived from mAb158 and selectively binds to soluble Aβ protofbril (Swanson et al., 2021; Tucker et al., 2015). In the phase II clinical trial with AD patients having MCI or mild dementia had verifed amyloid pathology through amyloid PET or CSF Aβ1-42 and the results showed significant and dose-dependent reduction of Aβ plaque(Swanson et al., 2021). The outcomes were positively judged in all primary and secondary measures, that include Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog14), AD Composite Score (ADCOMS), and AD Cooperative Study–MCI-Activities of Daily Living Inventory ADCS-MCI-ADL scores (van Dyck et al., 2023). The phase III clinical trial for Lecanemab is currently on progress.

Discussion and Conclusion

The regulatory mechanisms underlying the pathology of dementia in AD or ADRD is highly complex, and it needs to be examined from several angles to uncover different regulatory pathways that would enable to design appropriate medicine for treatment or cure the cognitive deficit symptoms of the diseases. Enormous efforts with thoughtfully designed vast studies have been carried out and as a result dysregulation of several molecular and cellular signaling pathways have been identified that play potential roles in causing mild/moderate cognitive deficits and dementia of AD/ADRD. Discovering of these pathways has directed to designing and producing drugs for treatment to reduce or recover memory lost occurred to the affected individuals. However, several clinical trials using different probable drugs that have been conducted over the past two decades have not been able to provide an appropriate drug for cognitive deficit or dementia of AD/ADRD. This reveals insufficiency of the available data and the need to take up greater challenges in finding suitable medicine for the treatment. While most of the drugs have failed to demonstrate positive result, immunotherapy looks to be hopeful. The three FDA approved drugs Aducanumab, Lecanemab and Donanemab which target Aβ plaques/protofibrils, are still undergoing phase III clinical trial to further examine preventive effects and moreover comparing the therapeutic effects and data among these trials are believed to help in directing the next steps of AD drug development. The ongoing clinical trials are mainly based on pathophysiology, disease-modifying therapies, and the recruitment of participants in earlier stages of the disease which underline the importance of conducting fundamental research on pathophysiology, prevention, and intervention prior to occurrence of brain damage caused by AD. So far, most drugs that have been designed centralized to the inhibition of formation of toxic Aβ and pTau aggregates. However, recent vast studies have expended the previous knowledge with new findings that include the promising outcomes of clinical trials of Aducanumab, Lecanemab and Donanemab which are monoclonal antibodies resulting in successful clearance Aβ and thereby promising approach in passive immunotherapy linking to neuroinflammatory response. These positive outcomes provide new hopes for AD treatments if the disease is detected at early stages. Other two monoclonal antibodydrugs that are currently undergoing phase III trials are Remternetug (ClinicalTrials,gov.identifer: NCT05463731) and Solanezumab (ClinicalTrials, gov.identifer: NCT01760005). Besides, Sodium Oligoman-nate Capsule (GV-971) is and anti-inflammatory drug that inhibits Aβ fibril formation (ClinicalTrials, gov.identifer: NCT05181475). Moreover, medical research has revealed existence of common disease pathways among neurodegenerative diseases (Bogar et al., 2022) suggesting that the findings in AD/ADRD will also be applicable to other neurological diseases with cognitive deficit or dementia. A vast number of studies have similarly evidenced the improvements in Aβ clearance occurred in the brain through the modulation of chronic neuroinflammation by different receptor ligands, modulation of microglial phagocytosis, and increase in myelination etc. Currently there are many anti-neuroinflammatory drugs which are currently undergoing phase III trials that include Hydralazine hydrochloride

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(ClinicalTrials,gov.identifer: NCT04842552), KarXT(xanomeline-trospium) (ClinicalTrials, gov.identifer: NCT05511363), Masitinib (ClinicalTrials, gov.identifer: NCT05564169), NE3107 (ClinicalTrials, gov.identifer: NCT04669028), and Spironolactone (ClinicalTrials, gov.identifer: NCT04522739). Inflammatory pathways related to inflammasomes that associates with potential biomarkers of neuroinflammation associated with AD such as NF-κB, NLRP3 and TREM2, Micorglia have shown to be potential drug targets for AD (T. Li et al., 2022) and further suggests inflammatory pathways connection to Aducanumab, Lecanemab and Donanemab. As there are multiple pathways in neurodegeneration leading to cognitive deficits in AD or ADRD, drugs targeting single target site so far is not working, it is important to find multiple drugs to target multiple sites that could be treated simultaneously. The above several lines of enormous studies and several more that have not been covered in this review, has strongly indicated that, to bring better understanding of AD and ADRD pathophysiology and for treatment or cure requires understanding of histopathologic changes in neurodegenerative diseases as it could highlight key aspects of the degenerative process leading to dementia. Essentially, the questions that arises in the massive failures in clinical trials needs to be thoroughly addressed in moving forward to drug designing and greater success in clinical trials for treating dementia of AD or ADRD.

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