

# Personalizing the Care and Treatment of Alzheimer's Disease: An Overview

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**Abstract:** Alzheimer's disease (AD) is a progressive, complex, and multifactorial neurodegenerative disorder, still without effective and stable therapeutic strategies. Currently, available medications for AD are based on symptomatic therapy, which include acetylcholinesterase (AChE) inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonist. Additionally, medications such as antipsychotic drugs, antidepressants, sedative, and hypnotic agents, and mood stabilizers are used for the management of behavioral and psychological symptoms of dementia (BPSD). Clinical research has been extensively investigated treatments focusing on the hallmark pathology of AD, including the amyloid deposition, tau hyperphosphorylation, neuroinflammation, and vascular changes; however, so far without success, as all new potential drugs failed to show significant clinical benefit. The underlying heterogeneous etiology and diverse symptoms of AD suggest that a precision medicine strategy is required, which would take into account the complex genetic, epigenetic, and environmental landscape of each AD patient. The article provides a comprehensive overview of the literature on AD, the current and potential therapy of both cognitive symptoms as well as BPSD, with a special focus on gut microbiota and epigenetic modifications as new emerging drug targets. Their specific patterns could represent the basis for novel individually tailored approaches aimed to optimize precision medicine strategies for AD prevention and treatment. However, the successful application of precision medicine to AD demands a further extensive research of underlying pathological processes, as well as clinical and biological complexity of this multifactorial neurodegenerative disorder.

**Keywords:** Alzheimer disease, therapy, precision medicine, gut microbiota, epigenetics

## Alzheimer Disease

Alzheimer's disease (AD) is a slow, irreversible, but progressive, complex and multifactorial neurodegenerative disorder and the most common form of dementia, corresponding from 60% to 80% of all dementia cases.<sup>1</sup> Cases occurring before the age of 65 are considerably rarer, constituting less than 5% of all AD cases and are termed the early-onset AD (EOAD), while the majority of cases occur after age 65, representing the late-onset AD (LOAD) or sporadic AD. Estimated 1–2% of AD cases have very early age of disease onset, with a more rapid rate of progression and sometimes associated with other neurologic symptoms less frequently present in sporadic AD, and it is inherited in an autosomal dominant fashion.<sup>2</sup>

AD is not an age-related disorder; however, older age is a major risk factor for AD.<sup>3</sup> Specifically, the risk of developing AD significantly increases after 65 years of age, and it reaches up to 31% for individuals beyond the age of 85.<sup>3,4</sup> According to the age-dependent hypothesis, cognitive functions are slowly reduced

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during normal aging. However, certain alterations, such as neuroinflammation, changes in the cell biology, or injuries, might cause a switch from normal aging to AD pathophysiology.<sup>5</sup> It is assumed that age affects inflammatory processes in the brain, resulting in an imbalance between anti- and pro-inflammatory factors and leading to chronic low-grade inflammation.<sup>6</sup>

Furthermore, loss of sex steroid hormones, estrogens and androgens with age represents one of the significant risk factors for AD development.<sup>7</sup> In general, women show slower cognitive decline during aging and better results in verbal tasks, while men are better in coordination and visuospatial tasks.<sup>8</sup> On the other hand, women with AD show faster decline in cognitive functions and lower score in verbal tasks, compared to men. Moreover, it has been reported that women over 89 years of age had a higher prevalence of AD in comparison to the male subjects.<sup>9</sup> Such differences might be a result of different rate of brain atrophy in men and women. Specifically, it has been observed that brain atrophy rate is 1–1.5% faster in women than in men. In addition, higher levels of neurofibrillary tangles in certain brain areas were found in women, with no observed differences in A $\beta$  burden between subjects of different gender.<sup>8</sup> The gender differences are not affecting only disease progression, but comorbidity as well.<sup>10</sup> Although female patients with AD show larger neuroanatomical and cognitive reduction, men have higher comorbidity burden than women, which might be a reason for higher mortality of male subjects with AD.<sup>10</sup> Sex differences in behavioral symptoms of AD have also been observed. Specifically, while women tend to exhibit symptoms like depression, delusions, maniac symptoms and emotional lability, men more often express apathy, abusive and inappropriate behavior.<sup>8</sup>

In addition, AD variability has been associated with different ethnicity. For example, according to some authors, African Americans had a higher prevalence of AD and greater disease progression, compared to Caucasians.<sup>11</sup> On the other hand, the study by Mehta et al<sup>12</sup> demonstrated that African Americans and Latino population with AD might have better survival rates than Caucasians and American Indians, whereas the lowest AD-related mortality was reported for Asian subjects.<sup>12</sup>

Other risk factors of developing AD are genetic<sup>13</sup> and acquired factors. While the mutations in genes for amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) usually cause early AD, late-form AD is

mainly associated with a polymorphism in apolipoprotein E gene (*APOE*), especially the presence of  $\epsilon 4$  allele.<sup>14</sup> *APOE* gene encodes apoE, a key lipid transport protein in the brain that is produced by astrocytes and plays a critical role in the synthesis and delivery of cholesterol in the brain. Humans have three apoE isoforms (apoE2, apoE3 and apoE4) and the carriers of a  $\epsilon 4$  allele have an increased risk of developing AD, while  $\epsilon 2$  allele acts protectively for its carriers.<sup>15</sup> Acquired risk factors include cerebrovascular diseases as the most commonly reported risk factor, type 2 diabetes mellitus, hypertension, obesity, dyslipidemia, marital status, stress, depression, inadequate sleep and smoking.<sup>16</sup> Some of the protective factors that can lower the risk for developing AD are physical activity, Mediterranean diet and vitamin D.<sup>17</sup>

Due to the accelerated aging of human population, the number of AD patients rises each year.<sup>3</sup> This high prevalence contributes to the great societal burden, especially for the caregivers, and increases medical health expenses, which is why it is recognized as a major economic problem of the modern society and a fatal global epidemic worldwide.<sup>18</sup> The onset of the disease occurs between 15 (for the EOAD) and 20–30 (for the LOAD) years before the appearance of any clinical symptoms. The silent and asymptomatic initial stage of AD, also called preclinical AD, is characterized by the development of pathophysiological hallmarks, which can be analyzed in the cerebrospinal fluid (CSF) or in the brain with amyloid positron emission tomography (PET) imaging.<sup>17</sup>

AD typically manifests through a progressive loss of episodic memory and cognitive function, leading to language and visuospatial skills deficiencies.<sup>19</sup> These deficiencies are often accompanied by behavioral symptoms, such as apathy, aggressiveness and depression.<sup>16</sup> Mental status examination plays a crucial role in the determination of clinical manifestations of neurologic and psychiatric diseases.<sup>20</sup> Subjective cognitive decline (SCD) is a self-experienced cognitive decline, not detectable on standardized testing, which often occurs in the late stage of preclinical AD. SCD is considered a preclinical manifestation of AD and one of the earliest noticeable symptoms of dementia.<sup>21,22</sup> At some critical point, when a level of cognitive decline cannot be compensated, it passes into mild cognitive impairment (MCI), which can be manifested on standardized tests.<sup>23</sup> However, although the risk for MCI and dementia is increased in individuals with SCD, it is not always prodromal to AD and subjects with SCD may not show progressive cognitive decline.<sup>24</sup> Mini

Mental State Examination (MMSE), Clinical Dementia Rating Scale (CDR), Global Deterioration Scale (GDS), Neuropsychiatric Inventory (NPI), Barthel Index of Activities of Daily Living (ADL), and Seoul Neuropsychological Screening Battery (SNSB) are neuropsychological measures used for testing these cognitive symptoms.<sup>25</sup> The diagnosis of AD is still made post-mortem and post-mortem studies demonstrated wide variability in terms of accuracy of clinical diagnosis and highlighted the challenges and limitations. Frequently, there are only serial assessments and long-term follow-up demonstrate the progression typical for AD. In addition to the basic assessment of a patient with suspected AD and the early neuropsychological profile of the AD amnesic presentation, there are also cognitive screening instruments for dementia such as Addenbrooke's Cognitive Examination (ACE-III), Montreal Cognitive Assessment (MoCA), Neuropsychiatry Unit Cognitive Assessment Tool (NUCOG), Rowland Universal Dementia Assessment Scale (RUDAS) and the previously mentioned Mini Mental State Examination.<sup>26</sup>

Several hypotheses try to explain the development of AD: the hypotheses based on protein deposits, which include the beta-amyloid (A $\beta$ ) cascade hypothesis and the tau hypothesis, the hypothesis of reactive processes of neuroinflammation as the first event in AD and the group of hypotheses based on the loss of function, which include calcium disbalance hypothesis, vascular hypothesis and oxidative stress hypothesis.<sup>27</sup> AD pathology is very complex with four core features. The first core feature is hyperphosphorylation of tau protein. Tau is an intracellular microtubule-associated protein within neurons, important for structural support and axonal transport. Its hyperphosphorylation leads to microtubule collapse and aggregation into neurofibrillary tangles (NFTs). Further, cleavage of APP by  $\beta$ - and  $\gamma$ -secretase enzymes causes the extracellular accumulation and aggregation of A $\beta$  protein fragments, visible as amyloid plaques in the AD brain.<sup>28</sup>

Although accumulation of A $\beta$  plaques and formation of NFTs have been associated with the etiology of AD for over a century, neither the exact pathophysiological mechanism of the disease nor definite treatment options have been found so far. The amyloid cascade hypothesis has been challenged with the amyloid  $\beta$  oligomer (A $\beta$ O) hypothesis proposing that AD is instigated by soluble, ligand-like A $\beta$ O, that were shown to be neurotoxic.<sup>29</sup> Besides A $\beta$ , other products are generated following  $\beta$ - and  $\gamma$ - secretase cleavage of APP in the amyloidogenic

processing pathway, including soluble APP $\beta$ , C99, and AICD.<sup>30</sup> These potentially important APP fragments have not been studied in detail yet. Moreover,  $\gamma$ -secretase has over 90 known substrates that all could interfere with A $\beta$  production, making the idea that APP metabolism and A $\beta$  production in sporadic AD cases depend on interaction and competition among  $\gamma$ -secretase substrates, very likely.<sup>31</sup> One of the currently most investigated concepts proposes that the development of AD is triggered by impairment of APP metabolism and then further progresses through tau pathology, rather than through A $\beta$  accumulation.<sup>29,32</sup> This concept is supported by the fact that tau pathology is also a major age-related event in persons with Down syndrome, 88% of whom develop dementia before the age of 65, caused by an extra copy of the *APP* gene.<sup>33,34</sup> Therefore, it has been hypothesized that tau pathology within selected projection neurons with susceptible microenvironments may, by itself, initiate sporadic AD.<sup>35</sup> This is in line with the findings of late amyloid accumulation in accelerated-senescence non-transgenic OXYS rats,<sup>36</sup> used as an animal AD model, and with the finding that functional integrity of synapses in the central nervous system (CNS) of cognitively intact individuals with high AD neuropathology is associated with the absence of synaptic tau oligomers.<sup>37</sup> Hence, in comparison to Braak stage-specific readouts, connectivity-based, personalized tau-PET readouts reduced the sample size of planned patient-centered simulated tau-targeting clinical trial interventions by approximately 40%.<sup>38</sup>

CNS inflammation starts in the very early stages of AD, probably decades before its clinical manifestation, and the characteristics and the intensity of the inflammatory process change with the progression of the disease. We still know very little about the initial process of inflammation compared to the neuroinflammatory processes present in the later stages of AD.<sup>39</sup> Cuello suggests that neurons burdened with A $\beta$  could be the initiators of inflammation and activators of disease-aggravating inflammatory process mediated by mobilized microglia.<sup>39</sup> This early process could be manageable by the anti-inflammatory agents, unlike the CNS inflammatory process in the late stages of AD. Microglia, the resident macrophages of the CNS, which are activated in AD, produce cytokines, such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , and nitric oxide (NO) that affect neuroinflammation.<sup>28</sup> Several recent findings revealed that the probable major links between disordered APP metabolism and tau pathology are microglial and inflammasome activation and

transmissible exosomes containing tau oligomers.<sup>40</sup> Microglia are the primary innate immune cells of the brain, acting nonspecifically against any foreign antigen, and are considered to be implicated very early in AD pathogenesis. Microglia can acquire two functional states depending on environmental cues: pro-inflammatory (cytotoxic, M1) and anti-inflammatory (immunosuppressive, M2). However, it has been observed that microglia, although abundant in the AD brain, fail to efficiently eliminate AD deposits.<sup>41</sup> Despite the onset of AD being dominated by anti-inflammatory microglial phenotype, pro-inflammatory cytokines eventually induce a transition to pro-inflammatory microglial type in the course of the disease progression.<sup>41</sup> M1 microglia release pro-inflammatory cytokines such as IL-1 $\alpha$ , TNF- $\alpha$ , and complement components that subsequently induce neurotoxic A1 reactive astrocytes. As pro-inflammatory cytokines such as IL-1 $\alpha$ , IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , promote inflammation and neurodegeneration, while anti-inflammatory cytokines, such as IL-10, oppose their action,<sup>41–43</sup> single nucleotide polymorphisms of the genes, coding for those proteins, influence the susceptibility to the AD pathology.<sup>44</sup>

However, the evidence suggests that the link between neurodegeneration and microglia could be more complex than was initially thought. Different neurodegenerative diseases and aging have been associated with the loss of microglial homeostatic functions, resulting in chronic neuroinflammation.<sup>45</sup> In addition, disease-associated microglia (DAM) were recently identified as a subset of microglia that can be found at sites of neurodegeneration.<sup>46</sup> This subset of microglia is characterized by a specific transcriptional and functional profile,<sup>47</sup> which includes the expression of a gene coding for triggering receptor expressed on myeloid cells 2 (TREM2), a receptor which is necessary for the activation of DAM.<sup>47,48</sup> In addition, *TREM2* mutations were previously associated with AD development,<sup>49,50</sup> while TREM2 deficiency was shown to potentiate accumulation of A $\beta$  and loss of neurons in the mouse model of AD.<sup>51,52</sup> Transcriptome profiling additionally identified APOE and transforming growth factor beta (TGF- $\beta$ ) as important regulators of DAM phenotype.<sup>53</sup> Krasemann et al identified the TREM2-APOE pathway as a key regulator of microglia phenotypic change in neurodegenerative diseases.<sup>53</sup> The activation of this pathway led to the microglial phenotype switch from a homeostatic to neurodegenerative phenotype and resulted in the inability of microglia to maintain brain homeostasis. Therefore, understanding and

recognizing the different roles of microglia in the process of AD initiation and progression is invaluable for future potential therapeutic strategies and application of precision medicine approaches.

Moreover, vascular pathology and blood-brain barrier (BBB) disruption have been linked to AD too. Damage to the blood vessels consequently leading to BBB dysfunction and causing impaired brain perfusion is hypothesized to precede neurodegeneration and exist long before other characteristic features of the disease appear.<sup>41,54</sup> The first affected area in AD-related neurodegeneration is the entorhinal cortex, spreading to the subiculum, CA1 hippocampal subregion and basal forebrain networks. As the disease progresses, neurodegeneration expands throughout the temporal lobes, affecting the majority of cortical layers,<sup>28</sup> where mass neuronal and synaptic loss correlates with cognitive decline in AD.

Despite accumulating data about AD etiology and pathophysiology, there is still an incomplete characterization of the molecular mechanisms underlying AD due to its significant clinical, pathological and biological complexity. Specifically, the risk factors, biomolecular profiles, as well as specific underlying pathophysiological processes in AD patients demonstrate high variation. In addition to age, ethnicity and sex, the disease heterogeneity is also influenced by the extensive genetic variation underlying AD. So far, a variety of enrolled genes has been identified, with individual genetic variants having a small effect on disease risk.<sup>55</sup> However, there are still many unknown genetic factors contributing to AD and further sequencing studies are necessary in order to identify genetic risk variants and to determine the specific molecular pathways involved. In addition, AD has a considerable non-genetic component, with different environmental factors, including cerebrovascular disease or traumatic brain injury and lifestyle factors, such as intellectual activity, affecting the risk for AD development and significantly interacting with individual genetic background. Specific latent pathophysiologic processes in AD patients are now more accessible by the application of brain imaging technologies and by quantification of blood and CSF biomarkers. Therefore, successful application of precision medicine to AD is needed, in order to specifically target underlying molecular and clinical heterogeneity of AD and to administer a preventive or therapeutic intervention that is personalized to the identified molecular pattern of risk and disease processes.<sup>55</sup>

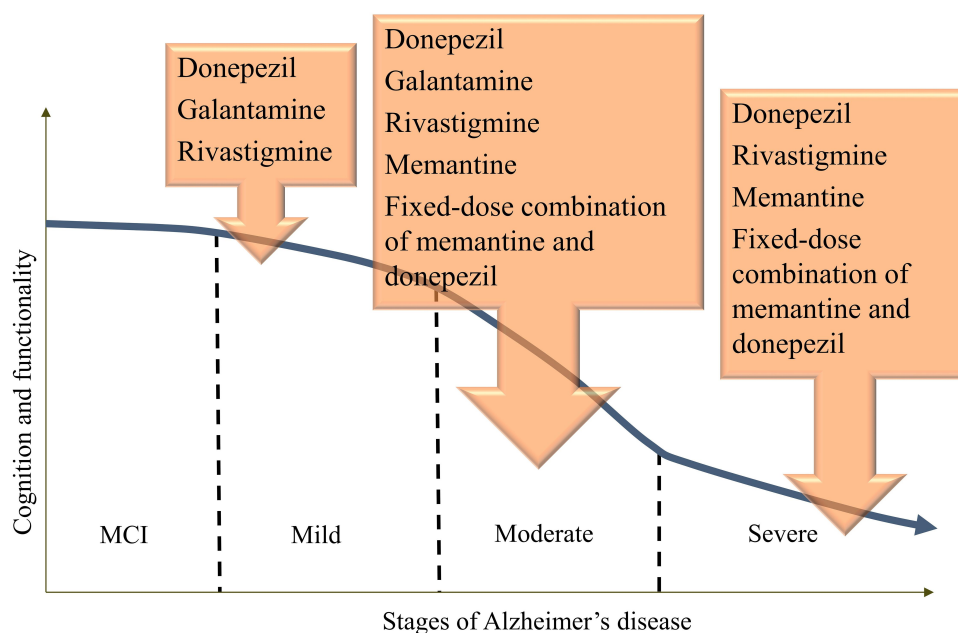
## Pharmacological Treatment of AD

The effective and stable therapeutic strategies for AD still do not exist and the failure rate in clinical trials is higher than for any other disease (99.5%). Starting of treatments late during the course of AD progress, inappropriate drug doses, invalid target selection, and predominantly an insufficient knowledge of the diverse pathophysiology of AD are the reasons for failures of disease-modifying treatments for AD.<sup>56</sup> It has been proposed that some promising drugs that failed to show clinical improvement in subjects with MCI or moderate stage of AD were administered too late in the disease course.<sup>57</sup> In addition, so far most of the clinical trials have neglected the underlying clinical and molecular heterogeneity of AD and considered AD as a homogeneous disease, which could be one of the main reasons for their failure to identify an AD effective therapy.

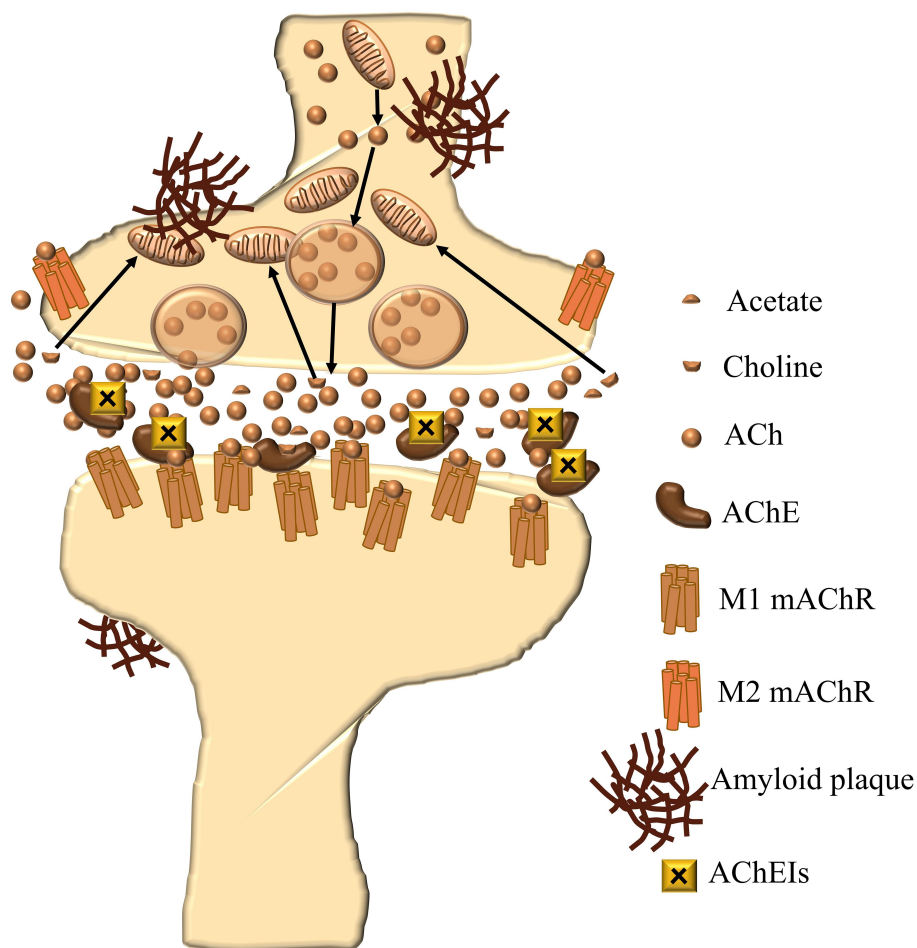
Currently, treatment of AD is targeted toward symptomatic therapy, although clinical research is developing towards a more definitive treatment of the hallmark pathology in AD, with the expectation that these therapeutic options will attenuate the progressive decline associated with AD. Various trials are underway that aim to reduce the production and overall burden of pathology within the brain.<sup>58</sup> Finally, precision medicine is now beginning to be incorporated into AD clinical trials, which are focusing on subgroups of subjects with known genetic risk for AD and specific biofluid or neuroimaging biomarkers.<sup>55</sup>

However, the treatment of AD has not been significantly changed or improved in the last decade. It includes four approved medications:<sup>59</sup> acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine, and N-methyl-D-aspartate (NMDA) receptor antagonist memantine (Figure 1), which were approved by US Food and Drug Administration (FDA). Out of three AChE inhibitors, galantamine and donepezil are AChE inhibitors, and rivastigmine inhibits both AChE and butyrylcholinesterase (BChE). These medications are based on the assumption that, according to the cholinergic theory, loss of acetylcholine in the brain is responsible for the development of AD symptoms since the cholinergic system plays an important role in cognitive processes.<sup>60</sup> Therefore, inhibition of the enzymes that degrade acetylcholine, AChE and BChE (Figure 2), is the first line of AD treatment.<sup>61</sup>

These medications have been shown to improve cognitive functions and some of them may also have positive effects on behavioral symptoms.<sup>62</sup> However, none of these drugs affect the course and the outcome of the disease.<sup>63</sup> The pharmacological treatment of AD differs according to the stage of disease (Figure 1), and AChE inhibitors are used for mild to moderate AD, while the antagonist of NMDA receptors, memantine, is used to treat moderate to severe AD.<sup>64</sup> These drugs provide symptom relief; however, sometimes they induce side effects. Unfortunately, they are not disease-modifying



**Figure 1** FDA-approved treatments across phases of AD.



**Figure 2** Cholinergic synapse in AD during treatment with AChE inhibitors.

and they do not represent a cure.<sup>65</sup> They cannot slow down the disease progression, but only temporarily improve brain function, and slow down the cognitive deterioration via reduction of AChE activity, resulting in higher acetylcholine levels.<sup>66</sup> Other investigated AChE inhibitors were characterized with significant side effects: physostigmine (diarrhea, stomach cramps, increased salivation, excessive sweating), tacrine (nausea, vomiting, loss of appetite, diarrhea, clumsiness, hepatotoxicity, impractical dosing schedule (4 times daily) due to the short half-life) and metrifonate (neuromuscular and respiratory side effects after the long-term use), and therefore were not approved for the treatment of AD.<sup>61</sup>

The results of a Cochrane study for donepezil, which included 8257 subjects with mild, moderate, and severe AD, showed statistically significant improvement in cognitive functions, activities of daily living, and clinician-rated global impression of change scale, with no significant effects on behavioral symptoms. Both doses

(5 mg and 10 mg) of donepezil were effective, with more adverse effects (Table 1), mainly gastrointestinal effects, reported for the higher dose.<sup>67</sup>

The other AChE inhibitor, rivastigmine (1.5–6 mg twice daily), was approved by the FDA for all stages of AD. It was associated with cognitive improvement/stabilization, especially if the treatment started in the early phases of AD.<sup>68</sup> Rivastigmine has led to statistically significant improvement in cognitive functions in patients with mild to moderate AD when administered in high doses (6–12 mg). It had no significant effect on behavioral symptoms. Adverse effects (Table 1) were quite common with high doses, mostly gastrointestinal symptoms, although headaches and syncope were also reported. The rivastigmine transdermal patch was also tested. A smaller patch with a lower dosage was as effective as both the bigger patch (higher dosage) and the perioral form of the medicine, which was given in the equivalent daily dose but had less adverse effects.<sup>68</sup>

**Table 1** Adverse Reactions of Acetylcholinesterase Inhibitors

Body System	Effects	Precaution
Cardiovascular system	↑ Vagal effects on the sinoatrial and atrioventricular nodes, bradycardia, heart block and/or syncopal episodes	Patients with cardiac conduction disturbances, combination with $\beta$ -blockers, calcium channel blockers, digoxin, pilocarpine or drugs known to prolong QTc interval, due to potential to induce bradycardia and arrhythmia
Muscular system	↑ Succinylcholine-type muscle relaxation	During anesthesia with succinylcholine-type muscle relaxants
Gastrointestinal system	↑ Gastric acid secretion, ↑ risk for developing peptic ulcers	Patients with the history of ulcer disease, and those receiving nonsteroidal anti-inflammatory drugs
	Nausea, vomiting, diarrhea, possible dehydration, weight loss	Undernourished patients
Respiratory system	↑ Bronchial secretion	Patients with a history of asthma or obstructive pulmonary disease
Central nervous system	Worsening of extrapyramidal symptoms	Patients with Parkinson's disease

**Note:** ↑Increased effects in comparison to the condition without acetylcholinesterase inhibitors.

The effects of galantamine (4–12 mg twice daily) were also analyzed in a meta-analysis, and the results showed a statistically significant improvement in cognitive functions in mild to moderate AD. The side effects (Table 1) were similar to those of other AChE inhibitors.<sup>69</sup> This review suggested that, according to the stage of AD, clinical characteristics and tolerability, titration of the dose and switching between AChE inhibitors might improve the response rate. Switching between AChE inhibitors may prevent issues related to the lack of efficacy or safety/tolerability in patients with AD.<sup>69</sup>

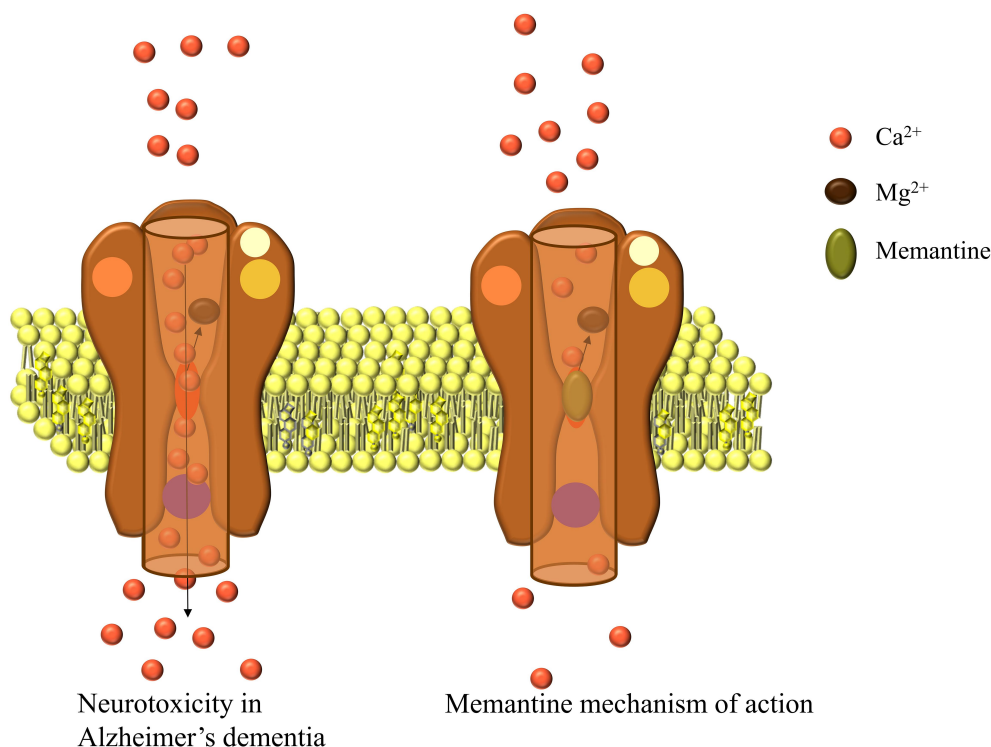
In AD, the amyloid plaques affect glutamatergic neurotransmission, elevate synaptic and extrasynaptic glutamate levels and elicit excitotoxicity. This leads to hypoactivity, neuronal loss, progression of AD, and cognitive deficits. The activation of synaptic NMDA glutamate receptor is critical for the survival of neurons,<sup>64</sup> but excessive glutamatergic stimulation leads to excitotoxicity, which causes loss of synaptic function and neuronal death, processes believed to be a part of the pathogenesis leading to neurodegenerative changes in AD.<sup>70</sup> Memantine is a non-competitive NMDA receptor antagonist, which binds to the receptors when high concentrations of glutamate are present in the synaptic cleft (Figure 3), as is the case of AD.<sup>71</sup>

A 2017 meta-analytic study compared the efficacy and safety between monotherapy of donepezil and combined therapy with donepezil and memantine in subjects with

moderate and severe AD. The study analyzed cognition, behavioral and psychological symptoms, and global functions. The results showed the combination therapy to be superior in all domains, without significant adverse effects.<sup>72</sup> A 2018 meta-analysis compared the safety and effectiveness of AChE and memantine, and according to this study,<sup>70</sup> the most effective approach to improve cognitive functions in mild to moderate AD was (individually) donepezil 10 mg and galantamine 24 mg or 32 mg daily. For moderate to severe AD, the most effective therapy was a combination of memantine 20 mg and donepezil 10 mg. Memantine had the best acceptability profile.<sup>70</sup> No effects on behavioral symptoms were registered.<sup>73</sup>

Although many new drugs with novel mechanism of action were effective in animal models, only a few of them showed efficacy in improving cognitive decline. In addition, until now, most of the studied drugs (nicotinic receptor agonists, glutamate receptor modulators,  $\gamma$ -secretase inhibitors, growth factors, statins, monoclonal antibodies, tau inhibitors, serotonin receptor modulators, etc.) are either under development or suspended in phases 1–3 of clinical trials. As a result, many new potential drugs failed to show clinical benefit in double-blind placebo-controlled trials and were discontinued due to the serious side effects, resulting in no new AD drugs in the last ten years.

In addition to AChE and NMDA receptor inhibitors, other neurotransmitters-based therapies have been also investigated for AD in preclinical studies and clinical



**Figure 3** Overstimulation of NMDA receptors in AD and memantine mechanism of action.

trials, including GABAergic modulators, serotonin and adenosine receptor modulators, as well as histaminergic modulators.<sup>74,75</sup>

One of the most extensively investigated therapeutic strategies for AD is the inhibition of A $\beta$  cascade, either by inhibiting  $\beta$ -secretase (verubecestat, lanabecestat, elenbecestat, atabecestat, CNP520) or  $\gamma$ -secretase (tarenflurlil, semagacestat, avagacestat), or more recently by increasing  $\alpha$ -secretase activity.<sup>76–78</sup> Passive immunotherapy using the anti-A $\beta$  antibodies destabilizing or clearing A $\beta$  oligomers (bapineuzumab, gantenerumab, aducanumab) has been another developing strategy targeting A $\beta$  pathology. In addition, the metal protein attenuating compounds (clioquinol-1-PBT1, PBT2) have emerged as potential anti-A $\beta$  aggregates preventing A $\beta$  oligomerization. The potential of nilvadipine, Ca<sup>2+</sup> channel antagonist, for reducing the A $\beta$  levels in the brain is also investigated.<sup>76–78</sup> Limitations and inadequacies of targeting most popular amyloid cascade and A $\beta$ O hypotheses may originate from disregarding the physiological function of A $\beta$ . Indeed, ancestral APP gene arose hundreds of millions of years ago, and would not be so highly conserved throughout evolution unless being important.<sup>41</sup> Firstly, it has been observed that A $\beta$  resembles molecules from the group of so-called “antimicrobial peptides” and subsequently demonstrated that it

could inhibit growth of eight human pathogens, thus providing evidence that A $\beta$  might function as a part of the innate immune system.<sup>41</sup> Secondly, previously mentioned BBB breakdown manifests in the form of cerebral microbleeds.<sup>54</sup> Amyloid plaques form at sites of these microbleeds and seal vascular ruptures thus preventing major bleeding and hemorrhagic strokes.<sup>41</sup> Additionally, A $\beta$ , likewise APP containing Kunitz protease inhibitor domain called protease-nexin 2 (PN-2), is able to inhibit serine proteases, like trypsin and coagulation factors, acting as an anticoagulant.<sup>41</sup> The A $\beta$  is demonstrated to exhibit apolipoprotein-like function thereby enhancing cholesterol efflux from cells and reducing cellular cholesterol levels through interaction with ABCA1 transmembrane protein. It enhances memory in physiological, picomolar concentrations, while it impairs cognition only when present in excess amounts.<sup>79</sup> Finally, A $\beta$  is associated with a reduced risk of cancer. Experimental evidence suggests that A $\beta$  may inhibit tumor cell growth and slow tumor growth by retarding neovascularization and even by slowing down the proliferation of tumor cells by limiting the availability of essential micronutrients due to its high binding affinity for iron, copper, and zinc. It is also assumed that A $\beta$  may act by intercepting oncogenic viruses.<sup>80</sup> Hence, still underappreciated physiological



roles of A $\beta$  range from protection against infections, prevention of strokes, promotion of recovery after brain injury, cholesterol transport, to synaptic function, regulation and possible contribution to tumor suppression.

Therefore, A $\beta$  immunization or any other procedure aimed at removal, neutralization or suppression of A $\beta$  production should be preceded by an assessment of potential activators of A $\beta$  production and deposition, such as infections, brain injuries, type 2 diabetes mellitus, tumors, etc. This could be a part of the routine clinical evaluation when checking for reversible causes of dementia, such as pseudodementia due to depression and B12 hypovitaminosis (treated with antidepressants and vitamin B12, respectively). Subsequently, on the basis of such an assessment of a patient with suspected or overt dementia, and before considering any amyloid removal interventions, we suggest that the next step should be aimed to treat: 1) possible infection, 2) other established, but treatable risk factors that accelerate amyloid production and deposition, especially type 2 diabetes mellitus, and 3) imminent neuroinflammation due to possible microglial activation. So far, a single clinical trial has introduced antibiotic minocycline to AD subjects but failed due to the inclusion of the small number of patients only with advanced dementia.<sup>41</sup> In addition, AD proof-of-principle clinical trials with antiviral drugs, such as acyclovir, and antifungal drugs, such as ketoconazole, together with likely beneficial immuneselective anti-inflammatory derivatives, are required in the near future.

The inhibition of tau hyper-phosphorylation, aggregation, or tau expression level and activity, by using tau expression inhibitors (antisense oligonucleotides), phosphatase modifiers (PPZ, OKA, memantine), tau kinase inhibitors (tideglusib, lithium, amino-thiazole, oxindolequinazoline, sirenade, R-roscovitine, aloisine), tau acetylation inhibitors (salsalate), tau deglycosylation inhibitors (phosphodiesterase type 4 inhibitor), tau aggregation inhibitors (methylene blue, LMTX), or microtubule stabilizers (epothilone D, NAP, TPI 287), could also be potentially effective therapeutic approaches preventing AD progression.<sup>76–78,81</sup>

In addition, the inhibition of inflammatory response, targeting the innate immunity by inhibiting cascades such as JAK2/STAT3, NF- $\kappa$ B/NLRP3, p38 MAPK, calcium/calmodulin-dependent protein kinase II (CaMKII)/NFAT, TREM2, TLR, or RAGE/CSF1R/P2Y1R pathways (stattic, SB203580, SB202190, SP600125, NJK14047, VIVIT peptide, tacrolimus, anti-apoE, anti-TREM2, GW2580, MRS2179), as well as

targeting adaptive immune system, by treatment with A $\beta$ -specific Th2 lymphocytes and anti-A $\beta$  IgG, could represent novel strategies to reduce symptoms in AD associated with neuroinflammation. Nonsteroidal anti-inflammatory drugs, such as aspirin and ibuprofen, are currently used for the treatment of AD patients.<sup>76–78,81</sup> In addition, vitamin E (an antioxidant) supplementation is currently administered to AD patients since neuroprotective effects of antioxidants represent a promising preventive and therapeutic strategy.<sup>77</sup>

Additional potential therapeutic strategy for AD is neuroregeneration by direct supplementation of neurotrophins (hNGFp, AAV2-NGF, BDNF) or indirectly via increase of neurotrophic effects by peptide mimetics that target neurotrophin receptors (7,8-DHF, doxygedunin, LM22A-4, bicyclic BDNF loop mimetic). Another strategy to address AD is to promote neuroregeneration. This could be achieved by supplementing the functional neuronal cells either by the glia-neuron conversion (using neurogenin 2, Dlx2, the combination of various molecules) or by the transplantation of stem cells that are genetically modified to encode neurotrophic factor genes or pre-treated with neurotrophic or growth factors.<sup>76–78,81</sup>

Complementing traditional drug discovery with drug repositioning and repurposing is another approach aiming to maximize the efforts for AD drug development.<sup>78,82</sup> For instance, metformin, type 2 diabetes drug, was repurposed for AD treatment, due to its anti-inflammatory and neuroprotective properties in AD.<sup>78</sup> Five classes of compounds for repurposing as treatments for AD are suggested; tetracycline antibiotics, calcium channel blockers, angiotensin receptor blockers (ARBs), glucagon-like peptide 1 (GLP1) analogues and retinoid therapy. However, the three highest priority candidates for repurposing in AD, which were most recently selected are ROCK2 inhibitor fasudil, the cholinesterase inhibitor phenserine, with novel anti-apoptotic properties, and the antiviral drugs: aciclovir, valaciclovir and famciclovir.<sup>82</sup>

Multi target directed ligand (MTDLs) is a novel approach in AD therapeutic strategies targeting several molecular targets synergistically. For example, new compound, named RPEL, is a piperazine derivative that contains the pharmacophore fragment of tacrine. It is a dual-action compound found effective in preventing cognitive impairments, which showed the inhibitory potency against cholinesterase, reduced the phosphorylation of tau protein and inhibited the release of the A $\beta$  peptide.<sup>78,83</sup>

## Treatment of Behavioral and Psychological Symptoms of Dementia

Besides memory and learning impairments, as well as other cognitive disturbances,<sup>84</sup> AD patients also show “non-cognitive” symptoms, known as behavioral and psychological symptoms of dementia (BPSD). BPSD are heterogeneous group of behaviors, psychiatric symptoms and mood disorders,<sup>85</sup> diagnosed in approximately 90% of AD patients. BPSD encompass symptoms such as sleep disturbances, anxiety, aggression, depression, wandering, delusion, hallucinations, and disinhibition,<sup>84–87</sup> which are clustered as 1) apathy; 2) affective (anxiety, depression); 3) psychosis (paranoia, delusions, hallucinations); and 4) disinhibition (motor hyperactivity, impulsivity, aggression).<sup>84,86</sup> More than 50% of AD patients show more than four neuropsychiatric symptoms at the same time. Therefore, the presence of such symptoms affects normal functioning, as well as further cognitive decline,<sup>88</sup> and represents one of the main reasons for the institutionalization of AD patients.<sup>84</sup> Gender differences have been observed between female and male AD patients with BPSD. It has been noted that females are more prone to develop AD compared to males, whereas female AD patients usually develop depressive symptoms, while male AD patients more often express aggressive behavior.<sup>87</sup> Likewise, differences between patients with EOAD and LOAD with diagnosed BPSD were noticed. LOAD patients had higher BPSD severity compared with EOAD patients.<sup>89</sup>

The development of BPSD in AD patients is a result of neuronal loss in various brain areas, including the hippocampus, brain stem nuclei, and parahippocampal gyrus, as well as glutamate reduction; changes in cholinergic and dopaminergic neurotransmission in the frontal and temporal cortex assumed to be associated with motor hyperactivity and aggression, and altered GABA and serotonin concentrations that might lead to the development of apathy and depression.<sup>90</sup> Management of BPSD is highly individualized and requires detailed evaluation of presented symptoms in order to determine appropriate, effective treatment strategy.<sup>91</sup> However, due to complex etiopathogenesis of BPSD and AD, the choice of adequate treatment is often challenging.<sup>90</sup>

Due to the complex etiology and symptoms diversity, the treatment of BPSD involves different therapy approaches.<sup>92</sup> The part of BPSD treatment includes pain

management, as well as treatment of comorbid somatic disorders. Although pharmacotherapy for BPSD is provided, it might cause certain side effects and it should be prescribed only when it is necessary. Hence, non-pharmacological approaches for BPSD are suggested before any pharmacological treatment.<sup>90,91</sup> Behavioral, individual, caregiver and environmental interventions<sup>92</sup> aim to educate and provide support to the family members and other caregivers. It includes different trainings, development of communication skills, dementia care mapping, psychosocial interventions, physical activity, sensory stimulation, reality orientation, cognitive stimulation, validation therapy, psychotherapeutic interventions, and reminiscence therapy.<sup>90,91</sup>

Psychoeducational trainings for family members have shown benefit in more than 86% of studies, while support groups were beneficial for both, caregivers and patients. Physical activity has many beneficial effects on the human organism, improving cognition, fitness and behavior.<sup>90,91</sup> Therapy that involves sensory stimulation might have beneficial effect in patients with BPSD, especially in the reduction of agitation and behavioral disturbances. Several studies showed that music sessions help with the reduction of agitation, delirium, irritability, depression and anxiety, as well as improve the memory and orientation in AD patients.<sup>93,94</sup> Bright Light Therapy (BLT) has a positive outcome in patients with BPSD, by reducing agitation, aggression and improving cognitive performance and motor behavior.<sup>93</sup> Furthermore, problem solving and reminiscence therapy for treating depression and anxiety have been shown beneficial in patients with dementia.<sup>91</sup> Psychological interventions are mostly effective in later stages of dementia, especially when both, the caregivers and the patients, are involved in the therapy. Such approach helps with dealing with aggression, depression, anxiety and agitation.<sup>90</sup> However, due to heterogeneity of BPSD in AD, these approaches sometimes do not show adequate efficacy, leading to strategies based on drug treatment.<sup>92</sup>

Pharmacological treatment is usually administered if none of the non-pharmacological interventions lead to improvement, in large patients’ distress, or in subjects who represent a danger to themselves or others.<sup>90,91</sup> For BPSD, antidepressants are usually prescribed since they show low side effects.<sup>90</sup> Some of the prescribed antidepressants include citalopram, sertraline, escitalopram, trazodone and mirtazapine.<sup>90,92</sup> However, their efficacy is questionable. For instance, mirtazapine, which is usually

used for the treatment of patients with depression, has not demonstrated therapeutic effects in AD patients.<sup>91</sup> Antidementia drugs, AChE inhibitors and memantine, might also be useful in BPSD treatment. AChE inhibitors, such as donepezil, rivastigmine and galantamine are usually prescribed for BPSD treatment in patients with dementia. Starting and recommended doses for rivastigmine are 4.6 mg/24h patch, 9.5 mg/24h patch and 13.3 mg/24h patch.<sup>88</sup> However, treatment with donepezil was not effective in BPSD reduction in AD patients, compared with placebo.<sup>88,90</sup>

Another group of medication, which has been prescribed for BPSD, are antipsychotics. They are often administered together with anti-dementia drugs or antidepressants.<sup>95</sup> Atypical antipsychotics showed some therapeutic effect in patients with BPSD, while most effective are risperidone, olanzapine, quetiapine and aripiprazole. However, antipsychotic drugs often cause extrapyramidal side effects, including parkinsonism.<sup>16</sup> For certain BPSD symptoms, especially aggression, antipsychotics might be useful in the alleviation of symptoms; however, their use must be limited and controlled.<sup>90</sup> Specifically, evidence suggests that some other serious side effects, such as cerebrovascular adverse effects, cognitive decline and even death, also occur when antipsychotics are used among individuals with BPSD.<sup>88</sup> Therefore, antipsychotic treatment should be prescribed only in the case of severe or refractory symptoms, where non-pharmacological or other pharmacological approaches were not effective or possible. After a risk-benefit analysis, the lowest effective doses of antipsychotics should be used for the shortest possible time, with adequate oversight in order to maximize the gain and minimize the harm from antipsychotic treatment.<sup>96</sup> Special caution should be taken when administering antipsychotic drugs to female patients since some serious side effects of these medications are more often seen among women than among men.<sup>97</sup>

Benzodiazepines are commonly used in patients with BPSD, although their efficacy is usually blurred with caused side effects. However, occasional use of certain benzodiazepines might help with aggression, agitation and sleep disturbances,<sup>91</sup> while mood stabilizers are usually not recommended.<sup>90</sup> Combination of different pharmacotherapeutics might be more beneficial in treatment of AD subjects with BPSD. For example, the combination of memantine and citalopram led to symptom reduction in AD subjects. Sleep disturbances, aggression, agitation, irritability, caregiver distress, apathy and anxiety

were lower after the combined treatment.<sup>98</sup> Furthermore, AD patients who were receiving donepezil in combination with memantine showed improvement in BPSD, global functions, as well as in cognitive functions compared to patients that were only receiving donepezil.<sup>72</sup> Patients who were treated with donepezil and choline alfoscerate (n=57) showed significant improvement in certain BPSD symptoms, including depression, apathy, agitation and anxiety, compared with patients treated with donepezil and placebo (n=58).<sup>99</sup> Therefore, in AD patients with BPSD, the combination of several medications might have a beneficial effect in comparison with monotherapeutic approach.

## Personalizing the Care and Treatment of AD

Personalizing the care and treatment of AD intends to change the current treatment and social care of AD patients, by implementing precision medicine approach. Precision medicine is an approach that takes into account individual differences in biology, lifestyle and environment, aiming to optimize maximally the effectiveness of disease prevention and treatment. It has a multidisciplinary character and integrates a series of mechanisms to investigate, prevent, treat and cure complex diseases, such as AD. This approach needs accurate diagnosis and aims to minimize side effects,<sup>55</sup> and is based on the knowledge of the specific biological and genetic background, but also on the biomarker, phenotypic and psychosocial characteristics of the individual patient. Improved understanding of different factors responsible for development of AD onset and progression allows for better disease prevention and personalized treatment strategies.<sup>55</sup> For application of precision medicine in AD, it is also necessary to identify and validate disease-specific, mechanism-based, or (epi)genetics-dependent biomarkers of AD, which can improve and increase the accuracy of AD clinical diagnosis and patients' susceptibility, monitor disease progression and therapeutic efficacy, as well as to analyze the benefits and adverse effects of particular drugs.

Personalizing the care and treatment should allow independence, choice and control over the services for the patients with AD. The underlying heterogeneous pathways for AD development and diverse AD symptoms require precision medicine strategy.<sup>100</sup> This strategy includes the collection of demographic information for each patient (ie, APOE genotype, age, gender, education, environmental

exposure, lifestyle, medical history), as a basis for patient stratification and incorporation of in-depth information to facilitate the design of precision medicine strategies, such as physical activity, diet, brain stimulation, social communication and medication.<sup>100</sup> Assessment of the patients with AD, but also their family members, caregivers and care partners, should be person-centered. According to the recent study,<sup>101</sup> systematic, comprehensive and temporary assessments should be done using a collaborative team approach, utilizing files, documentation and communication systems to ease the delivery of person-centered information, with aim to gather information, and build relationship, education, and support. These person-centered assessments should result in better planning to optimize physical, psychosocial and fiscal wellbeing, with a main goal to enlarge the knowledge of the possible care options, palliative care and hospice.<sup>101</sup> Precision medicine approach is necessary since neither the exact pathophysiological mechanism of AD, nor the definite treatment options that are suitable for all AD patients, have been found so far.

Nevertheless, progress in life sciences and emergence of multi-omics studies (such as genomics, transcriptomics, epigenomics, proteomics, metabolomics, microbiomics, etc.) have shifted focus to precision medicine, promising improvements in both diagnostics and treatment of AD, as in other still untreatable or undertreated diseases.<sup>41</sup> However, for the development of customized diagnostics and therapeutic interventions in precision medicine, big omics data should be integrated with clinical information, increasing the understanding of heterogeneous pathophysiology of AD. Taking into account the complex genetic, epigenetic, and environmental landscape of AD,<sup>102</sup> in order to create the most effective implementation of precision medicine for patients with AD, patient stratification needs to be established based on comprehensive collection of both demographic (APOE genotype, age, gender, education, environmental exposure, life style, medical history) and in-depth information (genomic variations, brain imaging, central and peripheral biomarkers, functional assays on patient-derived neurons).<sup>100</sup> Regarding environmental impact, a study was designed to determine a correlation between living near major roads and incidence of neurological diseases<sup>103</sup> in two population-based adult cohorts and the results showed that living near major roadways was significantly associated with higher incidence of dementia. Suspected factors responsible for observed association were traffic-related air pollutants (ultrafine

particles, nitrogen oxides, etc.) probably leading to neuroinflammation and oxidative stress, and noise, possibly through effects of sleep fragmentation and impaired cognition.<sup>103</sup>

Simultaneously, emerging technologies, such as induced pluripotent stem cells (iPSC), are highly valuable in the search for genetic determinants and environmental modulators of the disease, as well as in the screening of potential drugs that will, hopefully, revolutionize the treatment of AD patients.<sup>104</sup> Some interventions have been already recognized as significant in prevention and treatment in early stages of AD: physical activity, brain stimulation through music and art, social communication, diet, supplements for energy supply, and drugs targeting neural transmission. For moderate and severe stages of AD, stage-specific intervention strategies in recent years move towards drugs targeting neural inflammation and neural regeneration therapy.<sup>100</sup>

However, in the next chapters, we focus on gut microbiota and epigenetic modifications as new emerging targets for AD management. Their immense variation and specific patterns could represent the basis for novel individually tailored approaches aimed to optimize precision medicine strategies for AD prevention and treatment.

## Gut Microbiota as a Target for AD Treatment

The human gut is a habitat for around 1000 species, with the bacterial density estimated to cca 10<sup>11</sup> per mL.<sup>105</sup> Gut microbiota are different between individuals, which is a phenomenon affecting the differences in biochemical and genetic individuality, as well as the resistance to diseases in humans.<sup>106,107</sup> In adult individuals, the composition of gut microbiota is influenced by a variety of individual factors such as host genetics, age, the status of the host immune system, emotional stress, diet, and exercise,<sup>108</sup> resulting in immense compositional variation of gut microbiota between and within individuals.<sup>109</sup> Considering the great number of metabolic enzymes synthesized by the gut microbiota, it is no wonder that gut microbiota is regarded as an additional (metabolic) organ in the human organism.<sup>110</sup>

It is bidirectional, constant communication between the gastrointestinal tract and the CNS called the brain-gut axis or more recently, due to the major role of the gut microbiota, the brain-gut-microbiota axis.<sup>107</sup> This communication is conducted through neural, immune, endocrine and metabolic signaling.<sup>111</sup> A chronic inflammation in the

elderly, caused by the hyperstimulation of the immune system,<sup>112</sup> may also be associated with a persistent inflammatory state of the gut mucosa leading to the gut barrier breakdown, further increase of proinflammatory cytokines in the circulation, the BBB impairment and neuroinflammation.<sup>113</sup> Besides, there is a direct synthesis of various neurotransmitters and neuromodulators, including serotonin and dopamine, by the gut microbiota.<sup>114</sup>

Therefore, a contribution of the brain-gut-microbiota axis disturbances to the pathogenesis of neurodegenerative disorders, including AD, is more than expected,<sup>114</sup> with a growing body of experimental and clinical data confirming it. Since bacterial cells produce amyloids to bind to each other, the gut microbiota is a source of a significant amount of those proteins.<sup>115</sup> Bacterial and human CNS amyloids differ in their primary structure, but share similarities in their tertiary structure.<sup>116</sup> It is assumed that the exposure to gut bacterial amyloids could cause priming of the host's immune system, thus enhancing inflammatory responses to endogenous neuronal amyloids.<sup>115</sup> Besides amyloids, gut microbiota produces lipopolysaccharides which activate toll-like receptor (TLR) 4 promoting inflammatory response through the interactions with CD14.<sup>116</sup> The same pathway is included in the inflammatory response to A $\beta$ .<sup>117</sup> Furthermore, a marker of intestinal inflammation, calprotectin, is a heterodimer of S100A8 and A9, the two proteins that can form amyloid oligomers and fibrils similar to A $\beta$  and  $\alpha$ -synuclein and even induce A $\beta$  fibrilization.<sup>118</sup> In the CSF and the brain of AD patients, calprotectin levels are significantly higher, promoting amyloid aggregation and co-aggregation with A $\beta$ .<sup>118</sup> Additionally, calprotectin levels are elevated also in feces of AD patients, with the assumption that it can enter the circulation and contribute to neuroinflammation.<sup>119</sup>

Obviously, gut-derived inflammatory response in aging and poor diet in the elderly may promote the pathogenesis of dementia,<sup>120</sup> suggesting that the therapy directed to the modification of the gut microbiota composition represents a new therapeutic option in AD. Manipulation of gut microbiota by antibiotics in animal models showed an association of consequential dysbiosis with changes in behavior and brain chemistry.<sup>121</sup> In humans, it was shown that the antibiotic treatment of *Helicobacter pylori* is associated with neurological disorders including anxiety, panic attacks, major depression, psychosis and delirium.<sup>122</sup> On the other hand, the use of probiotics and prebiotics seems to reduce the risk of AD<sup>123</sup> and improve cognition

in AD patients.<sup>124</sup> It was already shown that the diet might influence the development of AD. For example, antioxidant polyphenols from coffee beans can reduce oxidative stress induced by brain injuries and lower the risk of AD,<sup>125</sup> but the bioavailability and the activity of polyphenols depend strongly on healthy gut microbiota.<sup>126</sup> Additionally, there are evidence that high-fat diet induces changes in gut microbiota leading to an increase of intestinal permeability and lipopolysaccharide absorption, which causes endotoxemia and systemic inflammation.<sup>127</sup> Caloric restriction, on the other hand, can optimize the gut microbiota composition by increasing the proportion of *Lactobacillus*.<sup>128</sup>

There are some clinical studies dealing with the new potential anti-AD therapeutics directed to gut microbiota. For example, a Phase 3 clinical trial in China reported sodium oligomannate suppressing gut dysbiosis and the associated phenylalanine/isoleucine accumulation, suppressing neuroinflammation and reversing the cognitive impairment.<sup>129</sup> A recent study, conducted on AD-like pathology with amyloid and neurofibrillary tangles (ADLPAPT) transgenic mouse model of AD, showed that the ADLPAPT mouse differed from the wild-type (WT) mouse in the composition of the gut microbiota and was characterized by the loss of epithelial barrier integrity and chronic intestinal and systemic inflammation.<sup>130</sup> In this study, a frequent transfer or transplantation of the fecal microbiota from WT mice into ADLPAPT mice reduced the formation of amyloid  $\beta$  plaques and neurofibrillary tangles and improved glial reactivity and cognitive impairment.<sup>130</sup> There is growing evidence suggesting that AD is closely related to the imbalance of gut microbiota or may even begin in the gut. Considering an immense compositional variation of gut microbiota between and within individuals, therapeutic interventions targeting microbiota have a great potential to become a new tool of precision medicine approach in AD.

## Potential Epigenetic Therapy for AD

Various findings suggest that epigenetic editing might offer future therapeutic approaches in AD,<sup>131</sup> targeting DNA methylation, chromatin remodeling, and non-coding RNAs.<sup>132</sup> Among the common epigenetic mechanisms, histone modifications are involved in the regulation of gene expression and play an important role in AD pathogenesis.<sup>133,134</sup> Histone acetylation is the most-studied histone posttranslational modification, and the results of the studies using cellular and animal models of AD

demonstrate a consistent reduction in histone acetylation.<sup>135,136</sup> Therefore, a variety of histone deacetylase inhibitors (HDACi) have been tested for their potential in reversing pathological hallmarks of AD both in vitro and in vivo.<sup>133</sup> HDACi have been shown to affect AD pathology, including A $\beta$  accumulation and tau phosphorylation, as well as to improve synaptic plasticity, learning and memory.<sup>137,138</sup> The pan-HDACi such as vorinostat (SAHA), trichostatin A (TSA), valproic acid (VPA), sodium butyrate (NaB), sodium 4-phenylbutyrate (4-PBA) and entinostat (MS-275), which affect class I, II and IV HDACs, as well as nicotinamide, a specific inhibitor for sirtuin class III HDACs have been shown to reverse the hypoacetylation and have beneficial effects in AD animal studies.<sup>137,138</sup> The efficacy of HDAC-inhibitor, vorinostat in attenuating the expression of transcription factor PU.1 in human microglia has been shown, suggesting that it may be useful to reduce microglial-mediated immune responses, such as the excess inflammation observed in AD.<sup>139</sup> In addition, treatment with some recently developed HDACi, such as hydroxamide-based class I and II HDACi (I2) and mercaptoacetamide-based class II HDACi (W2) with longer half-life and better ability to cross the blood brain barrier, restored learning and memory in AD mice.<sup>140</sup> These compounds have shown some promise in the studies of AD since they appear to reduce AD pathology in vitro and memory impairments in vivo.<sup>141</sup>

Some of HDACi, such as VPA, nicotinamide, and 4-PBA, have been investigated in clinical trials for AD treatment.<sup>132,142</sup> However, HDACi and especially pan-HDACi usually exhibit toxic effects, limiting their clinical application,<sup>143</sup> and different strategies can be employed to overcome these drawbacks. The HDACi are usually non-selective and affect not only histones but also other cytoplasmic proteins.<sup>144</sup> It has been observed that increased HDAC2 and HDAC3 activity exerts a negative impact on cognition, while reduced HDAC1 activity may be neurotoxic; therefore, HDAC-based therapy inhibiting HDAC2 or HDAC3, but not HDAC1 could represent potential therapeutic target for AD.<sup>141</sup> For instance, RGFP-966, a selective HDAC3 inhibitor has been shown to decrease pathological tau phosphorylation and A $\beta$  protein expression, improve learning and memory and normalize a number of AD-related genes in cellular and animal AD model.<sup>145</sup> Other examples of specific HDACi are tubacin, a selective HDAC6 inhibitor, and suramin, a selective SIRT1 and SIRT2 inhibitor.<sup>137</sup> Improved spatial memory

and cognitive performance, decreased expression of APOE $\epsilon$ 4,  $\beta$ -amyloid,  $\beta$ -secretase and phosphorylated tau, as well as elevated levels of BDNF, ADAM10, SIRT1, REST, BIN1, MINT2 have been observed in mice after treatment with HDACi M344 with substrate selectivity for HDAC6.<sup>140,146</sup>

An additional strategy, which suits AD very well due to its multifactorial origin, is the development of multitarget drugs (MTDs).<sup>143</sup> The examples of HDACi-based MTDs include the concomitant modulation of HDACs with phosphodiesterase 5 (PDE5),<sup>147,148</sup> antioxidant properties,<sup>149</sup> transglutaminase 2 (TG2)<sup>150</sup> and glycogen kinase synthase 3 $\beta$  (GSK3 $\beta$ ).<sup>151</sup> In the AD mouse model, chronic treatment with CM-414 that acts as a dual inhibitor of PDE5 and HDACs, rescued the impaired long-term potentiation in hippocampal slices, diminished brain A $\beta$  and tau phosphorylation levels, increased the inactive form of GSK3 $\beta$ , reverted the decrease in dendritic spine density on hippocampal neurons and reversed cognitive deficits.<sup>152</sup>

Another potential therapeutic approach might be the increase in histone acetyltransferases (HATs).<sup>153</sup> Activation of specific HATs may reinstate general acetylation balance and activate gene expression programs involved in neuroprotection. Several HATs, including CBP (cAMP-response element binding protein), p300 and PACAF (p300/CBP-associated factor) showed more specific performance than non-selective HDACi. However, the poor solubility and membrane permeability of HAT activators make them rather unsuitable for AD treatment.<sup>132</sup> Nevertheless, a recent study demonstrated that CSP-TTK21, a small-molecule activator of CBP/p300 HAT efficiently reverses epigenetic, transcriptional, synaptic plasticity, and behavioral deficits in a mouse model of AD.<sup>154</sup> Alternative strategies also consider natural products, such as curcumin and derivatives, which inhibit the formation of A $\beta$  oligomers and tau aggregation, and have anti-inflammatory and antioxidative properties.<sup>155</sup> Curcumin has been considered as a selective inhibitor of the p300/CREB binding protein HAT activity.<sup>156</sup> Several clinical trials investigated the combinations of curcumin with other natural compounds as potential treatment for AD and mild cognitive impairment.<sup>132,142</sup> Other phytochemicals such as resveratrol and epigallocatechin gallate (EGCG) have been shown to regulate histone acetylation. Resveratrol was identified as activator of the conserved HDAC class III family of the sirtuins. Resveratrol has antioxidant, anti-inflammatory, and neuroprotective properties and can decrease the

toxicity and aggregation of A $\beta$  peptides in the hippocampus of AD patients, promote neurogenesis, and prevent hippocampal damage.<sup>157</sup> The key neuroprotective mechanism of resveratrol in AD seems to be linked with SIRT1 activation.<sup>158</sup> Although, clinical trials are evaluating the potential of resveratrol in the prevention of cognitive impairment and cerebrovascular dysfunction in AD,<sup>132,142</sup> evidence-based clinical studies are still insufficient. Citicoline or cytidine-5'-diphosphate-choline is a naturally occurring cholinergic compound in human cells, with particularly high abundance in the brain tissue where it serves as a precursor to the neurotransmitter acetylcholine. It was proven to have beneficial effects on cognitive functions in AD patients when combined with memantine treatment,<sup>159</sup> treatment with AChE inhibitors,<sup>160</sup> or as triple therapy with memantine and AChE inhibitors.<sup>161</sup> Citicoline is also an important intermediate in the biosynthesis of phospholipids, essential components in neuronal membranes, and a potential neuroprotective agent due to its positive effect on sirtuin 1 (*SIRT1*) expression.<sup>162</sup> Hypermethylation of the *SIRT1* gene and decreased expression of *SIRT1* is a common finding in AD, related to pathogenic mechanisms such as abnormal APP processing, neuroinflammation, neurodegeneration, and mitochondrial dysfunction.<sup>163</sup> Neuroprotective effects of citicoline could also be associated with its ability to modulate the activity and expression of certain MAP-kinase family members, which are involved in neuronal death.<sup>164</sup>

Histone methyltransferase inhibitors, such as S-adenosyl methionine (SAM), which is one of the main methyl donors in the body, as well as DNA and histone methylation activator, might also have potential therapeutic effects in AD.<sup>132</sup> However, large loss of methyltransferase function has been associated with learning deficiencies in both AD patients and mouse models of AD. Therefore, only partial histone methyltransferase inhibition could help restore balanced enzyme function.<sup>141</sup> In summary, despite substantial progress, the role of histone epigenetic modifications in AD and their potential for AD treatment require further investigation. In the future, obtained pharmacoepigenetic data could help to optimize the precision medicine approach to AD.

Numerous studies have reported dysregulation of specific miRNAs associated with AD pathology and suggested that this dysregulated miRNA pattern could be used in order to improve AD diagnostics and serve as the basis for a novel and more effective therapeutic

approach.<sup>165–167</sup> Parsi et al<sup>168</sup> suggested miR-16 as a good candidate for future development of AD therapy. Using brain delivery of miR-16 mimics in mice, they achieved the downregulation of APP, BACE1, and tau in a region-dependent manner. They also identified additional targets of miR-16, including nicastrin,  $\gamma$ -secretase,  $\alpha$ -synuclein and transferrin receptor 1 (TfR1). Similar effect on tau protein expression was observed in Neuro2a cells for miR-132 mimics.<sup>169</sup> Treatment with miR-132 mimics had a beneficial effect on memory function in mice and supported the role of miR-132/212 in the regulation of tau pathology.<sup>169</sup> The importance of miR-132 in AD pathology and its therapeutic potential were confirmed by intracerebroventricular injections of miR-132 mimics, which resulted in upregulation of inositol 1,4,5-trisphosphate 3-kinase B (ITPKB), an enzyme involved in A $\beta$  deposition and tau phosphorylation.<sup>170</sup> Transfection of PC12 and SH-SY5Y cells with miR-193a-3p mimics reduced A $\beta$ -induced neurotoxicity by targeting the expression of phosphatase and tensin homolog (PTEN) gene.<sup>171</sup> The miR-107 was shown to have neuroprotective effects in PC12 cells and in mice after the treatment with 6-hydroxydopamine, suggesting that miR-107 plays an important role against neurotoxicity by inhibiting the expression of programmed cell death 10 (PDCD10) protein.<sup>172</sup>

Administration of miR-326 lentiviral vectors into AD mice inhibited c-Jun N-terminal kinase (JNK) signaling pathway, downregulated the expression of proto-oncogene VAV1, and inhibited tau phosphorylation, leading to improvements in cognitive function.<sup>173</sup> Based on these results, miR-326 might also be a promising target for AD treatment. The use of miR-34c antagomir (AM34c) ameliorated the cognitive function in SAMP8 mice by negatively regulating the expression of synaptotagmin 1.<sup>174</sup> A similar effect was achieved with miR-188-5p oligonucleotide transfection in 5XFAD mouse model of AD.<sup>175</sup> Zolochovska et al<sup>176</sup> used in vivo mouse model and intracerebroventricular injections to demonstrate that miR-149, miR-485 and miR-4723 could prevent A $\beta$  oligomer binding to the synapses. The miR-200b and miR-200c mimics were also able to prevent A $\beta$ -derived toxicity in mice.<sup>177</sup> Injection of lentiviral particles encoding miR-31 in 3xTg-AD mice resulted in APP and BACE1 downregulation improved cognitive functions and decreased anxiety levels.<sup>178</sup>

Recently, the potential of blocking miR-592 in order to lower oxidative stress injury in astrocytes was reported and it was suggested to be mediated by dyslexia-associated

protein KIAA0319 and (Kelch-like ECH-associating protein 1) nuclear factor erythroid 2 related factor 2-antioxidant response element (Keap1/Nrf2/ARE) signaling pathway.<sup>179</sup> Wang et al<sup>180</sup> detected upregulation of miR-33 expression in SH-SY5Y cells after treatment with A $\beta$ <sub>25–35</sub>. Downregulation of miR-33 suppressed inflammation, oxidative stress, and cell apoptosis, while also improving synaptic plasticity.<sup>180</sup> The protective effect of miR-33 downregulation was achieved by suppressing Akt/mammalian target of rapamycin (mTOR) signaling pathway activation.<sup>180</sup> Intra-hippocampal injection of miR-342-3p antagomir in 3xTg-AD mice confirmed the association between miR-342-3p and AD, suggesting that miR-342-3p inhibition can improve cognitive deficits.<sup>181</sup> Downregulation of miR-342-3p also attenuated the hippocampal A $\beta$ -plaque burden revealing the important effect of miR-342-3p on A $\beta$  metabolism pathways in AD and suggesting its therapeutical potential.<sup>181</sup> The miR-299-5p treatment was shown to affect the levels of autophagy related 5 (ATG5) protein and attenuate autophagy in different cell lines, while the injection of miR-299-5p into cerebral ventricles of AD mice model inhibited autophagy and apoptosis, resulting in improved cognitive performance and pointing to miR-299-5p as a potential neuroprotective factor in AD.<sup>182</sup>

Pereira et al<sup>183</sup> made a big step towards the usability of miRNA-based therapeutics by successfully encapsulating pre-miR-29b into polyplexes and by verifying that chitosan/pre-miR-29b and polyethylenimine/pre-miR-29b systems efficiently deliver pre-miR-29b to cell cytoplasm and reduce BACE1 expression and A $\beta$ 42 levels. Gabr and Brogi<sup>184</sup> used high-throughput screening in order to identify multitargeted therapeutics for AD. They focused on ligands capable of inhibiting AChE and miR-15b biogenesis. The dual screening strategy yielded a multitarget-directed ligand, MG-6267, which acts through dual inhibition of AChE and miR-15b biogenesis.<sup>184</sup> Cellular assays confirmed effectiveness of MG-6267 in protecting neuroblastoma SH-SY5Y cells from A $\beta$ -induced cytotoxicity.<sup>184</sup>

Berberine, which is most commonly used to help treat diabetes, obesity, and inflammation, was shown to increase circRNA histone deacetylase 9 (circHDAC9) expression and decrease miR-142-5p level in human neuronal cells treated with A $\beta$ 42.<sup>185</sup> Zhang et al<sup>185</sup> suggested that berberine has neuroprotective effect in AD since it protected human neuronal cells from neuronal damage induced by A $\beta$ 42 by regulating the circHDAC9/miR-142-5p axis. Berberine treatment, along with lncRNA  $\beta$ -amyloid cleaving enzyme

1 antisense RNA (BACE1-AS) interference, protected neuronal cells treated with A $\beta$ <sub>25–35</sub> and recovered their viability.<sup>186</sup> Berberine was suggested to act, at least partly, through BACE1-AS/miR-132-3p axis, suggesting the potential of combined berberine treatment and BACE1-AS depletion in AD therapy.<sup>186</sup> Osthole, a naturally active coumarin, was shown to upregulate the expression of miR-101a-3p.<sup>187</sup> In APP/PS1 mice, osthole increased learning and memory abilities<sup>187</sup> and enhanced cell viability, prevented cell death, and reversed the downregulation of synapsin-1, synaptophysin, and postsynaptic density-95 (PSD-95) protein in a cellular model of AD.<sup>188</sup> This effect of osthole was associated with the upregulation of miR-9 and consequent decrease in calcium/calmodulin dependent protein kinase kinase 2 (CAMKK2) and phospho-AMP-activated kinase  $\alpha$  (p-AMPK $\alpha$ ) levels. Jiao et al<sup>189</sup> additionally demonstrated an effect of osthole treatment on miR-107 expression. Administration of osthole to APP/PS1 mice increased miR-107 expression, resulting in BACE1 inhibition, significant decrease of A $\beta$  in hippocampal and cortex regions, and in the improvement of memory and learning abilities.<sup>189</sup> These results suggested protective effect of osthole and its potential to delay the development of AD.

Memantine which is traditionally used to treat patients with AD, was demonstrated to ameliorate BBB permeability.<sup>190</sup> This NMDA receptor antagonist downregulated the expression of long non-coding RNA LINC00094 and decreased the permeability of BBB by upregulating miR-224-4p/miR-497-5p and thus inhibiting the expression of endophilin-1, a multifunctional protein which, among other things, regulates BBB permeability.<sup>190</sup> Therefore, a combination of LINC00094 silencing and memantine treatment could be a novel target in AD therapy research. Donepezil, AChE inhibitor used for AD treatment, probably achieves its effect partially through its interaction with miR-206. Upregulation of miR-206-3p was detected in the hippocampus and cortex of APP/PS1 mice and it was normalized after administration of donepezil, suggesting that miR-206-3p could be a novel pharmacological target in AD and a mediator of anti-dementia effects of donepezil.<sup>191</sup>

There are studies showing that resveratrol, a natural polyphenol found in red wine, can reduce neuroinflammation and A $\beta$  deposition in patients with mild or moderate AD.<sup>192</sup> The 52-week phase-II clinical trial gave evidence that resveratrol reduced A $\beta$ 40 in CSF and plasma samples of individuals with mild to moderate AD.<sup>193</sup> It is interesting that resveratrol might exert its effect by



modulating the expression of specific miRNAs, including the downregulation of pro-inflammatory miR-155 and the upregulation of anti-inflammatory miR-663.<sup>194</sup> All the above mentioned evidence led Kou and Chen<sup>195</sup> to suggest resveratrol as a potential target in the prevention and/or treatment of AD. Simvastatin, used to lower cholesterol levels, was demonstrated to have a positive effect on memory deficits in patients with AD and in animal model of AD.<sup>196</sup> Simvastatin reduced the expression of inflammatory cytokines and mediators, suppressed the apoptosis and contributed to the survival of neurons in the study conducted by Huang et al,<sup>196</sup> suggesting that simvastatin could be used as an anti-AD treatment, achieving its effect through modulation of miR-106b expression. Therefore, miRNA-based therapy has a great therapeutical potential in complex diseases such as AD, in which the cause is related to a number of genes and biological processes. Future studies will try to implement anti-miRNAs or miRNA mimics as precision medicine approaches for the treatment of AD patients; however, there is still a long way to go before certain miRNAs will be available for AD therapy. Nevertheless, epigenetics represents a new powerful tool for precision medicine, by applying the knowledge of epigenetic mechanisms and epigenetic profiles of AD patients to personalized diagnostics and treatments in AD.

## Conclusion

Currently available medications for AD are based only on symptomatic therapy, and include AChE inhibitors and NMDA receptor antagonist. Clinical research has been extensively investigating treatments focusing of the hallmark pathology of AD, including amyloid deposition, tau hyperphosphorylation, neuroinflammation and vascular changes; however, so far without success since all new potential drugs failed to show significant clinical benefit. Due to the large heterogeneity of AD etiology, cognitive, behavioral and other symptoms, somatic comorbidities, and patient lifestyle, there is no preventive or therapeutic intervention suitable for all AD patients. Therefore, precision medicine strategy is urgently required to guide clinical practice. In addition to factors such as dementia stage, medical and psychiatric comorbidity, as well as major cognitive symptoms and BPSD, the complex interplay between genetic variability and environmental factors moderated by epigenetic changes, should be taken into account for each individual AD patient. Both gut microbiota and epigenetic modifications represent new emerging

drug targets, whose specific patterns could form the basis for novel individually tailored, patient-centered, multidisciplinary approaches aimed to optimize personalized prevention and treatment of AD. However, the successful application of precision medicine to AD demands a further extensive research of underlying pathological processes, as well as clinical and biological complexity of this multifactorial neurodegenerative disorder.

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## Disclosure

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