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Therapy for Alzheimer's disease: Missing Targets and Functional Markers?

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Abstract

The development of the next generation therapy for Alzheimer's disease (AD) presents a huge challenge given the number of promising treatment candidates that failed in trials, despite recent advancements in understanding of genetic, pathophysiologic and clinical characteristics of the disease. This review reflects some of the most current concepts and controversies in developing disease-modifying and new symptomatic treatments. It elaborates on recent changes in the AD research strategy for broadening drug targets, and potentials of emerging non-pharmacological treatment interventions. Established and novel biomarkers are discussed, including emerging cerebrospinal fluid and plasma biomarkers reflecting tau pathology, neuroinflammation and neurodegeneration. These fluid biomarkers together with neuroimaging findings can provide innovative objective assessments of subtle changes in brain reflecting disease progression. A particular emphasis is given to neurophysiological biomarkers which are well-suited for evaluating the brain overall neural network integrity and function. Combination of multiple biomarkers, including target engagement and outcome biomarkers will empower translational studies and facilitate successful development of effective therapies.

Graphical Abstract

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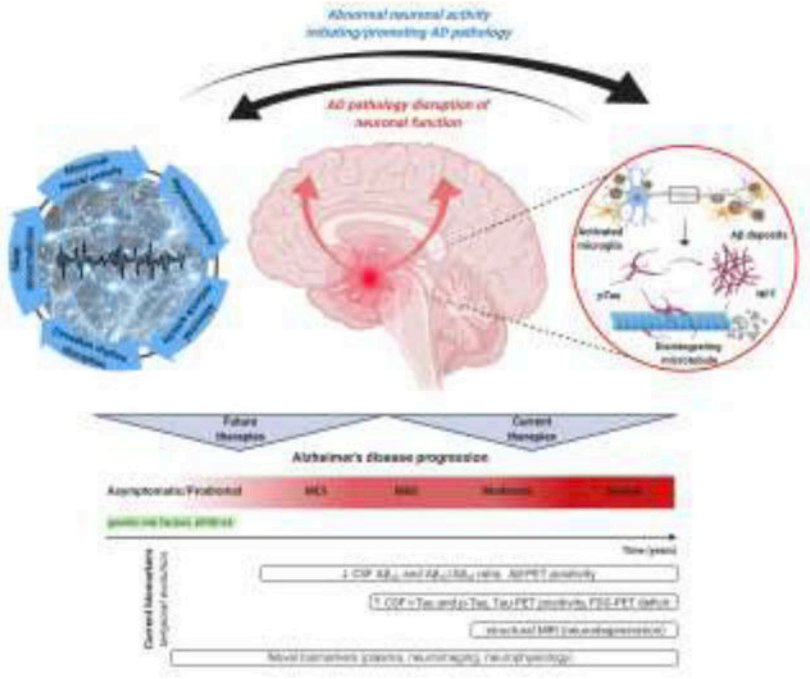

Keywords

Alzheimer’s disease; drug development; non-pharmacological treatment; clinical trials; novel biomarkers

1. Introduction

Worldwide increase in life expectancy has produced a dramatic rise in the prevalence, and thus impact of aging-associated diseases including Alzheimer’s disease (AD) on the biomedicine and society at large. It has been estimated that 5.8 million Americans live with AD in 2020, and that number is projected to triplicate by mid-century. Currently, it is the sixth leading cause of death in the United States and the fifth leading cause of death in patients 65 years of age and older (Alzheimer’s Association, 2020)

Clinically AD is characterized by slowly progressive neurodegeneration leading to overt cognitive decline involving loss of memory and higher executive functioning. The core pathological hallmarks of AD in the brain are accumulated extracellular plaques composed of amyloid-β (Aβ) proteins, and intracellular neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau (Fig. 1), both contributing to the damage and death of neurons (Ittner and Gotz, 2011). Recent research demonstrated that sustained neuroinflammation, impairments of mitochondrial bioenergetics and protein homeostasis have also prominent role in unfolding of AD (Kinney et al., 2018; Perez Ortiz and Swerdlow, 2019; Veitch et al., 2019), thus implying to multifactorial etiology of the disease. AD exists under two forms: sporadic AD (sAD), characterized by late onset and accounts for vast majority of AD cases, and familial AD (fAD), an early onset and dominantly inherited disease, which accounts for less than 1% of cases (Alzheimer’s Association, 2020). For sAD, age is the major risk factor,

but carrying the ApoE-ε4 genetic polymorphism highly increase the likelihood of developing disease in subjects older than 65 years. The fAD has more rapid progression affecting younger subjects with highly penetrant mutations in the genes encoding for amyloid precursor protein (APP), and presenilins 1 and 2 (PS1 and PS2) that result in accumulation of Aβ and formation of plaques (Bertram and Tanzi, 2012).

Despite significant advances in our understanding of pathological mechanisms involved in AD, treatment options are still limited. Existing drugs provide only short-term symptomatic benefits, while the development of effective disease-modifying therapeutic interventions that would prevent, halt, or reverse AD seems to be notoriously difficult task given the large number of compounds, particularly those targeting Aβ, which failed in late-stage clinical trials (Cummings et al., 2020; Long and Holtzman, 2019). Repeated setbacks in development of AD treatments recently prompted changes in the research strategy, which increasingly begins to focus on multifaceted targets and their possible interactions rather than just on disease canonical mainstays, Aβ and hyperphosphorylated tau. At this inflection point, it is necessary to critically evaluate all potential factors that influence negative outcomes in clinical trials, from translatability of results obtained in preclinical AD models to predictive validity of currently used biomarkers for treatment efficacy and improvement in the disease state.

In this review we provide an updated outline of the current therapeutic possibilities, status of AD drug development focusing mainly on compounds being tested in clinical trials, and an overview of emerging non-pharmacological treatment interventions. We also discuss challenges and limitations in AD discovery efforts, and importance of inclusion of functional biomarkers such as neurophysiological signatures of disease, which combining with currently used fluid and imaging biomarkers would form multicomponent biomarker panel for ensuring adequate translation of preclinical to human studies and leveraging treatment development research into patients benefit.

1. Current therapeutics

The current treatment for clinically diagnosed AD patients utterly relies on pharmacological modulation of cholinergic and glutamatergic neurotransmission. There are only five drugs approved for AD by the United States Food and Drug Administration (FDA), including cholinesterase inhibitors donepezil, rivastigmine, and galantamine, a N-methyl-D-aspartate (NMDA) receptor partial antagonist memantine, and a fixed-dose combination of donepezil and memantine (Alzheimer’s Association, 2020). All these drugs, however, have limited effectiveness and they do not reverse the course of the disease, or even substantially improve cognitive dysfunction, but rather temporarily delay the deterioration of AD symptoms (Birks and Harvey, 2018; Knight et al., 2018).

Cholinergic neurons in the basal forebrain are among the earliest targets of AD pathology, and their severe loss leads to decreased cholinergic neurotransmission consequently resulting in impairment of cortical activation with cognitive and behavioral symptoms characterized by memory, sensory processing and sleep disturbances (Mesulam, 2013). Accordingly, enhancement of cholinergic neurotransmission was recognized as tenable

treatment goal to ameliorate and delay these dysfunctions in AD patients. Cholinesterase inhibitors bind reversibly with and inactivate enzyme acetylcholinesterase (Nestler et al., 2015), thus inhibiting hydrolysis of neurotransmitter acetylcholine and increasing its concentrations at cholinergic synapses still unaffected by neurodegeneration. In the clinical treatment of AD, these symptomatic drugs are recommended as the first-line therapy for mild-to-moderate stage of the disease. However, systematic review of clinical data (Knight et al., 2018) showed that cholinesterase inhibitors have significant, though practically modest, effects in improving cognitive symptoms and maintaining patient functional ability over the period of 6 months to 1 year. Apart from the cholinesterase inhibitors, cholinergic drugs that directly modulate muscarinic and nicotinic acetylcholine receptors have also been considered as viable treatment options for AD, and several drug candidates are or were under development (*see below*).

Memantine is other FDA approved symptomatic treatment for AD in addition to the cholinesterase inhibitors. It is a low affinity and voltage-dependent antagonist of glutamatergic NMDA receptors (Nestler et al., 2015), which clinical effects likely resulted from neuronal protection of excessive NMDA activation associated with excitotoxicity. Supporting evidence suggest that memantine, at therapeutically relevant concentrations, preferentially blocks extrasynaptic NMDA receptors in condition of excessive stimulation, without disrupting synaptic NMDA receptor mediated neurotransmission (Lipton, 2005; Xia et al., 2010). Memantine is currently indicated for patients with moderate-to-severe AD as a monotherapy or in combination with cholinesterase inhibitors.

2. Potential therapeutic interventions

2.1. Drugs targeting Aβ

In the realm of AD research, amyloid cascade hypothesis (Hardy and Selkoe, 2002), has been a dominant strategy influencing considerable clinical, preclinical and drug discovery research for years. Conceptualized upon observations that increased Aβ production in neurons induces chain of neurotoxic events resulting in synaptic dysfunction and generation of tau-containing NFTs with consequent cell loss and progressive cognitive impairments, it offered an attractive framework to explain AD pathogenesis. Accordingly, pharmacologic interventions to counteract deleterious effects of Aβ by preventing its excessive production and buildups or promoting its clearance prevailed as promising approach to arrest or reverse AD. Intriguingly, even though amyloid pathology is undoubtedly involved in the trajectory of AD, none of the drug candidates targeting Aβ to modify this disease succeeded in clinical trials so far.

2.1.1. Drugs to reduce Aβ production—Aβ peptide is produced by sequential proteolytic processing of the APP by β- and γ-secretases, respectively (LaFerla et al., 2007). Inhibition of these enzymes reduces the level of Aβ in the brain and limits the deposition of amyloid plaques through the upstream interference with the amyloid cascade.

Development of β-secretase (β-site APP–cleaving enzyme 1) or BACE1 inhibitors have been considered as one of the priority disease-modifying treatment approach for AD, and several drugs have reached the late phase clinical testing, including atabecestat (JNJ-54861911),

verubecestat (MK-8931), and lanabecestat (AZD3293). All these compounds were found to significantly lower the brain Aβ levels measured by positron emission tomographic (PET) imaging and in cerebrospinal fluid (CSF), clearly indicating their target engagement. However, their further clinical development was discontinued due to the unacceptable side effects or ineffectiveness to improve cognitive status in AD patients (Das and Yan, 2019). Results from the recent clinical trials of verubecestat and atabecestat surprisingly showed that both drugs have even detrimental effects on cognitive function and brain structure (Egan et al., 2019; Henley et al., 2019). On the other hand, lanabecestat which was better tolerated than other two drugs, showed convincingly lack of improvement in cognitive function of AD patients. The reasons for these negative outcomes are not yet fully revealed, but some of the potentially contributing factors include the wide substrate-binding domain of BACE1 enzyme, and propensity for non-selective blockade of both BACE1 and BACE2 isoenzymes of some of these drugs (Barao et al., 2016). There are about 45 known substrates for BACE1 enzyme, and changes in their processing induced by these drugs might cause some of the observed side effects, or even mask their cognitive benefits. In fact, interference between some of BACE1 inhibitors and enzyme's non-amyloid substrates such as neuregulin-1, which is involved in myelination, or CHL1, the neural cell adhesion molecule close homolog of L1, involved in neurite outgrowth, might account for structural brain damage and cognitive worsening associated with their use (Ben Halima et al., 2016; Hitt et al., 2012; Zhu et al., 2018). Another possible explanation for inefficacy of these drugs is their excessive inhibition of BACE1, which in turn can compromise normal synaptic functions. For example, it has been suggested that moderate inhibition of BACE1 is sufficient to reduce the toxic effects of Aβ production while still allowing the physiological function of the enzyme at synapse, as observed in carriers of a rare APP mutation (Knopman, 2019). Non-selective BACE1/2 inhibition is additional challenging factor and some side effects reported after use of BACE1 inhibitors, like hair and skin depigmentation, could result from this property (Cebers et al., 2016). The two BACE1 inhibitors, umibecestat (CNP520) and elenbecestat (E2609), have been shown to have significantly higher selectivity to BACE1 over BACE2 enzyme comparing with formerly tested BACE1 inhibitors (Lynch et al., 2018; Neumann et al., 2018), thus lower chances to encounter targets that would lead to serious side effects. Moreover, umibecestat was shown not to produce hippocampal structural alterations as described for earlier BACE1 drugs, likely due to the more selective activity on enzyme's subcellular domain and sparing CHL1 processing (Barao et al., 2016). However, their late-stage clinical development has been recently terminated due to inefficacy.

In the biochemical network involved in generation and accumulation of Aβ, γ-secretase is the enzyme responsible for the final step in the amyloidogenic APP processing pathway. It is a membrane-embedded protease that cleaves APP within its transmembrane domain yielding to Aβ species of different lengths, including $A\beta_{1–40}$ and $A\beta_{1–42}$, the most common isoforms in the amyloid plaques. The catalytic core of γ-secretase consists of presenilins (PS1 and PS2), which missense mutations are a major cause of fAD, and three accessory proteins i.e. nicastrin, anterior pharynx-defective 1 (APH1) protein, and PS enhancer 2 (Pen-2) (De Strooper, 2003). This complex enzyme, besides cleaving APP also regulates processing of series of integral membrane proteins including Notch, N-cadherin and variety of other important cellular substrates making development of γ-secretase inhibitors (GSIs)

challenging similar to those for BACE1 inhibitors (Mangialasche et al., 2010). In the past decade, several GSIs progressed to clinical trials due to their high potency to lower Aβ production indicated at the preclinical level. These include: semagacestat (LY-450139), begacestat (GSI-953), and MK-0752. Unfortunately, none of these compounds were successful in clinical trials, as their use in AD patients was followed by lack of cognitive improvement and severe adverse gastrointestinal and dermatological side effects (Doody et al., 2013; Golde et al., 2013; Martone et al., 2009). Importantly, these adverse events were present at pharmacologically active concentrations and mostly account for the inherent mechanism based-toxicity, given their high affinity to block the Notch signaling pathway which is critically involved in synaptic plasticity, cell differentiation and survival (Ables et al., 2011). In an attempt to overcome toxicity issues, GSIs that are more restrictive to APP and with Notch-sparing property have been synthetized, such as avagecestat (BMS-708163) and nirogacestat (PF-3084014). Nevertheless, the effort has proven to be futile since neither lower toxicity nor increased efficacy were achieved in AD patients (Coric et al., 2015; Crump et al., 2012; Kumar et al., 2018). In addition to GSIs, γ-secretase modulators (GSMs) emerged as possibly safer agents for AD. These compounds interact with γ-secretase through the allosteric binding site without altering physiological activity of the enzyme. They were shown to reduce the deposition of pathogenic Aβ by shifting the profile of the secreted Aβ peptides toward the shorter non-amyloidogenic species (Bursavich et al., 2016). Both the first generation of GSMs, comprised of repurposed non-steroidal anti-inflammatory drugs ibuprofen, indomethacin and tarenflurbil, and second generation GSMs such as E2012, after initial promise did not show clinical benefits in AD patients (Eriksen et al., 2003; Green et al., 2009; Imbimbo, 2009; Nagy et al., 2010). Presently, it is not clear whether GSI or GSM discovery programs are completely abandoned, but in the current AD drug development pipeline there is no such drugs in clinical testing.

Experimental studies indicated that upregulation of α-secretase activity may also have therapeutic potential for AD (Lichtenthaler and Haass, 2004), since the activation of α-secretase decreases Aβ generation and concomitantly increases formation of neuroprotective soluble form of APP (APPa) by facilitating its proteolysis in non-amyloidogenic pathway (De Strooper et al., 2010). As a result development of α-secretase enhancers emerged as an innovative alternative to β- and γ-secretase inhibitors. However, even though early α-secretase enhancing compounds (Marcade et al., 2008; Snow et al., 2009) did not make significant progress in clinical studies, the rationale behind developing novel α-secretase modulators strongly recommended further efforts and thus two drug candidates, APH-1105 and ID1201, are currently in phase 2 clinical trials.

2.1.2. Drugs to facilitate Aβ clearance—Active and passive immunization against Aβ peptides has been considered as another promising therapeutic strategy to tackle AD pathology (Herline et al., 2018; van Dyck, 2018). Biochemical characterizations of toxic Aβ species that either in form of soluble oligomers, protofibrils or aggregates affect normal neuronal and synaptic functions, enable the development of both vaccines and specific antibodies with potential for their removal from the brain. Using this anti-amyloid approach considerable effects has been observed in transgenic animal models overproducing Aβ

(Wilcock and Colton, 2008), yet translation of its therapeutic potential in patients seems to be difficult given the number of Aβ immunotherapy trials that failed thus far.

An early clinical study with anti-Aβ vaccine AN1792 in mild-to-moderate AD patients was stopped when some subjects developed toxicity in the form of T cell-mediated meningoencephalitis (Gilman et al., 2005). Interestingly, a recent report of 15-year postmortem neuropathological follow-up of patients involved in this trial (Nicoll et al., 2019) showed extensive and persisted plaque clearance, but this effect unfortunately did not affect progression of severe cognitive impairments and spread of tau pathology nor prolong survival time. To achieve better safety profile of anti-Aβ vaccine that stimulates an immune response against Aβ by molecular mimicry of the parts of native Aβ sequence, such as B-cell epitope but not T-cell epitope in its antigenic component, has been tailored (Schneeberger et al., 2009). Although better tolerated, this vaccine also failed to produce significant clinical effects in AD patients (Schneeberger et al., 2015). Nevertheless, active immunization strategy is still considered as potential approach for AD therapy, particularly for use in early stage of disease, or even as a preventive measure. In the recent clinical trials there are four different anti-Aβ vaccines in evaluation. In the most advanced clinical phase is investigational vaccine CAD106 (Farlow et al., 2015), which is being tested (Table 1) in cognitively unimpaired individuals who have genetic profile that place them at high risk for developing AD (elderly homozygous ApoE4 carriers). Two other vaccines, ABvac40 and UB-311, are currently in phase 2, and one vaccine, LuAF20513, is in phase 1. The latter vaccine is engineered with aim to induce production of anti-Aβ polyclonal antibodies and robust “non-self” responses of preexisting memory T-helper cells stemming from previously immunized elderly individuals against tetanus (Davtyan et al., 2013).

The systemic application of anti-Aβ antibodies is another therapeutic approach to neutralize Aβ toxicity and promote plaque clearance. In contrast to active vaccination, passive immunotherapy using monoclonal antibodies has been seen as more viable strategy in directing the immune response towards particular epitope or isoform of Aβ. Also, this approach can improve treatment efficacy by preserving consistent antibody titer and enabling better control of possible adverse events. Over the past decade several monoclonal antibodies directed against Aβ such as bapineuzumab (AAB001), solanezumab (LY2062430), ponezumab (PF04360365), crenezumab (MABT5102A), gantenerumab (RG1450), aducanumab (BIIB037), donanemab (Ly3002813) and lecanemab (BAN2401) have being tested in AD patients (van Dyck, 2018), however just few of them are still in clinical evaluation (Table 1).

Bapineuzumab is a humanized IgG1 anti-Aβ monoclonal antibody corresponding to the murine clone 3D6 specific for an N-terminal Aβ epitope (residues 1–5) (Kerchner and Boxer, 2010). This was the first antibody tested in clinical trials. It binds to and clears soluble and fibrillar Aβ peptides by triggering microglial phagocytosis. Imaging analyses showed evidence of target engagement in lowering of Aβ in patients treated with bapineuzumab over placebo control, however, in two parallel phase 3 trials no significant clinical benefits on cognition were found in mild-to-moderate AD patients (Salloway et al., 2014). Moreover, high dose of bapineuzumab was associated with increased rate of symptomatic amyloid-related imaging abnormalities (ARIA) such as edema and

microhemorrhages (Sperling et al., 2012), leading to the discontinuation of its further development. Solanezumab is also humanized IgG1 monoclonal antibody designed to recognize an epitope within Aβ mid-domain (residues 16–26). It increases the clearance of soluble Aβ peptides from the brain leading to dose-dependent rise in plasma and CSF Aβ levels (Farlow et al., 2012). It has a favorable safety profile, but was without marked benefits for the cognitive and functional outcomes in patients with mild-to-moderate AD in phase 3 trials (Doody et al., 2014; Honig et al., 2018). Ponezumab is a humanized IgG2 monoclonal antibody with affinity towards C-terminus (residues 30–40) that binds to soluble Aβ (La Porte et al., 2012). This antibody has safe profile expressing a lower propensity to induce immune effector response comparing to other IgG1 antibodies in the class, however, two phase 2 studies revealed clinical inefficacy, and its development was also discontinued (Burstein et al., 2013; Landen et al., 2017). Crenezumab, a humanized monoclonal IgG4 antibody with ability to bind to different Aβ species (oligomeric, fibrillar, and plaque-embedded) was designed to minimize Fc gamma receptor-mediated inflammatory activation of microglia in order to lower the risk of ARIA (Adolfsson et al., 2012). Similar to others, clinical trials with crenezumab brought to one more disappointment, since no reduction in cognitive decline of treated AD patients was demonstrated (Cummings et al., 2018; Salloway et al., 2018). Gantenerumab is the first fully human IgG1 monoclonal antibody that binds to a conformational epitopes within the N-terminus (residues 3–12) and at central region (residues 18–27) of Aβ oligomers and aggregated fibrils. In transgenic mice, gantenerumab significantly reduced amyloid plaques in the brain by recruiting microglia, but without altering Aβ plasma levels (Bohrmann et al., 2012). Even though this effect was observed in early clinical evaluation in patients with mild-to-moderate AD, subsequent phase 3 study was abruptly terminated following an interim futility analysis and an increased rate of ARIA (Ostrowitzki et al., 2017). Recently, gantenerumab has brought back in clinical evaluation in four phase 3 trials, two ongoing, for evaluating its effect on cognition in prodromal and mild AD patients, and two currently recruiting patients with early AD (Klein et al., 2019). Aducanumab, is a potent recombinant human IgG1 monoclonal antibody developed through screening libraries of memory B cells produced in cognitively healthy aged donors reacting against aggregated Aβ. This anti-Aβ antibody binds the N-terminus (residues 3–6) of the Aβ sequence and specifically targets soluble oligomers and insoluble fibrils. Initial evaluation of aducanumab convincingly showed robust, dose-dependent clearing of fibrillary amyloid plaques measured by PET imaging together with slowing of cognitive decline both in preclinical models and in mild AD patients (Sevigny et al., 2016). Later clinical assessments in two phase 3 trials were stopped early possibly due to insufficient efficacy in an interim futility analysis (Selkoe, 2019), but subsequently aducanumab development has revived after additional analysis of larger dataset showing positive results in reducing clinical decline in AD patients (Howard and Liu, 2019). Back on track of aducanumab, together with two investigational monoclonal antibodies in underway clinical trials, donanemab and lecanemab keep optimism in success of Aβ-directed immunotherapy concept after more than a decade of research futility. Donanemab, a humanized IgG1 antibody is developed from murine mE8-IgG2a which specifically targets a pyroglutamate form of Aβ (pGlu-3 Aβ) aggregated in amyloid plaques (Cynis et al., 2016). Evidence suggest that pGlu-3 Aβ modified peptide has high amyloidogenic and neurotoxic potential given its high presence in diffuse plaques and vascular amyloids that cause cerebral

angiopathy in AD (Crehan et al., 2020). Preclinical study showed that donanemab reduces Aβ deposits in mice without causing ARIA (Dematttos et al., 2012), recommended its further development in ongoing phase 2 trial (Irizarry et al., 2018). Recent company's announcement hinted that compound has shown significant slowing of decline in a composite measure of cognition and daily function in subjects with early symptomatic AD, but official study report is yet to come. Lecanemab is another humanized IgG1, derived from the E22G arctic mutation in the APP that actively binds to and clears soluble Aβ protofibrils (Lannfelt et al., 2014). Driven by phase 2 data of significant plaque clearance and possible reduction in cognitive decline in patients with mild AD (Logovinsky et al., 2016), this compound has recently entered a phase 3 trial.

The passive immunotherapy using monoclonal antibodies has also been considered in primary and secondary prevention studies where it might provide better opportunity to modify disease in the protracted asymptomatic or prodromal phase of AD. Currently, solanezumab and gantenerumab are being tested in asymptomatic subjects with fAD mutations that have high risk for developing AD (Bateman et al., 2017) (Table 1), while crenezumab is in active phase 2 trial in Colombian preclinical autosomal-dominant carriers of PS1 E280A mutation (Tariot et al., 2018).

General characteristic of all failed anti-Aβ trials is that even though most investigational compounds showed robust target engagement, i.e. reducing Aβ in the brain measured by PET imaging and CSF biomarkers, they did not significantly improve performances in cognitive functions of AD patients. This dissociation demonstrates that these biomarkers are not surrogate markers for treatment efficacy in clinical trials, but more importantly question if the Aβ accumulation represents a proper target for disease modification after clinical symptoms arise. Compelling evidence showed that plasma and CSF Aβ levels are reliable indicators of pathological processes in the AD brains (Blennow and Zetterberg, 2019) and thus can serve as biomarkers for diagnostic assessment and perhaps stratification of patients in clinical trials. Similarly, imaging biomarkers facilitate accurate diagnosis and can allow tracking of distinctive changes in the brain that are characteristic for AD progression. However, the value of these biomarkers in predicting treatment benefit remains unclear, since trajectory of their changes usually does not parallel with response to treatment and clinical improvement (Penninkilampi et al., 2017), thus challenging the separation of drug from placebo in AD trials. Another frequently cited reason for lack of positive outcome in amyloid-targeted trials is probably belated initiation of the treatment when the window for disease modification has already passed and neuronal damage might advance to an irreparable stage (Jack et al., 2013; van Dyck, 2018). Therefore, demonstrating Aβ clearance in AD patients perhaps is not the ultimate marker indicating achievement of meaningful treatment benefits.

2.2. Drugs targeting tau

Disappointing clinical outcomes of drug candidates targeting accumulation of Aβ oligomers and plaque formation shifted drug discovery efforts to AD-related tau pathology. Microtubule associated protein tau (MAPT) has important cytoskeletal roles such as microtubule assembly and transport, and stabilization of neuronal axons that are impaired in

AD. Tau filaments and hyperphosphorylated tau accumulated intracellularly in NFTs directly contribute to neuronal destruction and neurodegeneration. Also, it has been shown that toxic tau isoforms spread via neuronal synapses in prion-like pattern (Jucker and Walker, 2018), which theoretically could be pharmacologically blocked. Thus, multiple strategies have been proposed for reducing tau pathogenicity including stabilization of microtubules, modulation of abnormal tau phosphorylation, and inhibition or prevention of tau aggregation, seeding and spreading. Early anti-tau therapies were primarily based on inhibition of tau hyperphosphorylation and NFTs formation by modulating activity of protein kinases (i.e. glycogen-synthase-kinase-3) involved in tau metabolism. However, these attempts have been discontinued because of toxicity or lack of efficacy (Congdon and Sigurdsson, 2018). Current clinical trials include inhibitors of tau aggregation, tau antibodies, and antisense oligonucleotides against the MAPT RNA (Bittar et al., 2020; Cummings et al., 2019a). Potential of methylene blue (TRx0237) for degradation of existing NFTs and prevention of new tau aggregates associated with AD is exploring in an ongoing phase 3 trial (Table 1). Tau-targeted active and passive immunotherapies are actively being tested for safety and efficacy in early-stage AD patients. Several compounds recently advanced to phase 2 trials including vaccine AADvac-1, and monoclonal antibodies directed toward different aspects of the pathological tau such as gosuranemab (BIIB092), semorinemab (RO7105705), zagotenemab (LY3303560), and tilavonemab (ABBV-8E12) (Bittar et al., 2020; Hoskin et al., 2019). An innovative and promising approach against tau pathology in AD brain is the use of antisense oligonucleotides which have potential to safely reduce MAPT mRNA impacting post-translational modifications of tau and thereby preventing expression and seeding activity of toxic isoforms in neurons. Intrathecal delivery of such a drug IONIS-MAPTRx is currently being tested in a Phase 1/2 trial in patients with mild AD (Mignon et al., 2018).

No clinical trials have been completed up to date, therefore no conclusion can be drawn on therapeutic benefits of treatments against tau pathology. In contrast to the well-demonstrated genetic link between Aβ pathology and development of AD (*see above*), no such a genetic risk factor for tau pathology has been established. Based on the lack of genetic connection to AD, and the late terminal role of tau in AD, doubts have been raised about tau-related drug treatment concept.

2.3. Miscellaneous drugs with symptomatic or disease-modifying promise

While most efforts and money have been invested in preventing Aβ and tau pathologies as potential treatments for AD, there is a burgeoning interest in identifying alternative drug targets beyond these miscreant peptides that can impact the disease pathology and translate to beneficial clinical outcome. Accordingly, numerous ongoing preclinical and clinical researches in AD are focusing on modifying neurotransmission, counteracting neuroinflammation, bioenergetics, epigenetics, and protein homeostasis that contribute to AD pathophysiology at different stages.

In AD drug pipeline, several small molecules targeting neurotransmitters' receptors in cognitive-related brain regions are in the development. This includes novel anticholinesterase inhibitor octohydroaminoacridine (Xiao et al., 2017) (Table 1), as well as

cholinergic agents that directly activate muscarinic M_1 or nicotinic α_7 and $\alpha_4\beta_2$ receptors which have shown potential to improve performance in a variety of preclinical cognitive assays and to modulate the pathogenic effects of APP/Aβ (Bertrand and Terry, 2018; Fisher, 2008; Sako et al., 2019; Stoiljkovic et al., 2015). Several selective agonists of M_1 receptors including talsaclidine, MK-7622, TAK-071, HTL0018318, and AGN-242071 have being recently evaluated in clinical trials for symptomatic treatment of cognitive deficits as adjunct therapy to standard AD treatment. Unfortunately, they were all withdrawn from further development due to safety and tolerability issues, or insignificant efficacy (Voss et al., 2018). Enhancement of cholinergic transmission via nicotinic receptors has also been investigated and selective agonists of α_7 (encenicline) and $\alpha_4\beta_2$ (ispronicline) receptors were tested in patients with AD, but without successful due to unexpected off-target toxicity (Bertrand and Terry, 2018). Targeting serotoninergic receptors is another potential therapeutic approach to improve cognition and memory (Calhoun et al., 2017). In recent years, inhibitors of $5HT_6$ receptors (idalopirdine, intepirdine) were in clinical consideration for mild-to-moderate AD. These receptors are wide spread in brain regions that mediate cognition and their blockade is shown to increase concentrations of multiple neurotransmitters facilitating oscillations in neuronal networks relevant in cognition (de Jong and Mork, 2017). Although, the rationale for $5HT_6$ receptors antagonist use was sound, trials ended as a failure (Bennett, 2018; Khoury et al., 2018). Another $5HT_6$ antagonist, masupirdine (SUVN-502) also recently failed in phase 2 trial for testing its efficacy as an add-on treatment in subjects with moderate AD being on combined therapy with donepezil and memantine. Phosphodiesterase (PDE) inhibitors are also being studied as potential AD symptomatic treatment. The expression of these enzymes in the brain, and their involvement in neuroplasticity and memory consolidation proposed evaluation of several PDE targeting compounds including PDE-9, PDE-4 and PDE-3 inhibitors in AD patients (Prickaerts et al., 2017) but results did not show clinical promise so far.

Given the high prevalence of neuropsychiatric symptoms observed in AD and lack of drugs approved by FDA for this indication, several neurotransmission-based multimodal compounds that can mitigate agitation, aggression, apathy, and sleep disturbances observed in AD patients are in currently active clinical trials (Table 1). These include drugs such as serotoninergic modulators pimavanserin, escitalopram and mirtazapine, melatonin and serotonin receptors agonist piromelatine, adrenergic α_2 agonist guanfacine, orexin receptor antagonists lemborexant and suvorexant, glutamate receptor antagonist riluzole, dopamine D_2 receptor agonist brexpiprazole, dopamine and norepinephrine reuptake inhibitor methylphenidate, synthetic cannabinoid nabilone as well as and $GABA_A$ receptors allosteric modulators zolpidem and zoplicone which trials are recently completed (Cummings et al., 2020; b). Compounds acting through sigma receptors, chaperon proteins that modulate intracellular calcium signaling, are under investigation for therapeutic use in AD. High affinity sigma1 agonist ANAVEX2–73 (blarcamesine) which also binds to muscarinic receptors, and AVP-786 and AXS-05 that act as sigma1 agonists and NMDA antagonists are in clinical evaluations for neuropsychiatric symptoms associated with AD (Stahl, 2018). Investigational drug elayta (CT1812) is a small molecule which binds to the neuronal sigma2/PGRMC1 (progesterone receptor membrane component 1) protein and disrupts attachment of oligomeric Aβ on brain cells preventing the Aβ-induced synaptic toxicity.

Compelling results in restoring cognitive deficits at preclinical studies, and good tolerance and safety profile in prior clinical study in AD patients (Grundman et al., 2019; Izzo et al., 2014) warrant it's further testing in two ongoing phase 2 studies. Azeliragon is an inhibitor of RAGE (receptor for advanced glycation end-products) with potential to slow cognitive decline in AD (Burstein et al., 2013). Upregulation of RAGE in hippocampus has been observed in people with AD and is thought to promote neuroinflammation and brain amyloid deposition. In preclinical studies, azeliragon decreased Aβ load and improved performance on behavioral assays in transgenic mice (Walker et al., 2015). The compound failed in trial in mild AD patients with impaired glucose tolerance. Interventions to tackle AD by improving mitochondrial metabolism in AD through mild ketosis induction such those with tricaprilin, an oral formulation of caprylic triglyceride (Henderson et al., 2009), or by inhibiting activity of gingipains, proteases produced by bacteria causing periodontitis and linked to neuroinflammation, astrogliosis and cognitive impairment, with compound COR388 (Dominy et al., 2019) are also in active clinical consideration (Table 1).

Neuroinflammation has been recognized as another promising target for intervention as several studies have identified a sustained immune response in the AD (Kinney et al., 2018). Activation of the resident microglia and other immune cells in the brain has been demonstrated to exacerbate both Aβ and tau pathology. Conversely, an efficient adaptive immune response during AD might ameliorate developing pathology by modulating microglial function (Marsh et al., 2016). Thus, modifiers of innate immune activity and of microglial responses are attractive therapeutic targets for AD. DNL747 is an inhibitor of RIPK1 (receptor-interacting serine/threonine-protein kinase 1), an enzyme that mediates disease-associated microglial activation and release of pro-inflammatory cytokine in AD. The finding that genetic and pharmacological inhibition of RIPK1 induced amyloid clearance and improved memory in transgenic mice overproducing Aβ (Ofengeim et al., 2017) gave impetus to its clinical consideration in subjects with AD. Neflamapimod (VX-745) which selectively inhibits p38 mitogen-activated protein kinase alpha (p38 MAPKα), an enzyme involved in neuroinflammation and possibly Aβ toxicity (Alam, 2015) is another anti-inflammatory small molecule designed to tackle AD. A good safety profile and results of recently completed proof-of-concept study where possible improvement in episodic memory and impact on Aβ production was found in patients with early AD (Scheltens et al., 2018) supported further clinical evaluation. However, newly released data from phase 2b study showed that neflamapimod failed to significantly improve memory although it decreased levels of hyperphosphorylated tau and total tau in the CSF of treated patients compared to those given a placebo (Scheltens et al., 2019). Masitinib, a selective tyrosine kinase inhibitor is in clinical consideration for AD treatment because of its presumed potential to modulate inflammatory and neurodegenerative processes, and disrupt Aβ signaling cascade. Experimental results (Li et al., 2020) and data of cognitive improvement in AD patients in phase 2 study supported its further development and multicenter phase 3 study for its effectiveness as an add-on therapy in patients on stable dose treatment with cholinesterase inhibitors and/or memantine has recently completed, but results are yet expected to come. A current trial also evaluates NE3107, an orally bioavailable synthetic sterol derivative with anti-inflammatory property which can supposedly target multiple mechanisms of pathology in AD (Table 1). The triggering

receptor expressed on myeloid cells 2 (TREM2) enhances microglial activity for Aβ uptake and modulates inflammatory signaling in AD. Moreover, mutations in the TREM2 gene have been found to increase risk for sAD similarly as observed in APOE-ε4 carriers (Gratuze et al., 2018). Also, increased levels of soluble TREM2 protein in the CSF are observed in the early symptomatic phase of AD reflecting changes of microglia activation status (Suarez-Calvet et al., 2016). These together make TREM2 an attractive target, and monoclonal TREM2 agonistic antibody AL002 heads to first-in-human study for testing safety, tolerability and its pharmacokinetic/pharmacodynamic properties (Long et al., 2019). In parallel, an antibody targeting SIGLEC-3 microglial receptor that interacts with TREM2 signaling is also in clinical development. The rationale behind this anti-SIGLEC-3 antibody named AL003 is that counteracting the function of this receptor can be more feasible way to tweak microglial activation (Timmins, 2019).

A novel strategy to harness neuroinflammation and therefore mitigate cognitive impairment in AD by remodeling the gut microbiota recently brought about approval of sodium oligomannate by China's regulatory agency (Wang et al., 2019). Even though conditional, this approval is the first in almost two decade-lasting effort to get new AD treatment to market. The drug is currently in US clinical trial for efficacy and safety evaluation in patients with mild-to-moderate AD (Table 1).

3. Repurposed drugs

Slow pace of development of new and highly needed effective treatments for AD set off identification of repurposable drug candidates. Evidence of frequent but usually clinically silent episodes of epileptiform hyperexcitability in AD patients, which occur in early disease stage and likely contribute to cognitive deficiency (Vossel et al., 2017) propose the use of antiepileptics. Levetiracetam, acting through SV2A glycoprotein to reduce presynaptic neurotransmitter release, is considered to be good candidate for stabilization of neuronal networks hyperexcitability and improvement of AD-related cognitive symptoms (Musaeus et al., 2017), and several clinical studies currently evaluate its effects in subjects with AD including one phase 3 trial (Table 1). Daratumumab is an FDA-approved human IgG antibody that targets CD38. It is in clinical treatment of multiple myeloma, but has a broad immunomodulatory effects including role in apoptosis and immune-mediated cytotoxicity (Touzeau and Moreau, 2017). The findings of increased expression on CD8+ T-cells in the blood during early stage of AD (Sommer et al., 2017), suggesting T-cells activation in the brain and possible toxic effects, triggered clinical exploration of daratumumab in mild-to-moderate AD patients. ALZT-OP1 represents combination of two FDA-approved drugs, mast cell stabilizer cromolyn and ibuprofen. Synergistic action of these drugs was shown to promote microglia recruitment and phagocytosis of Aβ deposits (Hori et al., 2015; Zhang et al., 2018), recommending its further clinical evaluation (Table 1).

Addressing the modifiable risk factors for developing AD was another option in consideration for AD treatment. Based on the premise that insulin resistance and peripheral hyperinsulinemia contribute to AD, antidiabetics such as insulin, and thiazolidinediones, rosiglitazone and pioglitazone, were tested in clinical studies (Arnold et al., 2018). In the current AD drug pipeline, long acting formulation of metformin is being tested in MCI

subjects without diabetes, for prevention of AD development (Luchsinger and Zetterberg, 2020). Notion that elevated cholesterol levels might promote disease progression triggered evaluation of statins, lipid-lowering drugs (Sparks, 2011), while neurovascular alterations well-known in AD prompted clinical testing of sartans, angiotensin II receptors blockers (Cooper et al., 2018). However, neither antidiabetics, statins nor sartans have shown efficacy on cognition or global function in AD patients so far.

4. Non-pharmacological treatments

The critical need for effective AD therapy has initiated exploration of several non-pharmacological interventions including lifestyle modification such as physical exercise, different diets, cognitive therapy (e.g. EXERT study https://www.exertstudy.org/) and neurostimulation. Currently, there are approximately 30 active clinical trials evaluating these therapeutics approaches. The preclinical and preliminary human studies testing these alternative strategies have signaled that some may have positive effects on maintaining or improving cognitive function and other aspects of well-being in people with AD, thus strengthening their further clinical development.

Lifestyle modification with regular aerobic exercising is considered as an approach with potential for delaying disease onset, slowing cognitive decline, and reducing the brain atrophy due to AD. However, a randomized multicenter trial exploring effects of aerobic fitness in patients with mild-to-moderate AD did not support an impact of regular physical training on AD-related structural and functional brain changes (Clemmensen et al., 2020; Frederiksen et al., 2018). Another attractive therapeutic concept to target attention and memory dysfunctions in AD patients is the use of personalized, interactive computer-based cognitive neurofeedback training. Although it demonstrated feasibility for use in elderly (Yeo et al., 2018), a large systemic review did not find strong evidence for meaningful benefits of this approach in improving either global cognitive functioning or performance in distinctive cognitive domains to support its certain clinical importance in AD treatment (Gates et al., 2020).

Multiple different neurostimulation techniques are in evaluation in current AD clinical trials, including deep brain stimulation, transcranial magnetic stimulation, transcranial alternating or direct current stimulation, multi-sensory gamma-range stimulation and photobiomodulation (Table 2). The underlying idea of all these approaches is that stimulating brain areas vulnerable to the developing AD pathology can modulate neural network dysfunctions and aberrant connectivity in memory circuitry and default mode network (Fig. 1) causing a clinically meaningful reduction of disease progression (Marron et al., 2018). Application of focused ultrasound stimulations (including low-intensity focused ultrasound and magnetic resonance guided focused ultrasound) are currently explored whether it can improve Aβ clearance and/or transiently open blood-brain barrier promoting CNS exposure of therapeutic agents (antibodies or other large molecule biologics) in the brain targeted regions of AD patients (Lee et al., 2019).

Deep brain stimulation (DBS) has emerged as a promising technique for treating various neuropsychiatric disorders. It involves the delivery of electrical current into specific areas of

the brain through implanted electrodes. Although the mechanism of DBS is still not completely understood, preclinical findings from animal experiments and clinical observations highlight a number of possible mechanisms as to how DBS may affect AD progression and memory deterioration (Jakobs et al., 2019; Lam et al., 2020; McKinnon et al., 2019). In transgenic AD rats, chronic DBS of the fornix significantly reduces amyloid deposition in the hippocampus and cortex, inflammation, and neuronal loss (Leplus et al., 2019). Recent phase 2 clinical study have shown that targeting fornix bilaterally with DBS is safe and well tolerated procedure. It increases glucose metabolism in temporo-parietal region and decreases atrophy in the hippocampus and default mode network exerting cognitive improvement in AD patients (Lozano et al., 2016). Interestingly this study indicated greater benefits in patients aged 65 and older comparing to younger patients (Leoutsakos et al., 2018). Currently, larger phase 2b/3 trial of fornix DBS is testing efficacy of two different stimulation paradigms, low frequency (40 Hz) and high frequency (130 Hz) in older (> 65 years) mild AD patients, in whom changes in glucose PET imaging and fluid biomarkers (Aβ and tau protein) are being monitored.

Non-invasive brain stimulation methods as treatment option for improving cognitive impairments present in neurodegenerative diseases attracted great interest (Sanches et al., 2020). In recent years, potential of transcranial magnetic stimulation (TMS) of the brain to reduce cognitive symptoms in AD, particularly in the early stage of disease, has been actively explored (Dong et al., 2018; Weiler et al., 2020). Evidence suggests that patterned repetitive TMS can induce long-lasting changes in neural plasticity which are associated with improved cognition both in patients (Kumar et al., 2017; Turriziani et al., 2019; Wang et al., 2020) and rodent models of AD (Huang et al., 2017; Zhen et al., 2017). Furthermore, it has been reported that high-frequency repetitive TMS of the precuneus resulted in improvement in episodic memory together with enhancement of brain oscillations in the beta band and a modification of functional connections within the default mode network in mild AD patients (Koch et al., 2018). The meta-analysis of the effectiveness of various patterns of repetitive TMS on different cognitive domains in patients with mild cognitive impairment and AD (Chou et al., 2019) revealed that both high frequency stimulation over the left dorsolateral prefrontal cortex and low frequency stimulation over the same region at the right side significantly improved memory function. Coupling repetitive TMS of distinct brain regions (prefrontal and somatosensory associative cortices) with adaptive computerized cognitive training in AD patients presents an innovative therapeutic concept that is rationalized on advantage in the synergy between exogenous (TMS) and endogenous (cognitive engagement) concomitant stimulations (Rabey and Dobronevsky, 2016). This combinatory treatment modality is currently under active exploration in patients with MCI and mild-to-moderate AD, and several pivotal short-duration (up to 6 weeks) clinical studies already provided encouraging evidence of low- risk benefits in cognitive improvement which lasted beyond treatment interventions, and surpassed effects of the pharmacological standard of care of those patients (Bagattini et al., 2020; Sabbagh et al., 2020). Interestingly, even though paired TMS-cognitive training seems promising, recent review of one such trial (NCT02166827) by the FDA expert panel, did not support its clinical approval yet, emphasizing the need for further investigation of this treatment approach.

Other noninvasive brain stimulation methods, such as transcranial alternating current stimulation (tACS), transcranial direct current stimulation (tDCS), and transcranial electromagnetic treatment (TEMT) are also under exploration for reducing or delaying cognitive decline and ameliorating neuropsychiatric symptoms associated with AD. It is presumed that electrical current stimulations either with tACS or tDCS can potentially normalize excitatory and inhibitory balance or modulate neuronal activity in the cortex, particularly in vulnerable cortical regions related to memory, attention and executive functions (for review see Grover et al., 2021). However, the exact mechanisms underlying the effects of tACS and tDCS have not been fully established yet (e.g. see Voroslakos et al., 2018). Similarly, biophysics and mode of action of the application of pulsed transcranial infrared or near-infrared light stimulation technology known as photobiomodulation (Zomorrodi et al., 2019), have not been explored to satisfaction. Therefore, appropriately designed, multi-site randomized large-size clinical trials are necessary to further explore the full therapeutic potential of these neuromodulation techniques in AD patients (Gonsalvez et al., 2017), and confirm initial promising results before FDA consideration as valid clinical treatments.

Currently, an alternative, non-invasive brain-stimulation method GammaSense, is evaluated in MCI and AD patients. Based on recent findings showing that 40 Hz gamma frequency audio-visual sensory stimulation reverses AD-related pathologies in transgenic mice (Iaccarino et al., 2016; Martorell et al., 2019), patients are exposed to 40 Hz audio-visual sensory stimulation over a period of time. Similar long-lasting gamma-band oscillation can be also elicited using sensory stimulation in humans and mild-to-moderate AD patients (Hajós et al., 2020; Tsoneva et al., 2015; Vialatte et al., 2010), and current clinical trials investigate if similar downstream mechanisms would be present in AD patients which were observed in experimental animal studies. The therapeutic effects of long-term, at-home gamma sensory stimulation on severity of clinical symptoms and AD biomarkers, such as Aβ PET signals are being investigated in clinical trials with MCI and AD subjects (NCT03543878; NCT03556280). Although no neuromodulation treatment of AD patients has been approved by FDA up to date, the agency granted Breakthrough Device Designation for three brain stimulation methods in 2020 and 2021. These neuromodulation approaches include therapy with DBS (Functional Neuromodulation, Inc) for patients 65 years and older with mild probable AD, therapy with TEMT (NeuroEM Therapeutics, Inc) for AD patients, and therapy with gamma sensory stimulation system (Cognito Therapeutics) for cognitive and functional symptoms associated with AD.

Advances in our understanding of pathological neuronal activities together with a better insight into interactions between brain stimulation and on-going neuronal activity will further the methodology and effectiveness of neuromodulation, leading to an improved clinical therapeutic outcome. Emerging closed-loop technology represents an inventive approach based on bidirectional brain-computer interface that enables optimization of stimulation parameters through real-time decoding of neuronal activities. In this adaptive neurostimulation paradigm, neurochemical and electrophysiological disease-specific signals recorded with intracranial microelectrodes or EEG are using for precisely-timed and feedback-responsive adjusting stimulations in individual patients (Price et al., 2020), making the closed-loop method personalized and informed treatment modality with the potential for

achieving better results with fewer side effects. Although there is still a relatively small number of available clinical studies using this approach, data on closed-loop DBS targeting lateral temporal cortex and fornix for improving memory encoding (Ezzyat et al., 2018; Mankin and Fried, 2020; Senova et al., 2018), as well as closed-loop acoustic stimulation during slow-wave sleep for enhancing memory consolidation (Ngo et al., 2013; Wei et al., 2020) suggest its applicability for AD treatment. Given the advantage of temporal precision for customized neurostimulation delivery with this approach, it can be possibly used for selective enhancement of reduced EEG rhythms associated with cognitive dysfunctions in AD (Babiloni et al., 2020), or for instantaneous suppression of aberrant neuronal activity such as clinically silent epileptic discharges (Vossel et al., 2017) found in some of these patients. Designing and further developing of neurostimulation methods with ability for fine-tuning stimulation parameters like closed-loop stimulations, can make neuromodulation part of precision medicine for AD therapy.

5. Functional biomarkers for assessing brain integrity and performance reflecting cognitive abilities

Functional biomarkers indicating global brain function and its subtle changes in response to therapy are underdeveloped. Many of the current clinical tests assessing cognitive function have low sensitivity and are not well suited to monitor short-term changes in patients' everyday function in response to treatment. Currently, a number of established and novel methods are under evaluation if they can detect brain function in prodromal and early AD or MCI, including neuroimaging methods, measurements of brain blood flow and various neurophysiological techniques (Fig. 2).

Functional magnetic resonance imaging (MRI) provides information on the brain metabolic activity by measuring blood oxygen level dependence and cerebral blood flow, detecting abnormal brain activities in MCI and AD patients, either at resting state or during cognitive challenges. Several, task-free magnetic resonance imaging (rsfMRI) reflecting default mode network (DMN) activity has shown altered connectivity in this network, including reduced connectivity between posterior cingulate cortex and precuneus in MCI or early stage of AD (Khan et al., 2020; Young et al., 2020). Task-based fMRI studies showed both hyper- and hypoactivation, which might reflect disease progression, but methodological differences between individual studies could also contribute to these findings (Young et al., 2020). This conundrum is well demonstrated by a recent report, showing that lack of established and validated analytical methods for processing complex data resulted in substantial variation in the results from 70 laboratories analyzing the exact same fMRI data (Botvinik-Nezer et al., 2020), demonstrating the challenges for integrating fMRI methods in drug discovery. Measuring cerebral glucose hypometabolism by 18F-FDG PET can detect declined activity in localized brain regions most closely associated with dementia, therefore could be also considered to discriminate in dementia due to AD, frontotemporal lobar degeneration, and dementia with Lewy bodies (Bailly et al., 2015; Moonis et al., 2020). Arterial spin labeling (ALS) MRI is an alternative method for measuring brain perfusion reflecting neuronal activity. Since ALS-MRI does not require a PET tracer, it is a clear advantage, particularly if patients are monitored longitudinally. Due to high variation in study design, such as

heterogeneity of patient/control group selection, differences in disease progression and methodology applied, it is hard to draw a coherent conclusion from the available ALS data (Sierra-Marcos, 2017). Nevertheless, some overlapping patterns in cortical hypoperfusion of MCI patients have become apparent, including bilateral parietal lobes, posterior cingulate cortex, precuneus and frontal lobes compared to healthy controls (Binnewijzend et al., 2013). Disrupted frontal and long-range connectivity in the resting state has been also reported in MCI and AD patients compared to individuals with normal cognition using functional near-infrared spectroscopy (fNIRS), to the study of cerebral oxygenation (Yeung and Chan, 2020). Although these functional neuroimaging methods have high sensitivity to detect functional brain abnormalities associated with dementia, but due to their lack of diagnostic specificity they need to be supplemented by disease-relevant objective markers, such as pathological CSF or plasma Aβ/tau or Aβ/tau-PET findings in AD patients. Also, once changes in functional neuroimaging signals are well established markers of disease progression, theoretically they will be sensitive enough to detect sublime changes related to cognitive function in response to drug treatment. Nevertheless, until now, application of these neuroimaging methods provided only limited values to drug discovery due to the shortcomings in experimental design and data interpretation (Canu et al., 2018).

Recently, various neurophysiological signals have been explored in MCI and AD patients reflecting brain global brain function and integrity of neuronal circuits (Babiloni et al., 2020; Horvath et al., 2018). Although these neurophysiological markers could be associated most closely with a certain type of neurodegenerative diseases, they are mostly agnostic to the exact underlying pathology. A broad variety of neurophysiological signals have been explored in MCI and AD patients, include alterations in power distribution of spontaneous electroencephalography (EEG) or magnetoencephalography (MEG). One of the most consistent findings is a shift of EEG power distribution to lower frequencies, resulting in a widespread higher delta and theta power and reduced posterior alpha and beta power, indicating a general slowing of cortical activity in MCI and AD patients (Babiloni et al., 2020; Horvath et al., 2018; Rossini et al., 2020). Similarly, power spectral analysis of MEG has consistently demonstrated slowing of brain activity in AD patients, displaying a reduction in the frequency of the main power spectrum peak or reduction in alpha peak (Lopez-Sanz et al., 2019). Both EEG and MEG signals correlate well with the severity of neurodegeneration assessed by MRI or Aβ pathology and shifting in power spectra to lower frequencies has been suggested as an excellent marker for predicting disease progression from MCI to AD, or from mild to a more severe AD stage. Accordingly, it has been found that integrative EEG markers can predict conversion from MCI to AD with high degree (>80%) of both sensitivity and specificity (Poil et al., 2013). A longitudinal study pairing frontal EEG recording with working memory task performance demonstrated that EEG signals can predict individualized MCI risk few years before clinical diagnosis (Jiang et al., 2021). Moreover, measuring EEG microstate complexity, which has potential to give insight into altered brain dynamics underlying cognitive impairment, was shown to highly predict progression from MCI to AD in a recent small cohort study (Tait et al., 2020), providing additional evidence for validity of neurophysiological markers to index early, prodromal brain dysfunctions associated with the disease.

EEG spectral power density changes in AD patients were well recognized and subsequently some neurophysiological studies were included in AD drug development in the late 1990s. These initial, and by now mostly forgotten studies showed an excellent correlation between acute EEG changes and benefit of clinical symptoms in response to acetylcholinesterase inhibitors, even potentially predicting clinical outcome of the treatment (Almkvist et al., 2001; Knott, 2000; Lanctot et al., 2003). None of the clinical trials on BACE1 inhibitors, γ-secretase inhibitors/modulators, or Aβ antibodies included EEG or neurophysiological measurement. In light of the clinical trials showing target engagements of BACE1 inhibitors and Aβ antibodies reducing Aβ plaque loads but without improvement of cognitive function, or even accelerating cognitive and morphological decline (*see above*), development and validation of an objective assessment of global brain function is imperative. An addition to a validated target-engagement biomarker, it would be particularly beneficial having markers of global brain function predicting clinical outcome in trails of disease modifying therapies lasting up to two or more years. These functional biomarkers could be based and designed on neuroimaging and/or neurophysiological findings. In addition to resting EEG/MEG spectra, additional neurophysiological tests could be considered, involving neurophysiological signals of sensory processing and cognitive tasks, together with application of cutting-edge signal processing.

In summary, identification, validation and implementation of biomarkers that indicate subtle AD-related alterations during transition from normal cognitive function to early dementia, and those potentially orthogonal to Aβ and tau pathology (Whelan et al., 2019) could improve chances of success in AD drug development. Such biomarkers will increase likelihood of optimum timing and dosing, target engagement and use of endpoints that are sensitive enough to detect response to a given treatment in trial. They can be also useful for proper selection of AD patients for clinical trials and to infer individual, precision-medicine approach particularly in light of recent report (Qiu et al., 2019) of phenotypic heterogeneity among typical amyloid-positive, mild-to-moderate AD patient population.

6. Concluding remarks

There must be multiple reasons for failing of almost all clinical trials for AD therapy. Limitations due to preclinical models is one: though some drug candidates show certain signals of efficacy (or at least target engagement) in AD related transgenic animals, they turn out to be without any clinical benefits in patients. It is safe to conclude that animal models do not capture the complexity of AD pathologies, which are not exclusively related to Aβ or tau, but it includes cerebrovascular, metabolic and CNS innate immunity pathologies. Similarly, it has been pointed out that preclinical models do not faithfully mimic interactions between the main pathologies of the disease and processes underlying aging as observed in humans (Drummond and Wisniewski, 2017). Therefore, a better insight to AD pathologies based on novel findings in genomics, proteomics, and metabolomics together with a better understanding of interactions between pathological neuronal activities and disease progression will identify novel, hitherto unrecognized drug targets. Other limitations relate to timing of intervention with therapy. Since there are no foreseen treatment options to restore or reverse neuronal death and large brain volume loss in AD patients, current clinical trials are recruiting patients at earlier disease stage, or even prodromal stage. Therefore,

development of novel predictive biomarkers for both diagnostics of prodromal AD and disease progression will have a profound benefit for developing disease-modifying therapies. Similarly, better functional assessment of brain function is needed, either with validated neuroimaging or neurophysiological methods. These markers should be sensitive enough to detect subtle improvements in brain function which are not easily detectable by currently used clinical cognitive assessments. Recognized surrogate markers of efficacy, reflecting global brain function would support clinical trials by providing early signals if the tested therapy would lead to clinical benefits or otherwise.

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Highlights

- Development of AD disease-modifying therapies is futile thus far
- Research efforts for effective AD therapy broaden targets and treatment options
- Current biomarkers are not reliable predictors of effectiveness of new treatments
- Advanced functional brain assessment tools can increase success in clinical trials

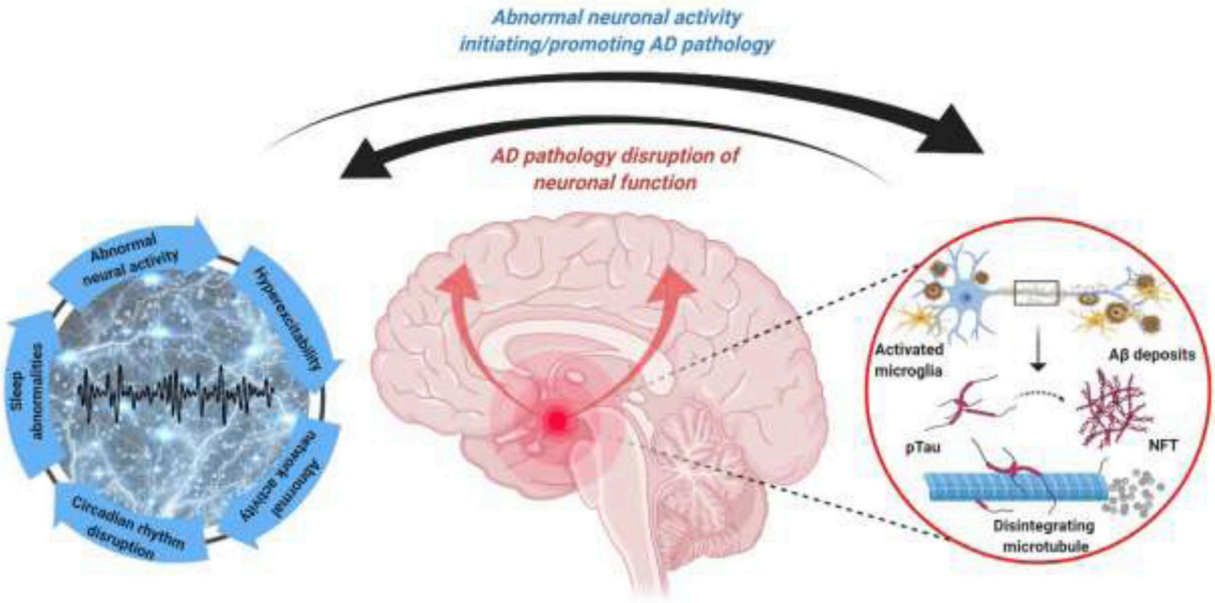

Figure 1.

Bidirectional interaction between AD pathology and abnormal neuronal activity. Detrimental effects of AD related pathology, such as Aβ and tau oligomers are well known, resulting in abnormal neuronal activity and neuronal network function. These abnormalities lead to hyperexcitability, epileptiform activity, altered sleep/wake activity, circadian rhythm, and disruption of coherent network activities supporting cognitive functions. However, aberrant neuronal and neuronal network activities, such as sleep abnormalities can initiate and further disease progression. Therefore, a bidirectional relationship between pathological neuronal activity and AD can be proposed, indicating a vicious circle contributing to AD progression. Figure created with BioRender.com

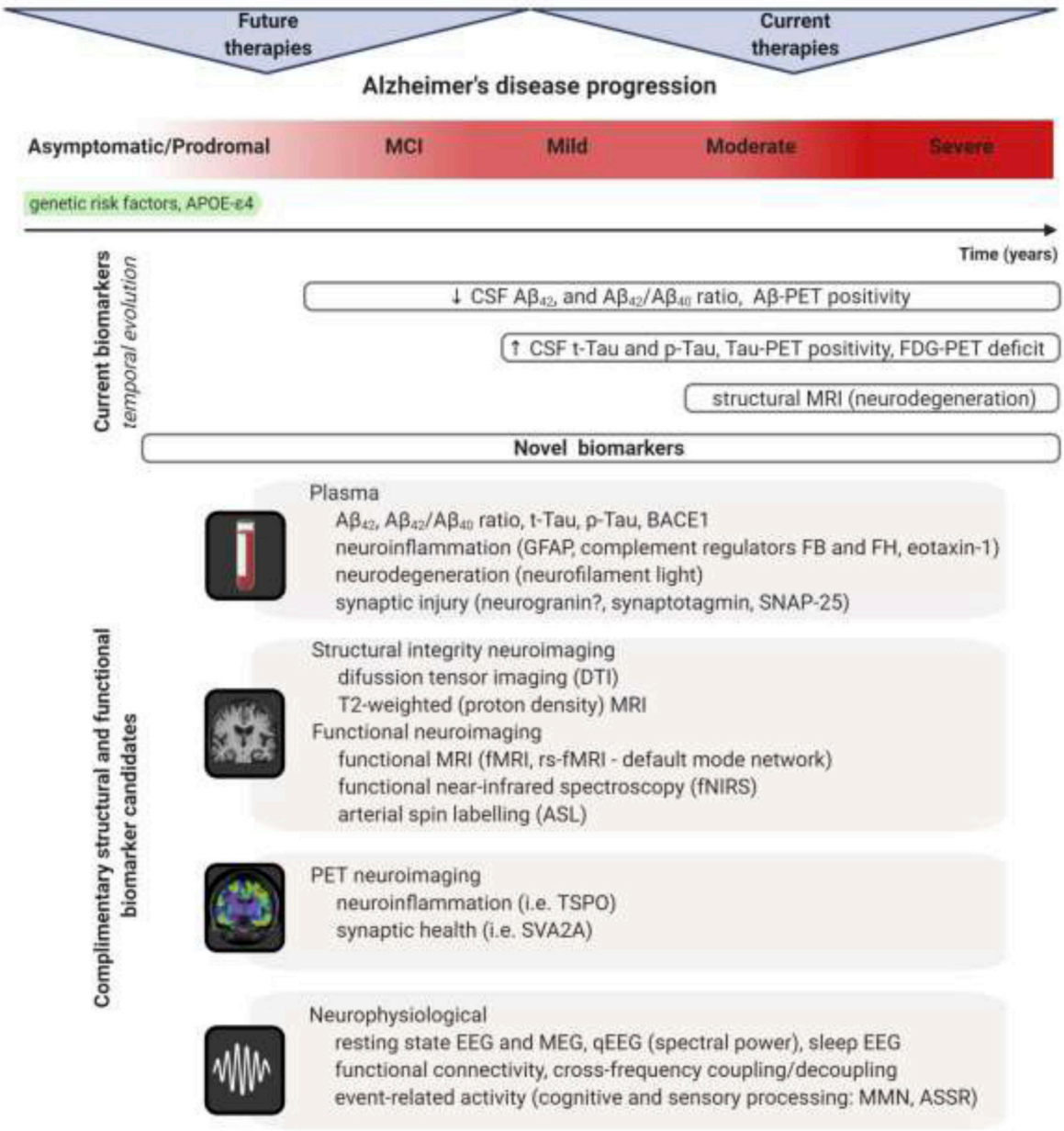

Figure 2.

Dynamical changes of biomarkers reflecting core AD pathologies during the course of disease progression. The process of AD begins in the brain with dormant deterioration of neurons and circuits lasting years, probably decades, before the first symptoms emerge. This asymptomatic/prodromal period of the disease represents the desirable window for disease-modifying therapeutic interventions. Currently used biomarker toolbox comprising of cerebrospinal fluid (CSF) and positron emission tomography (PET) measures of Aβ and tau has high diagnostic value indicating AD pathological processes, but cannot reliably index subtle functional changes in the advent of cognitive symptoms or predict treatment response in clinical trials. Additionally, ^{18}F-2fluoro-2-deoxy-D-glucose PET (FDG-PET), measuring neuronal activity through resting state metabolic rate of glucose in the brain, as well as

magnetic resonance imaging (MRI) measuring degree of neurodegeneration are nonspecific markers and may indicate several etiologies of brain damage. Improved analytical techniques facilitate development of novel biomarkers with potential for refined and/or less invasive measuring of AD associated morphological and functional alterations through diverse transition states of the disease. Plasma Aβ and tau profiles, and set of specific markers for neuroinflammation, neurodegeneration, and synaptic injury have emerged as clinically valid measures for early diagnosis and prediction of disease progression (Hampel et al., 2020; Mila-Aloma et al., 2019; Morgan et al., 2019). Advanced neuroimaging methods demonstrate high degree of sensitivity and specificity for detection of initial pathologic and functional changes which are important for staging progression and for selecting patients for clinical trials during the prodromal phase of AD (Marquez and Yassa, 2019). Certain neurophysiological signals and applied innovative approaches for analyses are proven to be valid proxies for subtle abnormalities at neural network level and for assessment of global brain function (Babiloni et al., 2020; Stoiljkovic et al., 2019). Pertinent combination of these novel biomarkers with traditional AD biomarkers can enable more sensitive tracking of early disease-associated alterations and specifically estimate the likelihood of responding to next generation AD treatment. *Abbreviations*: MCI – mild cognitive impairment; GFAP – glial fibrillary acidic protein; FB – complement factor B; FH – complement factor H; SNAP-25 – synaptosomal-associated protein, 25kDa; rs-fMRI – resting state functional magnetic resonance imaging; TSPO – translocator protein; SVA2A – synaptic vesicle protein 2A; MEG – magnetoencephalography; qEEG – quantitative electroencephalography; MMN – mismatch negativity; ASSR – auditory steady-state response.

Table 1.

Active Phase 3 clinical trials of pharmacological treatments in AD (clinicaltrials.gov as of February 10, 2021)

Investigational drug	Study population/treatment target	Type of treatment	Clinical trial identifier
Disease modifying treatment			
Gantenerumab	prodromal to mild AD	fully human monoclonal antibody	NCT03443973 NCT03444870 NCT02051608 NCT01224106
Solanezumab	asymptomatic AD, positive amyloid PET	humanized monoclonal antibody	NCT02008357
Aducanumab	prodromal to mild AD, previous participants in aducanumab clinical study	fully human monoclonal antibody	NCT04241068
Lecanemab (BAN2401)	prodromal to mild AD	humanized monoclonal antibody	NCT03887455 NCT04468659
TRx0237 (Methylene blue)	MCI and probable AD, positive amyloid PET	tau aggregation inhibitor	NCT03446001
AGB101 (Levetiracetam)	prodromal AD	anticonvulsant, SV2A modulator	NCT03486938
BHV-4157 (Riluzole prodrug)	mild to moderate AD	glutamate release inhibitor	NCT03605667
ALZT-OP1 (cromolyn +ibuprofen)	prodromal AD	mast cell stabilizer, microglial modulator, anti-inflammatory	NCT02547818
Sodium Oligomannate (GV-971)	mild to moderate AD	bioactive marine-derived oligosaccharide	NCT04520412
Tricaprilin	mild to moderate AD	inductor of ketosis	NCT04187547
NE3107	mild to moderate AD	sterol derivative	NCT04669028
COR388	mild to moderate AD	gingipains inhibitor	NCT03823404
Preventional treatment			
CAD106	elderly homozygous ApoE4 carriers at risk of clinical AD	anti-Aβ vaccine + BACE1 inhibitor	NCT02565511
Solenezumab	individuals at risk due to AD-causing mutations	monoclonal Aβ antibodies	NCT01760005
Metformin	early and late MCI	antihyperglycemic agent	NCT04098666
Symptomatic treatment			
Brexpiprazole	agitation due to AD	dopamine D_2 receptors partial agonist	NCT03594123 NCT03724942 NCT03548584 NCT03620981
AVP-786	agitation due to AD	NMDA receptors antagonist and sigma 1 receptors agonist	NCT03393520 NCT02446132
Escitalopram	agitation due to AD	selective serotonin reuptake inhibitor	NCT03108846
Mirtazapine	agitation due to AD	adrenergic α2 and serotonin 5-HT_2/5-HT_3 receptors antagonist	NCT03031184
Nabilone	agitation due to AD	synthetic cannabinoid	NCT04516057
Octohydroaminoacridine succinate	cognitive deficiencies in mild to moderate AD	acetylcholinesterase inhibitor	NCT03283059
ANAVEX2–73	cognitive deficiencies in prodromal AD	Sigma1 receptor agonist	NCT03790709
Guanfacine	attention deficit in AD	adrenergic α2 receptors agonist	NCT03116126

Investigational drug	Study population/treatment target	Type of treatment	Clinical trial identifier
Methylphenidate	apathy in AD	dopamine and norepinephrine reuptake inhibitor	NCT02346201

Table 2.

Active clinical trials of non-pharmacological neuromodulatory interventions in AD (clinicaltrials.gov as of February 10, 2021)

Investigational technique/device	Study population	Targeted area	Clinical trial identifier
Invasive brain stimulation			
Deep Brain Stimulation (DBS) - electrical, implantable device	mild AD mild to moderate AD	Fornix Nucleus basalis of Meynert	NCT03622905 NCT03959124
Non-invasive brain stimulation			
repetitive Transcranial Magnetic Stimulation (rTMS) - coil induced depolarizing magnetic field	mild AD	DMN-precuneus (20 Hz)	NCT03778151
		Dorsolateral prefrontal cortex	NCT04263194
	mild to moderate AD (with depression)	Dorsolateral prefrontal cortex unilateral (H1-coil)	NCT03665831
		Lateral parietal areas	NCT04260724
	mild to moderate AD (with apathy)	Dorsolateral prefrontal cortex bilateral (H-coil)	NCT04562506
		Dorsolateral prefrontal cortex (10 Hz)	NCT02190084
	prodromal AD (amnestic MCI)	DMN-angular gyrus (20 Hz)	NCT04045990
		DMN-prespecified cortical areas	NCT04294888
rTMS - intermittent Theta Burst (>5 Hz) Stimulation (iTBS)	MCI and mild AD		NCT04555941
Transcranial Electromagnetic Treatment (TEMT)	mild to moderate AD	MemorEM 1000 head device emitting electromagnetic waves in radiofrequency range	NCT03927040 NCT04271163
transcranial Alternating Current Stimulation (tACS) - sinusoidal low intensity electric current	mild to moderate AD	Areas with maximal tracer uptake on the amyloid PET (40 Hz)	NCT03290326 NCT03412604 NCT03880240 NCT04515433
	mild AD	Superior parietal cortex (40 Hz)	NCT03920826
		Wide cortical area (40 Hz, Nexalin device and conductive pads at forehead and mastoid processes) Wide cortical area (4 Hz, Nexalin device and conductive pads at forehead and mastoid processes)	NCT04088643
transcranial Direct Current Stimulation (tDCS) - direct low intensity electric current	mild AD mild to moderate AD	Dorsolateral prefrontal cortex	NCT03288363 NCT04404153
Sensory stimulation -GammaSense (audiovisual stimulation in gamma range)	MCI prodromal AD mild to moderate AD	Visual and auditory brain areas (40 Hz light flickers and tone pulses)	NCT03543878 NCT03556280 NCT03661034
Photobiomodulation (PBM) - near-infrared light stimulation	mild to moderate AD	transcranial/intranasal delivery of near infrared light 40 Hz	NCT03405662 NCT03160027
	subjects at risk of AD	pulses	NCT04018092
Low Intensity Focused Ultrasound Pulsation	MCI and mild AD	Hippocampus (50ms long bursts at 10 Hz)	NCT03347084