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**REVIEW ARTICLE**

# NMDA Inhibitors: A Potential Contrivance to Assist in Management of Alzheimer's Disease

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**Abstract:** Alzheimer's disease (AD) is an increasingly common neurodegenerative disease that attracts the attention of researchers and medical community in order to develop new, safe and more effective drugs. Currently available drugs could only slow the AD progression and relieve the symptoms, in addition to being linked to moderate-to-severe side effects. N-methyl D-aspartate (NMDA) receptors antagonists were reported to have the ability to block the glutamate-mediated excitotoxic activity being good therapeutic targets for several neurodegenerative diseases, including AD. Based on data obtained so far, this review provides an overview over the use of NMDA antagonists for AD treatment, starting with a key emphasis on present features and future aspects regarding the use of NMDA antagonists for AD, and lastly a key focus is also given on its use in precision medicine.

**Keywords:** Alzheimer's disease, neurodegeneration, N-methyl D-aspartate (NMDA) receptors, precision medicine.

## 1. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease of the brain, affecting 15 million people worldwide, and whose frequency is higher in aged individuals [1]. Indeed, 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 [2]. AD is a slowly progressive disease exerting a marked impact on both cognitive function and behavior, culminating in an extra need of healthcare providers. Among other dementia cases, AD corresponds to 60-80% of the total number [3], thus being linked to a heavy burden for the family and society.

Sometimes, AD is easily confused with Parkinson's disease (PD), as both diseases are characterized by unusual neuronal inclusion bodies. However, the inclusion bodies in PD are the Lew's body containing alpha-synuclein [4], while in AD, these inclusion bodies contain beta amyloid formed due to mutations in the beta-amyloid precursor protein (APP) [5, 6]. Nonetheless, AD is not a single cause disease; instead, it is caused by several factors such as genetic, environmental and lifestyle origin. Thus, several therapeutic targets for drug development have been established, including oxidative stress, neuroinflammation, angiotensin receptors, metal chelation, amyloid plaques, tau proteins (GSK-3), neurofibrillary tangles (NFT), acetylcholinesterase (AChE), α7 nicotinic acetylcholine receptor (α7 nAChR), receptor for advanced glycation end products, secretases, monoamine oxidase (MAO)-B, and *N*-methyl D-aspartate (NMDA) receptors [7].

Specifically, NMDA receptors have received an increasing attention in the last years due to their ability to block glutamate-mediated excitotoxic activity [8, 9] and have been revealed as most significant therapeutic targets for both AD and PD treatment [10]. In this sense, the present review aims

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to provide an overview of the use of NMDA antagonists for the treatment of AD, drifting from an evolutionary perspective of AD, with an emphasis on present aspects and future perspectives on the use of NMDA antagonists for therapeutic purposes, and lastly, a key focus is also given on its use as part of precision medicine.

## 2. ALZHEIMER'S DISEASE: AN EVOLUTIONARY PERSPECTIVE

Old theories assumed that carrying an apolipoprotein E (APOE)-ε4 allele is responsible for the appearance of AD regardless of the environmental influence [11]. However, new hypothesis based on the evolutionary medicine concept found that modern life in the developed world can enhance the appearance of several diseases including AD [11]. It is noteworthy that the industrialized world currently suffers from various metabolic syndromes linked to insulin resistance, such as type-2 diabetes mellitus and obesity [12]. Interestingly, the role of insulin resistance is so central in the development of AD that some researchers have referred to AD as "type-3 diabetes" or "diabetes of the brain" [13].

On the other hand, researchers reported that estrogens have the ability to inhibit Aβ formation [14], tau hyperphosphorylation [15], reduce brain oxidative stress and inflammation [16] and induce Aβ clearance [17], thus protecting against AD. Variuos studies have reported that pre-modem women were likely exposed to repeatedly higher doses of estrogen compared to women in industrialized environments [11, 18]. The relative influence of this exposure on AD risk should be further explored.

Additionally, environmental toxins such as air pollutants and heavy metals (lead, mercury, and cadmium) can cause severe harm to the central nervous system (CNS) in ways that exacerbate AD risk [19-23].

In conclusion, APOE-ε4, which was once considered by the medical community to be the primary genetic risk factor for sporadic AD through its effect on inflammation [24, 25], is currently recognized as not being the main cause of AD.

## 3. N-METHYL D-ASPARTATE (NMDA) ANTAGONISTS: PRESENT AND FUTURE ASPECTS

AD progression is associated with continuous dysregulation in the structure and function of the neocortex and hippocampus, the brain regions which are essential for memory and cognition [26]. Neuropathological features of AD are intra-neuronal NFT, formed by accumulation of abnormal hyperphosphorylation of tau protein and extracellular amyloid plaques, formed by irregular deposition of beta amyloid peptides [27, 28]. However, synaptic loss appears to have a stronger association with weakeness and loss of memory as compared to neuropathologic markers. Synaptic plasticity is a very important factor of learning and memory [29, 30]. Loss of synapse can occur due to neuron death or by dysfunction of existing neurons which are needed for maintaining the appropriate level of functional axons and dendrites [31-33]. The possible reason for synaptic dysfunctions can be the varying level of synaptic calcium ion, caused by over activation of ionotropic glutamate receptors, specifically NMDA receptors [26].

Presently, it has been proved that NMDA receptors are involved in controlling synaptic plasticity, synaptic transmission and help in conducting memory and learning functions [28, 34-38]. At excitatory synapses, rapid neuronal communication is particularly possible due to ionotropic glutamate receptors comprising three subfamilies: N-methyl d-aspartate receptor (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and Kainate receptor [39]. Other than acute effects, the chronic-mediated activation of NMDA receptors leads to excitotoxicity resulting in neurodegeneration [40-43]. Toxicity is primarily activated by excessive entry of $Ca^{2+}$, mainly through NMDA receptors, as NMDA receptors possess considerably higher permeability to $Ca^{2+}$ than other ionotropic glutamate receptors [44-47]. Glutamate is the principal excitatory neurotransmitter of CNS that induces hypofunction and excitotoxicity in NMDA receptors, and has recently been found to be linked to synaptic dysfunction in the pathogenesis of AD [35, 36, 48-50]. Pathological level of $Ca^{2+}$ signalling results in a progressive loss of synaptic function, leading to a gradual decrease in memory/cognition and a rise of neural anatomy is observed in patients suffering from AD [51]. Among the different NMDA receptor subunits with high importance, the GluN2B subunit has been reported to cause excitotoxicity in AD and, thus, using GluN2B subunit selective antagonists may be a potential approach to inhibit synaptic loss in AD [51, 52]. Over the past few decades, the promising activities of various NMDA antagonists have been studied in animal models against several neurodegenerative diseases, including AD.

### 3.1. NMDAR: Allies and Adversaries in AD

NMDA receptors are important ionotropic glutamate receptors which are named after their agonist N-methyl D-aspartate. Besides neurons, NMDA receptors are also articulated across non-neuronal cells, like pancreas, central glial cells, peripheral glial cells, bone, endothelium, kidney, *etc*. [53]. They are involved in bone matrix deposition and inflammatory bronchiole hyperactivity in lungs, they also influence the renal blood flow and filtration in kidney and both β-cells function and survival in pancreas [54-62]. NMDA has also an essential role in the region of blood brain barrier (BBB) as the unregulated level of glutamate is harmful for neurons, and disturbs the BBB integrity and the endothelial function [63, 64].

NMDA receptor is mainly composed of 7 different subunits, namely GluN1/NR1, GluN2A/NR2A, GluN2B/NR2B, GluN2C/NR2C, GluN2D/NR2D, GluN3A/NR3A and GluNR3B/NR3B [40]. The functional NMDA receptors are hetero-tetramers (Fig. **1**), comprising two GluN1 subunits at 2 domains and GluN2/GluN3 in the other two domains, despite the fact they can also be in the form of di-heteromers and tri-heteromers (Fig. **1**). The heterogeneity of the NMDA receptor subunits is further enhanced by alternative splicing of GluN1 and Glu3A subunits. All GluN subunits are composed of the N-terminal domain, the agonist/ligand binding site, the trans-membrane domain and an intracellular C-terminal domain, as shown in Fig. (**2**) [50, 65].

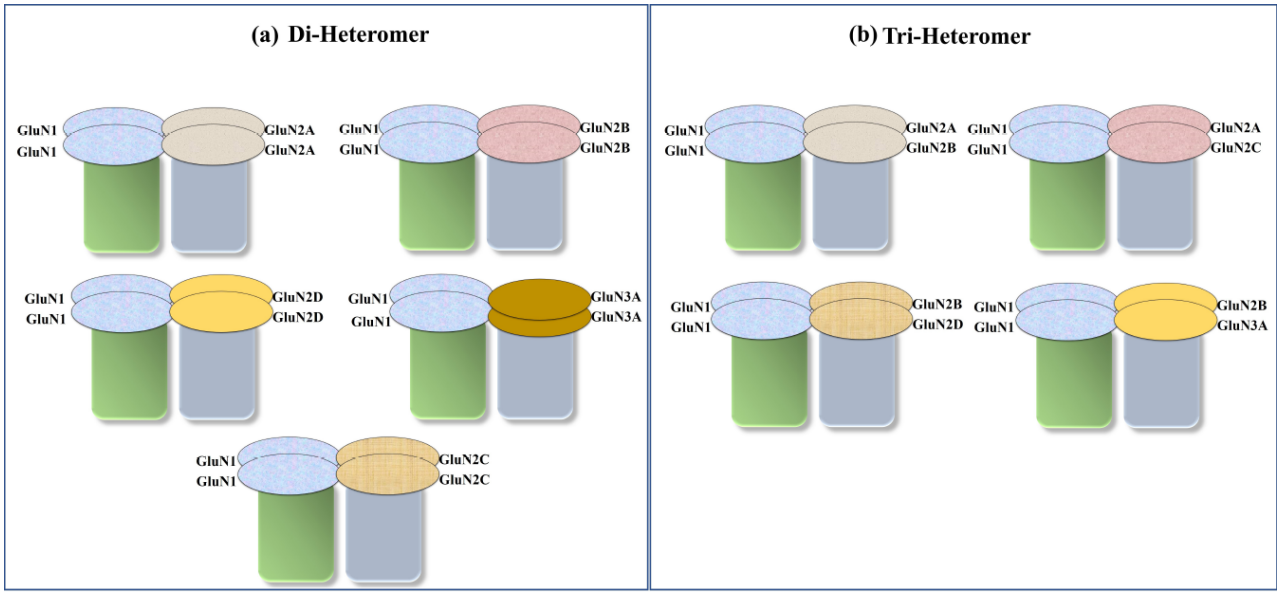


**Fig. (1).** Structure of functional NMDA receptors (**a**) di-heteromers forms; (**b**) tri-heteromers forms. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

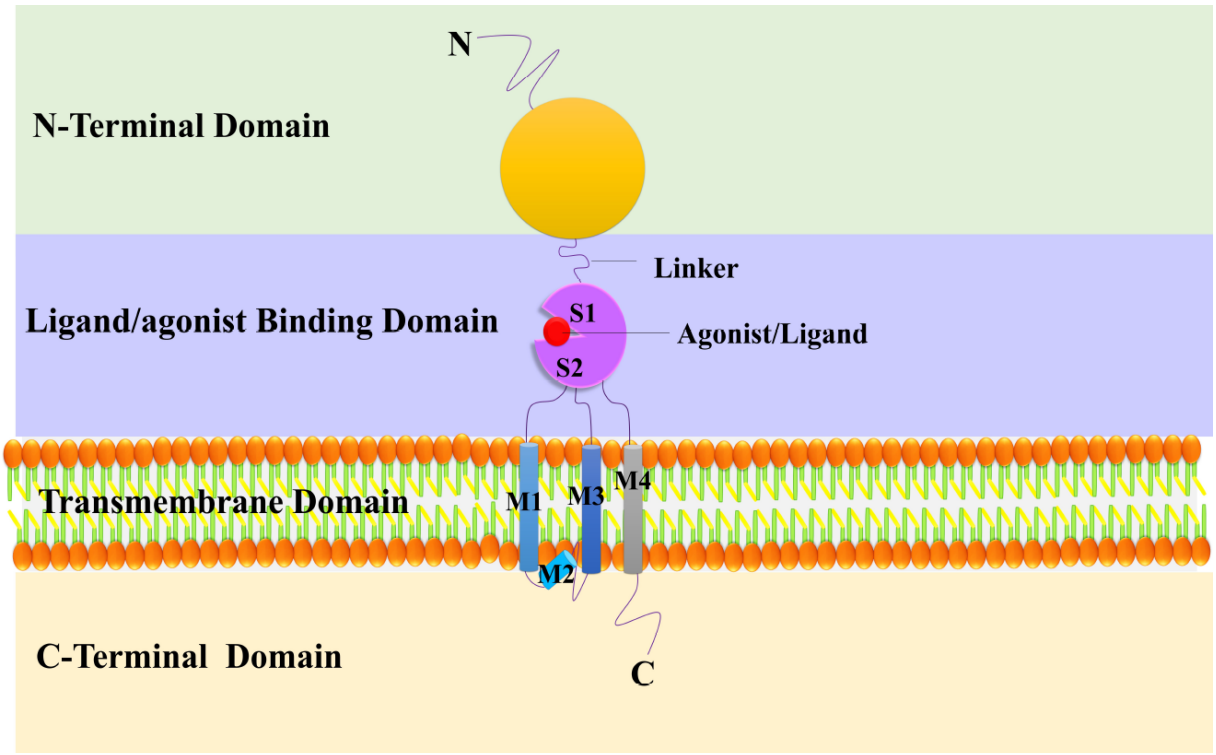


**Fig. (2).** NMDA receptor subunit highlighting major domains: amino terminal domain (ATD), ligand binding domain (LBD), transmembrane domain (TMD) comprising membrane-spanning helices (M1, M3 and M4) and P-loop region of M2 and C-terminal domain (CTD). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

GluN1 and GluN3 ligand binding site binds to glycine/D-serine, while GluN2 ligand binding site has affinity for the glutamate molecule. The activation of NMDA receptor requires the removal of $Mg^{2+}$ from the channel. At resting membrane potentials, external $Mg^{2+}$ penetrates the NMDA receptor pore and contrary to $Ca^{2+}$, they cohere together and inhibit ion permeation [66, 67]. However, at negative membrane potentials, a net inward driving force for $Mg^{2+}$ is generated due to different concentrations of extracellular (millimolar) and intracellular (micromolar) $Mg^{2+}$. To remove $Mg^{2+}$ from the pore and for permeant ion flow, a depolarization of adequate amplitude and duration is required. As a result, NMDA receptor acts as a molecular coincidence detector, *i.e.*, the opening of the channel requires the concomitance of presynaptic glutamate release and extreme postsynaptic membrane depolarization for

removal of $Mg^{2+}$ block from the channel [39, 67, 68]. These dual processes, simultaneously with their slow activation and deactivation kinetics, permit NMDA receptors to assimilate and decode the incoming synaptic activity. The high influx of $Ca^{2+}$ through NMDA receptors enables them to transfer specified patterns of synaptic input into long-lasting modifications in synaptic strength [69].

NMDA receptors have a pivotal role in the adequate development of the CNS and in maintaining the functional and structural plasticity of the brain. Specifically, they possess fusion of the special properties to carry out important tasks, including (a) high affinity, particularly for glutamate, an excitatory transmitter, (b) high permeability for $Ca^{2+}$ ions, (c) slow kinetics of activation and deactivation, (d) articulate voltage dependence and (e) substantial cytoplasmic domains, allowing them to be a part of and to establish the macromolecular synaptic signalling molecules [69].

Over the last few decades, many studies have been conducted to discover the impact of genetic alterations, Aβ oligomers, tau protein and several other factors on the functioning of NMDA receptors and AD. However, in AD, the main factors responsible for the alteration of NMDA receptor signalling include the availability of glutamate and the modification of NMDA channel functions [47]. Studies have shown the severe loss of NMDA receptors in the frontal cortex and hippocampus region, the lower level of D-serine and low uptake of D-aspartate in the patients suffering from AD [70-72]. Other experiments revealed that the accumulation of Aβ oligomers activates dysregulation of NMDA receptors resulting in abnormal $Ca^{2+}$ levels contributing to synaptic dysfunction in AD [73-75]. For example, in cultured cortical neurons, Ferreira and co-workers [76] proved that GluN2B subunit is the main site for Aβ oligomers accumulation which further stimulates the abnormal rise in $Ca^{2+}$, while Texidó and co-workers [77] showed that Aβ induced activation of Glu2A subunit of NMDA receptor in Xenopus laevis (non-neuronal cells). Lately, Sun *et al*. [78] reported that along with neuronal degeneration, the stimulation of extra-synaptic NMDA receptors generates tau protein overexpression. Indeed, tau, a key component of NFT, is an important pathological marker for AD. In the post-synaptic density, tau is essential for Fyn-mediated NMDA receptor. Fyn belongs to the Src family of tyrosine kinases that elevates GluN2B subunit activity of NMDA receptors by phosphorylation of Glu N2B subunit at Y1472 [79-81]. Thus, the excess of Fyn accompanies the excess of tau in AD dendrites which increases the activity of NMDA receptor, leading to surging the dendrites with harmful $Ca^{2+}$ level. The $Ca^{2+}$ driven excitotoxicity can damage the postsynaptic sites and ultimately cause neuronal death. Several studies have also suggested that glutamate-induced excitotoxicity is increased by the overexpression of tau protein and can be prevented by its reduction [51, 82-85]. Moreover, the hypo-functioning of NMDA receptors is also neurotoxic, resulting in deterioration and brain death [86, 87]. Sequentially, glutamate-induced excitotoxicity results in enhancing tau expression and phosphorylation, which also leads to neurodegeneration and loss of synaptic plasticity [88-90].

### 3.2. Current Approved Drugs Targeting NMDA: Pros and Cons

Globally over the past few decades, researchers have been continuously making significant efforts to discover new AD targets and develop therapeutic tools, techniques and agents for the successful treatment of AD. Though, the precise pathways and mechanisms responsible for AD are not yet well understood, which results in a high percentage of failure in current available therapeutic approaches. Currently approved therapeutic strategies to slow the rate of AD progression are generally based on symptomatic treatments and include the use of cholinesterase inhibitors, NMDA receptor antagonists, and combination therapy [7, 51]. The cholinesterase inhibitors group includes galantamine and rivastigmine, which are approved drugs for treating mild-to-moderate AD, and donepezil used for treating mild-to-severe AD [7, 91].

CNS disorders resulting from reduction and damaging of neurons due to excitotoxicity induced by glutamate have a potent ability to get treated by using NMDA receptor antagonists. Current studies suggest that these agents targeting the function and downstream signalling pathways of NMDA receptors are able to re-establish the neuronal network and can be effective against AD [92]. Phencyclidine (PCP), MK-801, ketamine and memantine are non-competitive antagonists used to treat AD targeting NMDA receptors (Fig. **3**). PCP is a synthetic arylcyclohexylamine developed in the 1950s that acts as an anaesthetic agent [93]. Briefly, it acts in preventing the opening of channel in the NMDA receptor complex [94, 95]. MK-801, also known as dizocilpine is an antagonist of excitatory amino acid transmitters at the NMDA receptor site [96]. Finally, the drug ketamine acts by the open channel block mechanism and is an approved anaesthetic compound that can be used alone or in combination [97]. Unfortunately, phencyclidine, MK-801 and ketamine show strong affinity and prolonged cohesion on the receptor and are linked to severe side effects, including developmental abnormalities, hallucinations, and even coma. So, their therapeutic implementation for AD is hindered [98-100]. Few other non-competitive NMDA receptor antagonists are also available, like ifenprodil, CP-101, 606 and RO 25-6981, which act on different subunits of NMDA receptors [101-105]. Memantine, also known as 1-amino-3,5, dimethylad amantane, was first discovered in the year 1963 and is the extensively studied and used molecule for treating AD among all the known NMDA receptor antagonists [106]. It is a derivative of an antiviral component amantadine and consists of 3 ring structure along with two methyl groups and one amine group (Fig. **3**) [107]. Relative to other NMDA antagonists, memantine possess lower affinity, avoids prolonged cohesion toward receptor and is well tolerated, and thus can be used for the treatment of AD at different stages [108, 109]. Among others, it prevents the excitotoxicity mediated by NMDA receptor and shows stronger functional voltage dependency and faster kinetics relative to other high affinity antagonists [42, 110]. Similarly to $Mg^{2+}$, memantine blocks the NMDA receptor channel and does not renounce the channel when tonic-pathological hyper-activation is present in the receptor, but at the same time, allows the channelling of transient signals important for functions, such as memory

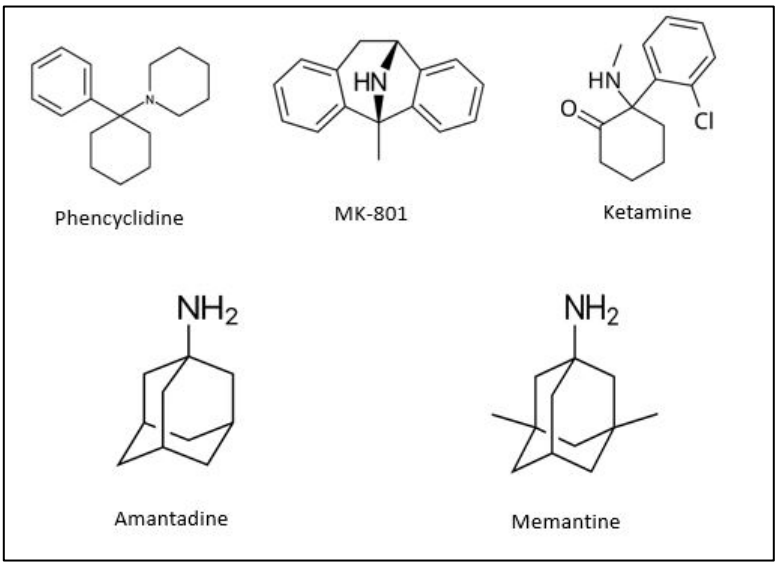


**Fig. (3).** Structures of NMDA receptor antagonists.

and learning. Also, it has been reported that memantine elevates the release of neurotrophic factors from astroglia which induces neuroprotective activity [111]. To date, it is known as a promising NMDA receptor antagonist and shows advantages against AD with few side effects [51, 110, 112]. However, combinational therapy, including the cholinesterase inhibitor, donepezil and memantine is proven to be more potent than the use of memantine alone [113]. Donepezil and memantine at a daily concentration of 28 mg and 10 mg, respectively, show beneficial results in symptoms relief, like those related to cognition, language and behaviour in AD patients [114, 115]. However, this combinational therapy has shown low effects in mild-to-moderate AD patients [116]. In conclusion, all available NMDA receptor antagonists used to treat AD can only provide symptomatic benefits.

### 3.3. From Immediate Symptoms Relief to AD Progression Blockage

The characteristic features of AD include impairment of memory, learning, cognitive skills and loss of proper brain functioning. However, behavioural and psychological symptoms of dementia (BPSD), apathy, depression, *etc*., are also strongly linked to AD progression and can worsen with time if not treated. Almost all of these symptomatic indications of AD are associated with synaptic plasticity, in which NMDA receptors are directly or indirectly involved. Briefly, the activation of NMDA receptors increases the intracellular concentration of $Ca^{2+}$, essential for synaptic plasticity with long-term potentiation and long-term depression [51, 117-119], where long-term potentiation is related with synapse growth and long-term depression is responsible for synaptic death. However, dysregulation of NMDA receptor can result in the induction of long-term depression and synaptic loss, leading to cognitive impairment, dementia, *etc*. [120-122].

Currently available drugs (cholinesterase inhibitors and NMDA antagonists) in the market used in the treatment of AD only result in symptomatic relief. Memantine consumed by AD patients with moderate-to-severe disease, shows better cognitive results than placebo [123, 124]. This antagonist also helps in reducing the symptoms of AD and acts as a neuroprotective agent [7, 125]. Several other studies reported the significant effect of memantine (20 mg/day) ameliorating both behavioural and psychological symptoms, like delusion, agitation/aggregation, irritability and hallucination in AD patients [126-128]. Additionally, memantine used in combination with donepezil at different doses also seems to be effective in treating moderate-to-severe AD patients [129-131]. Unfortunately, the currently available AD drugs do not fully treat the disease; instead, they assist in slowing down the AD progression and help in suppressing symptomatic problems, like dementia, cognitive and behaviour impairment, *etc*., that appear during the disease course.

## 4. PRECISION MEDICINE: PROMISSORY INTERVENTIONAL STRATEGY

The Precision Medicine Initiative, also known as personalized medicine, created by the National Institute of Health (NIH) and other research centers, is patient-focused approach with the ultimate goal of both improving short- and long-term outcomes, where all clinical decisions take into consideration the individual variability at genetic, environmental and lifestyle level [132]. According to epidemiological data, risk models have estimated that around 1/3 of AD cases can be prevented if modifiable risk factors are taken into account, namely dietary habits, physical activity and proper management of underlying diseases [133]. Environmental pollution has been increasingly reported as significantly impacting the incidence of neurological diseases, including AD, as it triggers neuroinflammation, oxidative stress, also exerting a marked effect on sleep fragmentation and impaired cognition. Results from a cohort study on two populations demonstrated that those living close to major roadways have a higher incidence of dementia [134], thus underlining the importance of establishing key interventions at environmental, behavioral and dietary levels [135]. Also, the contribution of brain-gut-microbiota axis disturbances to the pathogenesis of AD has been proved by many experi-

mental and clinical data. It has been assumed that gut bacterial amyloids exposure, which shares similarities in the tertiary structure with the human CNS amyloids, may enhance the inflammatory response to endogenous neuronal amyloids [136]. Moreover, high calprotectin levels, an intestinal inflammation marker that can form amyloid oligomers and fibrils similar to Aβ and α-synuclein, have been stated in the brain of AD patients [137]. Obviously, dysbiosis caused by poor diet, such as high-fat diet, especially in the elderly, may boost the pathogenesis of neurological diseases, meaning that the gut microbiota modulation-targeted therapy, namely rich in prebiotics and probiotics may be a new therapeutic strategy in AD [138, 139]. The use of sodium oligomannate was also found to be able to decrease the accumulation of phenylalanine/isoleucine, while it suppresses neuroinflammation and reverses cognitive impairment [140]. Polyphenols, antioxidants-rich molecules, may also contribute to counteract oxidative stress induced by brain injuries and ultimately decrease the risk of AD [141]. Caloric restriction has been identified as a good strategy to improve the proportion of *Lactobacillus* spp. [142]. Similarly, fecal microbiota transplant from wild-type mouse to amyloid and neurofibrillary tangles transgenic mouse model of AD led to a decrease in β-amyloid plaques and NFT formation, while improving glial reactivity and cognitive impairment [143].

### 4.1. APOE and Alzheimer Disease

As stated above, APOE-ε4 carrier is one of the most well-established genetic influencers on late-onset AD risk, whereas APOE-ε2 is linked to a reduced risk of AD [144-146]. Imaging studies have demonstrated that APOE-ε4 carriers possess higher and lower levels, respectively, of β-amyloid and CSF Aβ42 compared to non-carriers [147], being also stated that APOE-ε4 homozygotes have 5-fold higher risk of developing AD compared to heterozygotes [148]. Based on such findings, it has been proposed that combining drugs targeting APOE function along with other anti-Aβ approaches that either limit Aβ plaques or inhibit Aβ production can be a useful therapeutic strategy at different disease stages [149]. For example, bapineuzumab, a humanized monoclonal antibody targeting the Aβ N-terminal residues, prevents Aβ deposition, reduces the phosphorylated tau levels in the brain of APOE-ε4 carriers, although it exerts some adverse effects, like vasogenic cerebral oedema and microhemorrhage, and cannot avoid cognitive and functional decline in clinical studies [150].

Although results are still controversial, the levels of APOE in CSF and plasma tend to be lower in AD patients than in healthy individuals [151]. Therefore, the use of molecules capable of increasing the brain APOE expression may be a plus to block or even slow the AD progression all APOE genotypes. Briefly, peroxisome proliferator-activated receptor-γ and LXRs form complexes with RXRs and control the APOE expression; thus, agonists or antagonists of such nuclear receptors may be viewed as candidate APOE modulators [152]. An *in vivo* study demonstrated that the administration of bexarotene, an RXR agonist, decrease the Aβ plaque deposition and ameliorates cognitive function in an ApoE-dependent way [152]. Similarly, the LXR agonist (GW3965 and TO901317) also boosts brain APOE levels, facilitating Aβ42 clearance, and reversing contextual memory deficit in amyloid mouse models [153].

Anti-APOE4 immunotherapies are based on the use of anti-APOE-ε4 antibodies capable of crossing the BBB to counteract the negative effects of APOE-ε4 [154]. In APP transgenic mice, anti-APOE antibodies were able to prevent new Aβ plaques' deposition, clear pre-existing plaques and ameliorate the spatial learning performance and resting-state functional connectivity without exerting changes in total plasma cholesterol levels [155], since 'HAE-4' antibody recognizes in a better way the nonlipidated forms of APOE-ε4/APOE-ε3, effectively reducing the total Aβ plaque burden by a FcγR-dependent mechanism in an APP/APOE-ε4 mouse model [156].

Another class of promissory molecules is antisense oligonucleotides (ASOs), which are synthetic single-stranded strings of nucleic acids that selectively bind to specific pre-messenger ribonucleic acid (pre-mRNA)/mRNA sequences and alter protein synthesis through distinct ways [157]. In a study it was shown that 3 intracerebroventricular injections of ASO reduce APP levels by 43-68% in specific brain regions and ameliorate learning and memory deficits [158]. In addition, in mice, the intravenous administration of APP targeting ASO led to a marked reduction in AβPP-signal and neuroinflammation, while promoted learning and memory [159]. However, the advancement of ASOs targeting APP was delayed due to their poor capacity to cross the BBB [157]. Hinrich *et al*. (2016), in a study with mice, stated that a single dose of ASO corrected APOE ε2 splicing for up to 6 months and help in the improvement of synaptic function, memory, and learning [160]. In another study, ASO led to a selective decrease in human tau mRNA and tau protein in a mouse model of tauopathies through decreasing phosphorylated tau burden, hippocampal volume loss, and neuronal death [161]. In a recent study, the administration of ASO in mouse models expressing human tau led to a decrease in MTBRs without changing the total amount of tau protein [162]. A phase I/II randomized, double-blind, placebo-controlled study is currently being done by Ionis Pharmaceuticals Inc. to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of an intrathecally administered 2'MOE ASO (NCT03186989) in mild AD patients. Recently, Litvinchuk *et al*. (2021) found that the use of APOE ASOs reduces the APOE ε4 levels by almost 50% and those of neurofilament light chain (NfL) protein, also exerting protection against tau pathology and associated neurodegeneration, decreasing neuroinflammation, and preserving the synaptic density in ASO-treated mice [163].

As stated above, the structural correction of APOE-ε4 may be viewed as an interesting therapeutic approach for ApoE-related processes in AD. GIND25 and PH002, 2 small molecular compounds, have been identified as being able to reverse the detrimental effects of APOE-ε4 by blocking the neuronal domain-domain interaction [164], however their efficacy in *in vivo* models was still not addressed. Gene-editing CRISPR technique has also been used to convert APOE-ε4 gene to APOE-ε3, overcoming the APOE-ε4 problem without affecting APOE-ε3 expression [165]. In a study CRISPR/Cas9 systems were used to induce double-stranded DNA breaks in HEK293T cells and immortalized mouse astrocytes containing APOE-ε4, being stated no new double-stranded DNA breaks, meaning a lower risk of side effects

due to unwanted mutations [166]. In another study, Wadhwani *et al.,* (2019) investigated CRISPR/Cas9-mediated editing on iPSCs derived neurons from two patients with APOE-ε4/ε3 genotypes and isogenic neuronal cells with APOE3/E3 were produced, being comparable in terms of differentiation, survival rate, density and average neurite length per cell. However, the number of neurite branch points per cell was higher in E3/E3 neurons, being also more resistant to cytotoxins [167]. Nonetheless, the successful *in vivo* application of CRISPR to ApoE4 has not yet been reported.

APOE-mimetic peptides containing the receptor-binding region have also been studied *in vitro* in order to compensate the loss-of-functional aspect conferred by APOE4, being stated a good ability to suppress neuronal cell death and calcium influx associated with N-methyl-D-aspartate exposure [168]. For example, the APOE-mimetic peptide Ac-hE18A-NH2 that consists of tandem repeats of the apoE receptor-binding region, led to a decrease in Aβ production in wild-type mice [169] and ameliorated cognition however, it was observed to suppress glial activation/Aβ deposition in amyloid model mice [170]. Also, COG112, a chimeric peptide containing the receptor-binding region apoE but not lipid- or Aβ-binding region, was able to improve symptoms in adult neurogenesis in AD mouse models by reducing neuroinflammation, tau hyper-phosphorylation and defects [171]. However, these effects, despite promising, have not been fully evaluated in the presence of human APOE isoforms, being thus necessary for further efforts to deeper knowledge on this field.

APOE promotes the Aβ cellular uptake through LDLR and LRP1 receptors while also suppresses the Aβ interaction through competition for those receptor binding [172]. Thus, considering that such events have critical roles in brain Aβ clearance in AD [173]. Indeed, rifampicin, caffeine, and fluvastatin, drugs used to increase LRP1, are likely to have protective effects against AD [174]. In addition, given that APOE ε4 impairs the recycling of apoER2 and VLDLR, it may increase the Aβ output [175]. Taken together, data presented here underline that boosting the expression of such receptors is an upcoming therapeutic option to impair Aβ pathology, although further studies are needed.

### 4.2. MTHFR and Alzheimer Disease

A recent epigenome study in consecutive Alzheimer Disease & Memory Clinic patients revealed that metabolic folate pathways and methyl donor reactions facilitated by B-group vitamins may be critical in late-onset AD (LOAD) pathogenesis, with the high prevalence of methylenetetrahydrofolate reductase (MTHFR) mutations being found in about 92.5% of elderly patients [176], possibly due to the high levels of homocysteine, that are directly involved in the inflammation and significantly linked to cognitive decline and an increased risk of AD [177]. Thus, MTHFR genotype status may be viewed as a guide to design targeted AD preventive interventions. For example, supplementation with cyanocobalamin, folic acid, and pyridoxin revealed to be able to slow the cognitive decline in individuals with increased homocysteine levels [178]. Additionally, the replacement of the traditional B-vitamins by their methylated forms may improve clinical outcomes, as they do not require hepatic conversion to their active forms [179].

## CONCLUSION

AD progression is associated with continuous dysregulation in the structure and function of the brain regions, which are essential for memory and cognition; thus, several new techniques and approaches have been used to optimize the therapeutic potential against AD. Presently, it has been proved that NMDA receptors are involved in controlling synaptic plasticity, synaptic transmission and help in conducting memory and learning functions. However, all available NMDA receptor antagonists used to treat AD can only provide symptomatic benefits. Currently, precision medicine focusing on individual variability at genetic, environmental and lifestyle level is viewed as a key therapeutic strategy to optimize the clinical outcomes of AD.

It has been proposed that combining drugs targeting APOE function along with other anti-Aβ approaches can be a useful therapeutic strategy at different disease' stages. Anti-APOE4 immunotherapies and antisense oligonucleotides (ASOs) could ameliorate the synaptic function, memory and learning performance. The use of CRISPR/Cas9 systems and APOE-mimetic peptides still needs further efforts to gain deeper knowledge in this field. Additionally, MTHFR genotype status may be viewed as a guide to design targeted AD preventive interventions.

Despite all the advances stated and in the absence of any efficient therapy, additional researches dealing with new targets, techniques or novel neuroprotective agents against AD are still needed.

## LIST OF ABBREVIATIONS

PD = Parkinson's Disease

NFT = Neurofibrillary Tangles

AChE = Acetylcholinesterase

BBB = Blood Brain Barrier

## CONSENT FOR PUBLICATION

Not applicable.

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## CONFLICT OF INTEREST

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