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REVIEW ARTICLE

New therapeutics beyond amyloid-β and tau for the treatment of Alzheimer's disease

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As the population ages, Alzheimer's disease (AD), the most common neurodegenerative disease in elderly people, will impose social and economic burdens to the world. Currently approved drugs for the treatment of AD including cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and an *N*-methyl-*D*-aspartic acid receptor antagonist (memantine) are symptomatic but poorly affect the progression of the disease. In recent decades, the concept of amyloid-β (Aβ) cascade and tau hyperphosphorylation leading to AD has dominated AD drug development. However, pharmacotherapies targeting Aβ and tau have limited success. It is generally believed that AD is caused by multiple pathological processes resulting from Aβ abnormality, tau phosphorylation, neuroinflammation, neurotransmitter dysregulation, and oxidative stress. In this review we updated the recent development of new therapeutics that regulate neurotransmitters, inflammation, lipid metabolism, autophagy, microbiota, circadian rhythm, and disease-modified genes for AD in preclinical research and clinical trials. It is to emphasize the importance of early diagnosis and multiple-target intervention, which may provide a promising outcome for AD treatment.

Keywords: Alzheimer's disease; new therapeutics; gut microbiota regulators; anti-inflammatory drugs; lipid metabolism regulators; autophagic modifiers; circadian rhythm regulators; gene and cell therapies

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in elderly people. Worldwide, ~50 million people were living with dementia in 2019, and there are nearly 10 million new cases every year. The total number of people with dementia is projected to reach 152 million in 2050 [1]. As the population ages, AD will undoubtedly impose significant social and economic burdens to the world. Currently approved drugs for AD in clinical use, such as cholinesterase inhibitors (ChEIs, including donepezil, rivastigmine, and galantamine) and an *N*-methyl-*D*-aspartic acid (NMDA) receptor antagonist (memantine), have therapeutic effects on symptoms but do not effectively slow the progression of the disease [2]. Although great efforts have been made to develop new drugs for AD, current clinical trials have not yet yielded promising results. Amyloid-β (Aβ)-targeted immunotherapies and β-secretase (BACE1) inhibitors such as AN-1792 [3], bapineuzumab [4], solanezumab [5], aducanumab [6], gantenerumab [7], verubecestat [8], atabecestat [9], lanabecestat [10], and elenbecestat (E2609) [11] have shown a lack of efficacy in improving cognition in AD patients. Only a few therapeutics targeting Aβ and tau are currently still in clinical trials, including CAD106 [12], crenezumab [13], AADvac1 [14], ABBV-8E12 [15], and BIIB092 [16].

Increasing evidence has shown that the pathogenesis of AD is a complex pathological process. Senile plaques of deposited Aβ and neurofibrillary tangles formed by hyperphosphorylated tau are the two main pathological hallmarks of the AD brain. These abnormally accumulated proteins can cause synaptic damage, neuritic injury, and neuronal death, leading to neurodegeneration and cognitive impairment [17, 18]. In addition to Aβ and tau pathologies, evidence has also shown that chronic activation of the immune system by these protein aggregations may result in secretion of proinflammatory cytokines; chemokines; and neurotoxins including reactive oxygen species (ROS), nitric oxide, and excitatory amino acids, which can cause further neuronal damage and neurodegeneration [19, 20]. Excessive ROS production and impaired antioxidant defense cause oxidative stress in the AD brain, as evidenced by significantly increased oxidation products of proteins, lipids, DNA and RNA [21]. Mitochondrial dysfunction featuring reduced mitochondrial membrane potential, increased permeability, and excessive ROS production has also been reported in AD [22, 23]. Furthermore, the autophagy-lysosome system that degrades Aβ and various forms of tau protein has been found to be compromised in the AD brain [24].

On the other hand, acetylcholine is a major neurotransmitter in brain areas including the cortex, basal ganglia, and basal forebrain, and cholinergic transmission is critical for memory, learning, attention, and other higher brain functions [25]. The cholinergic hypothesis of AD pathogenesis suggests that dysfunction and degeneration of cholinergic neurons in limbic and neocortical systems contribute substantially to the memory and orientation loss, behavioral alterations, and abnormal personality that arise in AD patients [25]. Thus, ChEIs that increase the availability of

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acetylcholine at synapses are helpful for relieving symptoms of AD. In addition to cognitive impairment, behavioral and psychological symptoms such as agitation, aggression, depression, apathy, nighttime behaviors, and sleep disturbance are also reported in AD patients [26]. New pharmacotherapeutics for agitation and psychosis associated with AD, such as pimavanserin, scyllo-inositol, and mibampator, are in clinical trials [27]. In this article, we will focus on therapeutics for cognitive symptoms in AD beyond Aβ and tau in preclinical research and in clinical trials. In addition, since there is a strong correlation between sleep disturbance and cognition [28], we will also discuss the new development of sleep-related drugs to treat cognitive impairment in AD. It is believed that with a better understanding of the disease mechanisms of AD, more desirable and effective therapeutics will be developed to slow or even reverse the progression of AD.

THERAPEUTICS REGULATING NEUROTRANSMITTERS

New ChEIs

Based on the cholinergic hypothesis of AD, acetylcholine enhancers (including ChEIs) that can increase the level of acetylcholine at synapses may be helpful for AD treatment. Analogs and derivatives of the approved drugs donepezil and tacrine showed potential cholinesterase (ChE) inhibitory activity. A novel donepezil analog hybrid compound containing 2,3-dihydro-5,6-dimethoxy-1H-inden-1-one and piperazinium salts, which have inhibitory effects on acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), was less toxic than donepezil and inhibited BChE more effectively than donepezil or galantamine [29]. Tacrine-hydroxamate derivatives exhibited inhibitory activity against ChEs and histone deacetylase, and they also showed suppressive effects on Aβ42 self-aggregation and Aβ fibril formation [30].

Some natural compounds and herbal extracts are ChEIs that might be candidates for AD treatment. ZT-1, a novel analog of huperzine A, was well-tolerated by healthy volunteers [31]. Two benzophenanthridine alkaloids from *Zanthoxylum rigidum* root extract, namely, nitidine and avicine, showed dual inhibition of AChE and BChE and presented moderate Aβ42 anti-aggregation activity and monoamine oxidase A inhibition [32]. Helminthosporin, an anthraquinone isolated from *Rumex abyssinicus Jacq*., showed dual inhibitory action on AChE and BChE along with high blood–brain barrier permeability [33].

Other potential ChEIs are also under investigation. Methanesulfonyl fluoride, an irreversible inhibitor of AChE, was proven to be well-tolerated by healthy volunteers in a randomized placebo-controlled Phase I study [34]. 3-Arylbenzofuranone derivatives with AChE inhibitory activity similar to that of donepezil can also block monoamine oxidase B [35]. A bambuterol derivative lacking one of the carbamoyloxy groups on the benzene ring exhibited excellent ChE inhibition and the potential to permeate the blood–brain barrier, as did its analogs [36].

New NMDA receptor antagonists

Excitatory amino acid signaling, such as excitatory glutamatergic neurotransmission via NMDA receptors, is critical for synaptic plasticity and the survival of neurons. Excessive NMDA receptor activity results in excitotoxicity, which is mediated by excessive Ca^{2+} entry into neurons and causes gradual loss of synaptic function, neuronal death, and neurodegeneration in the AD brain [37]. Thus, NMDA receptor antagonists are potent anti-AD drugs. RL-208, a new NMDA receptor blocker, was shown to improve synaptic plasticity and decrease the protein levels of cyclin-dependent-like kinase-5 (CDK5) and the p25/p35 ratio, consequently lowering the phosphorylation of tau [38]. JCC-02, N-(3,5-dimethyladamantan-1-yl)-N′-(3-chlorophenyl) urea, is a novel NMDA receptor inhibitor for the treatment of AD, exhibiting blood–brain barrier permeability and anti-AD activity that improves cognitive and memory function [39]. A synthesized heterodimer (DT-010) of components isolated from the Chinese herbs *Salvia miltiorrhiza Bge*. and *Ligusticum chuanxiong Hort*. showed a protective effect against excitotoxicity by blocking the NMDA receptor in vitro [40]. Another compound, rhynchophylline, isolated from the Chinese herb *Uncaria rhynchophylla*, also showed inhibitory activity against NMDA receptors [41].

Adrenoceptor agonists

Guanfacine, an α-2A-adrenoceptor agonist that acts at postsynaptic α-2A receptors on prefrontal cortex spines, can strengthen the connectivity of the prefrontal cortex and improve its cognitive function by inhibiting the opening of potassium channels by cAMP [42]. A randomized clinical trial showed that guanfacine failed to improve prefrontal cognitive function in older individuals [42].

5-Hydroxytryptamine (5-HT) receptor antagonists

5-Hydroxytryptamine (5-HT) receptors in cortical and limbic areas are involved in cognition and emotional regulation [43]. 5-HT_6 receptor blockade may induce acetylcholine release and restore acetylcholine levels [44]. 5-HT_6 receptor antagonists were shown to have cognitive enhancing properties, with a modest side-effect profile [45]. However, idalopirdine, a selective 5-HT_6 receptor antagonist, did not improve cognition compared with placebo in three Phase III randomized clinical trials including 2525 patients [46]. Two other 5-HT_6 receptor antagonists, intepirdine and SAM-760, also failed to improve cognition in AD patients when compared with placebo in Phase II and III trials [45, 47]. SUVN-502, a novel orally active 5-HT_6 receptor antagonist meant to be used as an adjunct to donepezil and memantine, is now under investigation [45].

OTHER NEW THERAPEUTICS

Gut microbiota regulators

The gut microbiota, composed of a large number of microorganism species, is known to be associated with cognitive decline and AD [48, 49]. The gut microbiota plays very important roles in immune system development, barrier fortification, vitamin production, and nutrient absorption [48]. A clinical trial indicated that probiotic supplementation could improve cognitive function and mood in community-dwelling elderly individuals [50]. Sodium oligomannate (GV-971) is an orally administered mixture of acidic linear oligosaccharides derived from marine brown algae [51]. GV-971 was developed by Shanghai Green Valley Pharmaceuticals for the treatment of AD and was approved by China's regulators for the treatment of mild-to-moderate AD in November 2019 [51]. A study reported that GV-971 could remodel the gut microbiota by decreasing the concentrations of phenylalanine and isoleucine in the feces and blood and reducing T helper 1-related neuroinflammation in the brain [52]. In addition, GV-971 can easily penetrate the blood–brain barrier to directly bind to Aβ and inhibit Aβ fibril formation [51].

Anti-inflammatory drugs

Neuroinflammation is considered an important pathological mechanism that contributes to the pathogenesis of AD. Chronic activation of the immune system results in the release of proinflammatory cytokines and toxic factors [19]. Thus, anti-inflammatory drugs may also be worth considering as potential anti-AD therapeutics [53]. A meta-analysis showed that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was significantly associated with a reduced risk of AD in observational studies; however, in a single randomized controlled trial, NSAIDs showed no significant effect on AD risk [54]. Minocycline, an anti-inflammatory tetracycline, was able to protect against the toxic effects of Aβ in vitro and in animal models of AD but did not delay

the progress of cognitive or functional impairment in AD patients in a clinical trial [55].

Lipid metabolism regulators

Changes in lipid metabolism, apolipoproteins, and leptin are correlated with AD [56]. The apolipoprotein ε4 isoform variant is a major genetic risk factor for late-onset AD [57].

Fish oil rich in ω-3 long-chain polyunsaturated fatty acids is believed to be beneficial for cognitive function [58]. A study of 1293 older subjects with high cardiovascular risk found that multidomain intervention combined with polyunsaturated fatty acids might improve orientation and episodic memory [59]. However, a 3-year multicenter trial of 1680 participants showed that polyunsaturated fatty acids had no significant effects on cognitive decline [60].

Statins are a group of drugs commonly used to lower cholesterol levels in the blood. A preclinical study found that statins were able to reduce Aβ levels in yeast [61], and meta-analyses reported that statins might reduce dementia risk and have beneficial effects on Mini-Mental State Examination scores in AD patients [62, 63]. However, other studies and meta-analyses implied that there was insufficient evidence supporting the efficacy of statins in treating AD or lowering AD risk [64–66].

Autophagic modifiers

Autophagy is a cellular degradation system that clears aggregated proteins and dysfunctional organelles [67]. Autophagy in microglia is able to degrade extracellular Aβ fibrils, and the autophagy-lysosome system can degrade tau protein in various forms [68]. Thus, the use of autophagy inducers to promote the degradation of Aβ or tau may be a potential therapy for AD. Rapamycin and its analogs methylene blue and trehalose were shown to protect against Aβ and tau in AD animal models [69]. Quercetin-modified nanoparticles were also reported as a potential autophagy inducer to treat AD [70].

Circadian rhythm regulators

Epidemiological studies have shown that ~40% of AD patients have various types of sleep disorders [28, 71]. Evidence in animals also indicated that circadian rhythm and sleep disturbances were associated with cognitive impairment and Aβ production and removal [72, 73]. Thus, therapeutics targeting circadian rhythm and sleep regulation might be beneficial for AD patients. Melatonin is a hormone mainly generated in the pineal gland that regulates the circadian rhythm and shows neuroprotective effects against tau pathology [74]. A 6-month multicenter clinical trial showed that prolonged-release melatonin, compared with placebo, had positive effects on cognitive functioning and sleep maintenance in AD patients. However, an earlier study showed that melatonin was not effective for the treatment of insomnia in AD patients [75]. Ramelteon, a melatonin agonist, was shown to provide protection against delirium in elderly subjects [76]. Suvorexant, an orexin receptor antagonist that promotes sleep via selective antagonism of orexin receptors, was reported to ameliorate cognitive impairments and AD pathology in a mouse model of AD [77] and improve total sleep time and insomnia in patients with probable AD [78].

Natural compounds

The *Ginkgo biloba* extract EGb 761 is widely used in the treatment of neurological disorders, including AD. Studies showed that EGb 761 could significantly improve cognitive function, neuropsychiatric symptoms, and activities of daily living in patients with mild-to-moderate dementia and relieve symptoms in patients with mild cognitive impairment (MCI) [79]. Ginkgolide A, another compound extracted from *Ginkgo biloba*, was found to attenuate Aβ-induced abnormal depolarization and inhibit NMDA receptors [80].

Curcumin, a free radical scavenger with anti-inflammatory properties and the ability to permeate the blood–brain barrier, was reported to downregulate glycogen synthase kinase-3β (GSK-3β) and CDK5 [81]. Dietary supplementation with curcumin could reduce circulating levels of GSK-3β and alleviate markers related to insulin resistance to reduce the risk of type 2 diabetes mellitus and AD [82].

Coconut oil is a source of ketone bodies that can provide direct cellular energy. A randomized controlled trial showed that a Mediterranean diet enriched with coconut oil seemed to improve cognitive function in patients with AD; the effect differed by gender [83].

Receptor for advanced glycation endproducts (RAGE) inhibitors

The receptor for advanced glycation endproducts (RAGE) is a receptor that plays important roles in Aβ clearance, β- and γ-secretase regulation, and activation of the inflammatory response and oxidative stress in AD [84]. Azeliragon (TTP488) is an orally bioavailable small-molecule inhibitor of RAGE that showed promising results in preclinical and Phase IIb studies [85]. However, a Phase III trial of azeliragon was terminated due to a lack of efficacy. Another Phase III trial in mild AD is still underway.

σ-1 receptor agonists

Activation of the σ-1 receptor was shown to have neuroprotective effects and could reduce key pathophysiological processes in AD, including hyperphosphorylation of tau and oxidative stress [86]. Blarcamesine (ANAVEX2-73), a selective σ-1 receptor agonist, was reported to exhibit good safety and tolerability in patients with mild-to-moderate AD in a Phase IIa clinical study [87]. Phase IIb/III clinical studies are ongoing.

AVP-786 is a compound consisting of a combination of deuterated (d6)-dextromethorphan and an ultralow dose of quinidine; in vitro and in animal models, this drug was reported to be a σ-1 receptor agonist, a serotonin reuptake and glutamate release inhibitor, and an NMDA receptor antagonist [88]. It is now in clinical trials for the treatment of agitation in patients with AD [88].

GENE AND CELL THERAPIES

Antisense therapy

Antisense therapy uses antisense oligonucleotides (ASOs) to target mRNAs in order to preferentially alter mRNA expression. An ASO against Aβ precursor protein was reported to improve learning and memory and reduces neuroinflammatory cytokines in a mouse model of AD. Another study demonstrated that an ASO targeting histone deacetylase 2 (*HDAC2*) mRNA could improve memory in mice [89]. The codelivery of an antisense transcript (short hairpin RNA) against BACE1 and an antioxidant was also shown to remarkably improve the spatial learning and memory capabilities of AD mice [90].

MicroRNA (miR) therapy

MicroRNAs (miRs) are short, single-stranded RNAs that modulate protein expression. They play regulatory roles in neurite outgrowth, dendritic spine morphology, neuronal differentiation, and synaptic plasticity [91]. Preclinical studies indicated that miRs including miR-298, miR-31, miR-146a, miR-34a-5p, and miR-125b-5p showed anti-AD properties [92–95].

Stem cell therapy

Mesenchymal stem cell (MSC)-based stem cell therapy can be used in the treatment of AD by various mechanisms, including reduction of neuroinflammation, removal of Aβ and tau, functional recovery of autophagy, restoration of blood–brain barrier function, augmentation of acetylcholine levels, and restoration of mitochondrial transport [96]. MSCs were reported to improve cognitive

Table. 1. New therapeutics beyond amyloid-β and tau for Alzheimer's disease.

Classification	Drug	Mechanism of action	Status
ChEIs	Donepezil analog	ChE inhibition	In preclinical study
	Tacrine-hydroxamate derivatives	ChE inhibition; anti-Aβ aggregation; anti-inflammation	In preclinical study
	ZT-1	Huperzine A analogue; cholinesterase inhibition	In clinical trial (one trial: completed)
	Nitidine and avicine	Derived from *Zanthoxylum rigidum*; ChE and MAO-A inhibition; anti-Aβ aggregation	In preclinical study
	Helminthosporin	Derived from *Rumex abyssinicus Jacq.*; ChE inhibition	In preclinical study
	Methanesulfonyl fluoride	ChE inhibition	In phase I trial
	3-Arylbenzofuranone derivatives	ChE and MAO-B inhibition; antioxidant	In preclinical study
	Bambuterol derivative	ChE inhibition	In preclinical study
NMDA receptor antagonist	RL-208	NMDA receptor block; tau phosphorylation inhibition	In preclinical study
	JCC-02	NMDA receptor block	In preclinical study
	DT-010	NMDA receptor block	In preclinical study
	Rhynchophylline	Derived from *Uncaria rhynchophylla*; NMDA receptor block	In preclinical study
Adrenoceptor agonists	Guanfacine	α-2A-adrenoceptor activation	In clinical trial (one phase III trial: recruiting)
5-HT_6 receptor antagonists	Idalopirdine	5-HT_6 receptor block	Lack of efficacy (one phase I trial: completed; one phase I trial: terminated; four phase III trials: completed)
	Intepirdine	5-HT_6 receptor block	Lack of efficacy (one phase I trial: completed; five phase II trials: completed; one phase III trial: completed; one phase III trial: terminated)
	SAM-760	5-HT_6 receptor block	Lack of efficacy (one phase I trial: completed; one phase II trial: terminated)
	SUVN-502	5-HT_6 receptor block	In clinical trial (one phase II trial: completed, one trial: available)
Gut microbiota regulators	Probiotic supplementation	Gut microbiota regulation	In clinical trial
	GV-971	Gut microbiota regulation, anti-neuroinflammation; Aβ inhibition	Approved by China's regulator
Anti-inflammatory drugs	NSAIDs	Anti-inflammation	Lack of efficacy; associated with a reduced risk of AD (one phase II/III trial: completed; one phase IV trial: completed)
	Minocycline	Anti-inflammation	Lack of efficacy (one phase II trial: completed)
Lipid metabolism regulators	Polyunsaturated fatty acids	Neuroprotective properties	Contradictory results (one trial: completed)
	Statins	Lipid metabolism regulation; anti-Aβ	Contradictory results (one phase I/II trial: completed; five phase II trials: completed; two phase III trials: completed; three phase IV trials: completed)
Autophagic modifiers	Rapamycin and its analogs, methylene blue, trehalose, quercetin-modified nanoparticles	Autophagy inducement; anti-Aβ; anti-tau	In preclinical study
Circadian rhythm regulators	Melatonin	Neuroprotection; anti-tau phosphorylation	Contradictory results (one phase II trial: completed; one phase III trial completed; one trial: recruiting)
	Ramelteon	Melatonin agonist	Protection against delirium (one phase II trial: completed)
	Suvorexant	Orexin receptor antagonist	Beneficial for insomnia in AD (one phase III trial: completed)

Table 1. continued

Classification	Drug	Mechanism of action	Status
Natural compounds	EGb 761	Derived from *Ginkgo biloba;* antioxidant; neuroprotective properties	Beneficial effect (one phase I/II trial: completed; one phase II trial: completed; one phase II trial: terminated; one phase III trial: completed; two phase IV trials: completed)
	Ginkgolide A	Derived from *Ginkgo biloba*; anti-Aβ; NMDA receptor block	In preclinical study
	Curcumin	Anti-inflammation; GSK-3β and CDK5 inhibition	In clinical trial (one phase I/II trial: completed; one phase II trial: completed; one phase II trial: active)
	Coconut oil	Source of cellular energy	In clinical trial (one phase II/III trial: terminated)
RAGE inhibitors	Azeliragon (TTP488)	RAGE inhibition; anti-Aβ; secretase regulation; anti-inflammation	In clinical trial (two phase III trials: terminated; one phase II, trial: recruiting)
σ-1 receptor agonists	Blarcamesine (ANAVEX2-73)	σ-1 receptor activation	In phase II trial (two phase II/III trials: recruiting, one phase II trial: completed)
	AVP-786	σ-1 receptor activation; neurotransmitter regulation	In clinical trial for agitation (two phase III trials: completed, three phase III trials: recruiting)
Antisense therapy	ASOs	Altering mRNA expression	In preclinical study
MicroRNA therapy	miR-298, miR-31, miR-146a, miR-34a-5p, miR-125b-5p	Anti-Aβ; anti-tau; targeting BACE1	In preclinical study
Stem cell therapy	Mesenchymal stem cells	Anti-inflammation, Aβ and tau removal, functional recovery of autophagy, brain blood barrier function recovery, increasing acetylcholine level, and recovery of mitochondrial transport	In clinical trial (three phase I trials: recruiting, three phase I trial: completed, one phase II trial: recruiting, and other four trials)

Data of clinical trials come from the U.S. National Library of Medicine (ClinicalTrials.gov).
Aβ amyloid β, *AD* Alzheimer's disease, *ASOs* antisense oligonucleotides, *BACE1* β-secretase, *BDNF* brain-derived neurotrophic factor, *CDK5* cyclin-dependent-like kinase-5, *ChE* cholinesterase, *ChEIs* cholinesterase inhibitors, *HT* hydroxytryptamine, *GSK-3β* glycogen synthase kinase-3β, *MAO* monoamine oxidase, *MCI* mild cognitive impairment, *miR* microRNA, *NGF* nerve growth factor, *NMDA N*-methyl-*D*-aspartic acid, *NSAIDs* nonsteroidal anti-inflammatory drugs, *RAGE* receptor for advanced glycation endproducts.

deficits and alleviate neuropathology in animal models of AD [97]. A combination of stem cell transplantation and neurotrophic factors could replenish the target neurons and provide an improved microenvironment with neurotrophic factors for nerve repair and regeneration [98]. A recent study showed that intranasal delivery of the MSC secretome also displayed multilevel therapeutic potential for AD [99]. A Phase I clinical trial indicated that administration of MSCs into the hippocampus and precuneus by stereotactic injection was feasible, safe, and well-tolerated in nine patients with mild-to-moderate AD [100].

NONPHARMACOTHERAPEUTICS

Nonpharmacological interventions as supplements or substitutes for pharmacological treatment are an important part of therapy for AD [101].

Hyperbaric oxygen therapy

Increasing evidence indicates that hypoxia may affect many aspects of the pathogenesis of AD, including Aβ and tau pathology, autophagy, neuroinflammation, oxidative stress, and mitochondrial function [102]. Hyperbaric oxygen treatment to improve tissue oxygen supply and hypoxic conditions has been reported to ameliorate cognitive functions and enhance brain glucose metabolism in AD and aMCI patients [103].

Brain stimulation

High-frequency repetitive transcranial magnetic stimulation over the left and subsequently the right dorsolateral prefrontal cortices produced an improvement in activities of daily living, depression, and general cognitive function [104]. Transcranial direct current stimulation can facilitate cortical excitability and thereby neuroplasticity [105, 106]. Deep brain stimulation delivered to the hypothalamus or the fornix was reported to drive activity in mesial temporal lobe structures and modulate limbic activity [107, 108].

Other nonpharmacological interventions

A number of studies reported that cognitive stimulation, cognitive training, and cognitive rehabilitation improved well-being for both AD patients and family caregivers [109]. Light therapy attenuated cognitive deterioration and functional limitations, and it also ameliorated depressive symptoms [110]. Moreover, other nonpharmacological interventions, such as regular and long-term exercise [111, 112], acupuncture [113], musical interventions [114], aromatherapy [115], and vagus nerve stimulation [116], may have positive effects on cognitive and noncognitive function in AD patients.

CONCLUSION

Since clinical trials of Aβ immunotherapies and BACE1 inhibitors have had limited success in recent years, the Aβ cascade hypothesis has been challenged; however, the new drugs targeting tau have also failed to show any promising results to date. Early diagnosis with neuro-biomarkers and early intervention might be a potential strategy to stop the Aβ cascade before it produces symptoms. Therapeutics beyond Aβ and tau, including novel neurotransmitter regulators, anti-neuroinflammation drugs,

multitargeted treatment, natural compounds, and neurogenesis inducers, may hold promise for the treatment of AD (Table 1).

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ADDITIONAL INFORMATION

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