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REVIEW ARTICLE

Exploring NMDA Receptor Antagonists: Comprehensive Structural Analysis, Emerging Research Trends, and Therapeutic Prospects for Alzheimer's Disease

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SUMMARY

Alzheimer's disease is the leading neurodegenerative disorder worldwide. The NMDA excitatory glutamatergic receptor serves as a vital mediator in various intracellular signaling cascades for different physiological like maintenance of neuronal health, synaptic plasticity, homeostatic plasticity, excitatory transmission, memory, and learning function. Dysregulation and overactivation of this receptor lead to excitotoxity, contributing to neurodegeneration and loss of cognitive function. Understanding the underlying mechanisms of overactivation-induced neurotoxicity is of paramount importance for developing novel therapeutic strategies and exploring their effectiveness in managing memory loss. Memantine, the sole clinically approved NMDAR antagonist, selectively targets non-synaptic receptors. This review covers the organization and functional aspects of glutamatergic receptors, highlighting their role as neuroprotective alongside the deleterious impact of excitotoxicity, which results in synaptic disruption and neuronal death. It emphasizes recent advances in compounds targeting the NMDA receptor and the assessment of their potency through SAR investigation, structural attributes, and design strategies. Additionally, it explores clinical trials currently underway of agents that target NMDA receptors to gain a thorough grasp of their effectiveness in treating Alzheimer's disease.

Keywords: *Alzheimer's disease, NMDA receptor antagonist, excitotoxicity, amyloid plaques, tau neurofibrillary tangles.*

NMDA Reseptör Antagonistlerinin İncelenmesi: Alzheimer Hastalığı İçin Kapsamlı Yapısal Analiz, Yeni Araştırma Eğilimleri ve Terapötik Perspektifler

ÖZ

Alzheimer hastalığı, dünya genelinde en yaygın nörodejeneratif hastalıktır. NMDA uyarıcı glutamaterjikglutaminerjik reseptör, nöronal sağlığın sürdürülmesi, sinaptik plastisite, homeostatik plastisite, uyarıcı iletim, hafıza ve öğrenme gibi çeşitli fizyolojik süreçlerde yer alan hücre içi sinyal yolaklarının önemli bir aracısıdır. Bu reseptörün düzensizliği ve aşırı aktivasyonu, eksitotoksisiteye yol açarak nörodejenerasyona ve bilişsel fonksiyon kaybına katkıda bulunur. Aşırı aktivasyona bağlı nörotoksisitenin altında yatan mekanizmaların anlaşılması, yeni terapötik stratejilerin geliştirilmesi ve bunların hafıza kaybının yönetimindeki etkinliğinin araştırılması açısından büyük önem taşımaktadır. Klinik olarak onaylanmış tek NMDAR antagonisti olan memantin, seçici olarak sinaptik olmayan reseptörleri hedefler. Bu derleme, glutamaterjik reseptörlerin organizasyonu ve fonksiyonel özelliklerini kapsamakta; nöroprotektif rollerinin yanı sıra, sinaptik bozulma ve nöronal ölüme yol açan eksitotoksisitenin zararlı etkilerini vurgulamaktadır. Ayrıca, NMDA reseptörünü hedefleyen bileşiklerdeki son gelişmeleri; bunların etkinliğinin SAR incelemeleri, yapısal özellikler ve tasarım stratejileri aracılığıyla değerlendirilmesini ele almaktadır. Bunun yanında, Alzheimer hastalığının tedavisindeki etkinliklerini daha iyi anlamak amacıyla NMDA reseptörlerini hedefleyen ajanlara yönelik devam eden klinik çalışmaları da incelemektedir.

Anahtar Kelimeler: *Alzheimer hastalığı, NMDA reseptör antagonisti, eksitotoksisite, amiloid plaklar, tau nörofibriler yumaklar.*

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INTRODUCTION

Presently, a significant portion of the global population is affected by neurodegenerative disorders, which include Parkinsonism and Alzheimer's disease (AD), that are progressively escalating with the passage of time. AD is the biggest challenge of the century, and research is at the forefront. So far, there is no medication available that can completely reverse or prevent this neuronal loss (Tzioras, McGeachan, Durrant, & Spires-Jones, 2023). It is the most prevalent and insidious neurodegenerative disorder (Vejandla, Savani, Appalaneni, Veeravalli, & Gude, 2024). It is irreversible and incurable. Neurons are the elemental components of the nervous system, which is responsible for disseminating information in chemical and electrical forms throughout the body. The first region to show neurodegeneration is the part of the hippocampus in AD, and damage leads to cognitive deterioration, which brings about memory impairment (Mayeux, 2003). Impairments in non-memory aspects of thinking, including word processing, visual/spatial problems, reasoning, or decision-making. It is also seen early in astrocytes, such as glial cells, which also play a vital role in the progression of AD (Rostagno, 2022). It can occur sporadically or be inherited. Over the past decade, the prevalence of AD cases has become highly evident (Nguyen, Dang, Jang, & Park, 2023; Zeliger, 2023). AD is characterized by several pathological hallmarks (Figure 1.), which include: (i) amyloid plaques consist of beta amyloid peptide, which gets deposited outside the neuron, which interrupts the signaling and communication function, may spark inflammatory response and degrades nerve cell fragments (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011; Taniguchi et al., 2022); (ii) neurofibrillary tangles, which accumulate inside neurons, consist of tau protein with abnormal phosphorylation that are present inside the neurons, which interrupts the transportation system that delivers substances throughout the nerve cell and brings about cell death (Jadhav, Saraswat, Vyawahare, & Shirode, 2024); (ii) synaptic and neuronal loss (Meftah & Gan, 2023).

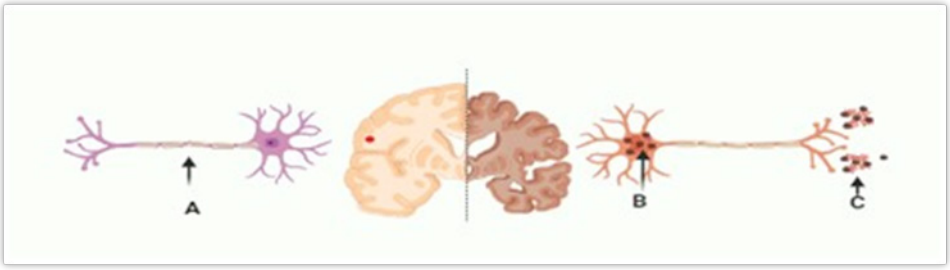


Figure 1. (A) Healthy brain with healthy nerve cell vs (B) Alzheimer's brain with Tau neurofibrillary tangles; (C) and Amyloid plaques. [included figure is original and non-published was created by using biorender.com]

Recognized pharmacological interventions for Alzheimer's disease

Until now, no treatment is available that can reverse or slow down AD; only symptomatic treatments exist, which aim to maintain neurotransmitter imbalances (Brenowitz et al., 2021; Pardo-Moreno et al., 2022). Table 1 and Figure 2 present the drugs donepezil, galantamine, rivastigmine, and memantine (Kabir et al., 2019; Lipton, 2004a), which are approved by the US Food and Drug Administration (Alhazmi & Albratty, 2022; Yiannopoulou & Papageorgiou, 2020). Currently, available therapies for Alzheimer's disease provide only symptomatic relief and aim to slow its progression rather than cure it. The FDA classifies these treatments based on cognitive assessment scores, which evaluate memory, learning ability, reasoning, and orientation to time and place. Since AD results in progressive neuronal damage, these drugs primarily support the function of surviving nerve

cells. Their overall purpose is to preserve cognitive abilities for as long as possible and enhance the patient's well-being. The neurotransmitter acetylcholine, essential for learning and memory, declines as nerve cells are lost. Cholinesterase inhibitors help by preventing acetylcholine breakdown in the synaptic cleft, thus maintaining higher levels of this messenger to support residual neuronal function. Memantine, in contrast, mitigates excitotoxicity by regulating excessive glutamate signaling, which otherwise contributes to neuronal injury. Moreover, monoclonal antibody therapies have been developed to target amyloid-beta plaques, a key pathological hallmark of AD, thereby reducing plaque accumulation and slowing cognitive decline (Alhazmi & Albratty, 2022; Singh et al., 2012; Yiannopoulou & Papageorgiou, 2020). Recently, donanemab (kisunla), an anti-monoclonal antibody targeting deposited amyloid-beta plagues, was approved by the U.S. Food and Drug Administration in July 2024 for the treatment of patients with early symptomatic Alzheimer's disease, including mild cognitive impairment and mild dementia due to Alzheimer's disease, with confirmed amyloid pathology. Donanemab represents a disease-modifying therapeutic approach designed to reduce amyloid-beta plaque burden and slow clinical progression.

Table 1. Approved drugs by the U.S. FDA for the treatment of Alzheimer's disease, along with their approval year, including their mode of action and brand name

Category	Drug/(Brand name)	How they act	Approval year
1.Cholinesterase inhibitors	Donepezil/ (Aricept®)	Boost the acetylcholine neurotransmitter level responsible for memory and learning function.	1996
	Rivastigmine/ (Exelon®)		2000
	Galantamine/ (Razadyne®)		2001
2. NMDA (N-methyl-D-aspartate) receptor antagonist	Memantine/ (Namenda®)	Glutamate neurotransmitter regulation.	2003
3. Monoclonal antibody	a)Aducanumab/ (Aduhelm®) b)Lecanemab / (Leqembi)	Target beta amyloid plaque.	2021 2023

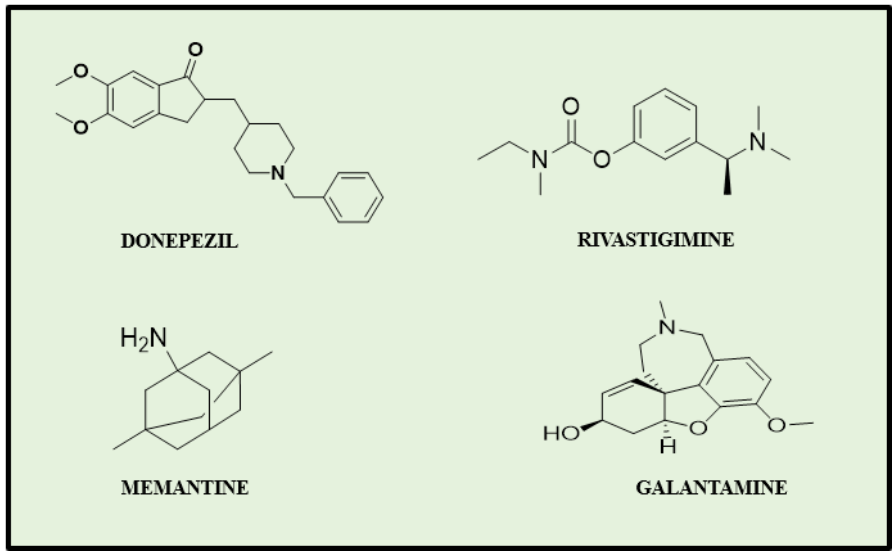


Figure 2. Currently approved therapeutics for the treatment of Alzheimer's disease [included structures were created by using ChemDraw]

NMDA RECEPTORS SIGNALLING TRANSDUCTION PATHWAYS FACILITATE SYNAPTIC PLASTICITY

The NMDA receptor is the central mediator in memory and learning functions (Tiwary, Oswal, Malvankar, & Kumar, 2023). It is an ionotropic excitatory glutamatergic receptor (Liu et al., 2023; Zhou & Tajima, 2023). It is heterotetrameric, which consists of two Glu 1-glycine/D-serine binding sites and two Glu 2-glutamate binding sites (Chen, Dong, Wu, & Yi, 2023; Vieira, Yong, Roche, & Anggono, 2020) (or Glu-3 subunits). This dimer represents the fundamental functional structure in the receptor (Egunlusi & Joubert, 2024; Karakas & Furukawa, 2014; Regan, Romero-Hernandez, & Furukawa, 2015). NMDA receptor organization comprises an amino-terminal domain present in the extracellular part and the ligand-binding domain, where glycine/D-serine and glutamate bind. It also has polyamine and redox regulatory sites (Stephenson, Cousins, & Kenny, 2008). Ion channels lie in the transmembrane domain, which contains a magnesium blockade site, and lastly the intracellular carboxyl terminal domain (Figure 3.) (Billard, 2018).

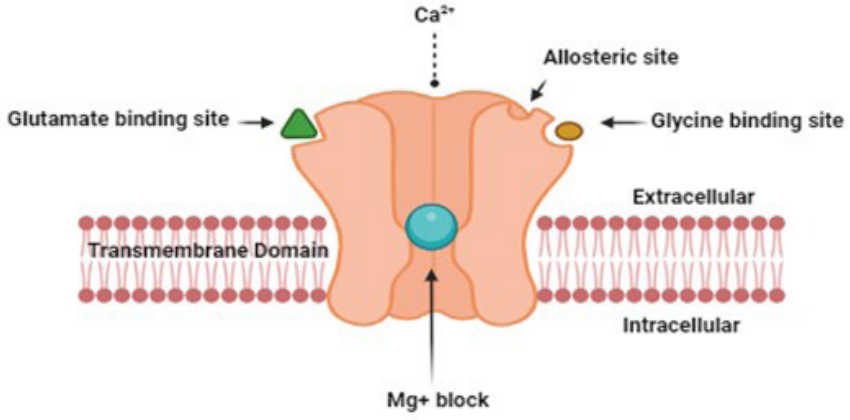


Figure 3. Organization of the NMDA receptor [included figure is original and non-published was created by using biorender.com]

A synaptic cleft is a place where one neuron makes a connection with another. Dendrite receives signals and passes them down to the axon terminal buttons, which contain neurotransmitter-filled vesicles. Action potential triggers the exocytosis release of neurotransmitter in the synaptic cleft, where it binds to its respective receptor present in the postsynaptic neuron, bringing about a cascade of chemical changes that leads to opening and closing the ion channels (Mony & Paoletti, 2023; Rajani, Sengar, & Salter, 2020). Ions exist at varying concentrations on the extracellular and intracellular sides, separated by ion-gated channels that regulate their movement into and out of the cell. The signaling pathways of the NMDA receptor proceed through the following steps:

AMPA receptor activation

After release of glutamate from presynaptic neuron to synaptic cleft, it binds to the AMPA receptor, which is permeable to Na^+, K^+ (Chang et al., 2006; Hardingham, 2009) and the NMDA (highly permeable to Ca^{2+} ion) receptor. After glutamate is released from the presynaptic neuron into the synaptic cleft, it binds to AMPA receptors, which are permeable to Na^+ and K^+, and to NMDA receptors, which have high Ca^{2+} permeability. At rest, the NMDA receptor is blocked by Mg^{2+} ions. Weak stimulation opens only the AMPA-mediated channels, allowing Na^+ influx into the postsynaptic neuron, causing membrane depolarization known as an excitatory postsynaptic potential (EPSP) and bringing the membrane closer to the threshold potential (Babaei, 2021; Keifer & Zheng, 2010; Pereyra & Medina, 2021).

NMDA receptor activation

The NMDAR involves the binding of glutamate and the removal of Mg^{2+} block to activate. Postsynaptic depolarization causes the electrostatic repulsion, which opens the Mg^{2+} block and activates the NMDAR, which ultimately causing more influx of Na^{+} ions as well as Ca^{2+} ions into the neuron (Whitehead, Regan, Whitcomb, & Cho, 2017).

Calcium signaling cascade

Calcium signaling plays a crucial role in synaptic plasticity. Acting as a second messenger, calcium activates multiple intracellular pathways by binding to calmodulin and subsequently triggering calmodulin-dependent protein kinase II (CaMKII). CaMKII then phosphorylates downstream signaling proteins, promoting the enlargement of dendritic spines. Additionally, it phosphorylates AMPA receptors in postsynaptic neurons, increasing Na^{+} conductance and facilitating the insertion of more AMPA receptors from intracellular stores into the membrane. This increase in receptor density enhances synaptic stimulation, induces long-term potentiation, and strengthens synaptic efficacy (Hetman & Kharebava, 2006; MacDonald, Jackson, & Beazely, 2006; Morris, 2013). Furthermore, increased calcium influx in dendrite spines stimulates the production of retrograde messengers such as NO, which generate a retrograde signal transmitting signal from the axon terminal back to the presynaptic neuron to modulate the release of neurotransmitters (Dugar et al., 2024; Hardingham, 2006).

Glutamate signal termination

i) Glutamate is removed from the synaptic cleft by excitatory amino acid transporters, which are mainly located on the membranes of nearby astrocytes (glial cells) (Qiao et al., 2021; Verkhratsky & Kirchhoff, 2007). Within these cells, it undergoes conversion to glutamine via the enzyme glutamate synthetase before being shuttled back to glutamatergic neurons, ultimately leading to signal termination (Fontana, 2015).

ii) After prolonged activation, both receptors are desensitized.

iii) Once the postsynaptic neuron potential reaches the resting phase, magnesium reblocks the NMDA receptor, thereby halting the Ca^{2+} ion influx.

iv) Calcium hemostasis decreases calcium ion concentration and stops its signalling pathways (Lau et al., 2009).

v) Inhibitory receptor activation causes hyperpolarization to counterbalance glutamate-induced depolarization, and the cellular negative feedback mechanism downregulates the activity of the NMDA receptor (Hardingham & Bading, 2003).

NMDA RECEPTOR OVERACTIVATION LEADS TO EXCITOTOXICITY IN ALZHEIMER'S DISEASE

Glutamate is the main excitatory neurotransmitter in the brain, playing a critical role in cognitive functions and regulating various neural processes (Benarroch, 2018; Butterfield & Pocernich, 2003; Walton & Dodd, 2007). Maintaining its extracellular concentration within an optimal range is essential, as excessive levels can overstimulate glutamate receptors, leading to excitotoxicity and neuronal death (Baracaldo-Santamaría et al., 2023; Francis, 2005; Mota, Ferreira, & Rego, 2014; Yamin, 2009). In Alzheimer's disease, the accumulation of beta-amyloid plaques and neurofibrillary tangles disrupts the balance between glutamate release and reuptake, causing excessive glutamate in the synapse and further promoting neurodegeneration (Bordji, Becerril-Ortega, & Buisson, 2011; Huang et al., 2017; Shankar et al., 2007). Overactivation of the NMDA receptor leads to a pronounced influx of calcium ions into the postsynaptic neuron, which stimulates the generation of reactive oxygen species and nitric oxide, resulting in oxidative stress and mitochondrial dysfunction (Forero, Casadesus, Perry, & Arboleda, 2006; Kamat et al., 2016). This sets off destructive cascade pathways, activating enzymes such as calpain, endonuclease, ATPase, and phospholipase, which degrade the neuron's cell membrane,

allowing harmful substances and ions to enter (Foster, Kyritsopoulos, & Kumar, 2017). Mitochondrial breakdown occurs, releasing toxins and apoptotic factors that initiate apoptosis (programmed cell death) cascades, resulting in cell death (Carvajal, Mattison, & Cerpa, 2016; Collingridge & Monaghan, 2022). Additionally, necrosis (uncontrolled cell death) can occur through cell membrane rupture and inflammation, further damaging surrounding tissues (Figure 4.).

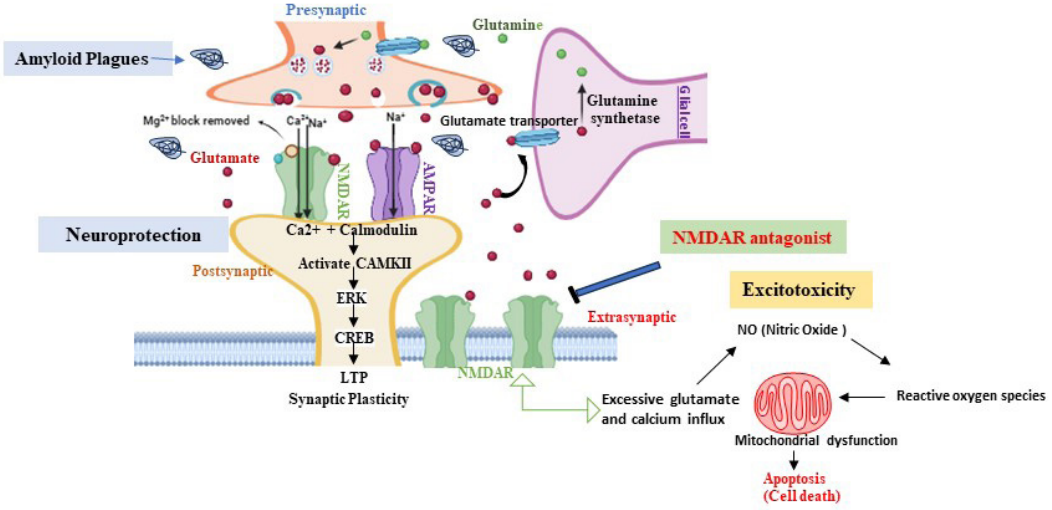


Figure 4. Systematic representation of neuroprotective mechanisms via NMDA receptor activation and excitotoxicity caused by overactivation of glutamate receptors. NMDA receptor antagonist (Memantine) prevents the binding of glutamate and calcium influx in nerve cells. [included figure is original and non-published was created by using biorender.com]

SYNTHETIC DEVELOPMENT AND SAR ANALYSIS OF NMDA RECEPTOR ANTAGONISTS

a) HDAC (histone deacetylases) inhibitors, like the NMDA receptor, play a pivotal role in synaptic plasticity and neuroprotection (Lu, Wang, Yu, Yu, & Yu, 2015). It has a close relationship to different hallmarks, i.e., beta-amyloid, tau phosphorylation, and oxidative stress (Noack, Leyk, & Richter-Landsberg, 2014; Olson et al., 2015; Xu et al., 2024) of AD, which makes it an interesting target against AD. He et al. (2020) designed various hydroxamic acid and anilide-based novel compounds (Figure 5.), in which they used different linkers and zinc binding groups to bind pharmacophoric moieties of memantine and SAHA (Vorinostat, HDAC inhibitor), which underwent evaluation for dual balanced inhibition of NMDAR (NMDA receptor) and HDACs. Their interactions are also supported by solved crystal structures of both the receptors (NMDAR subunit GluN1 and GluN2B (PDB: 4PE5) and hHDAC6 (PDB: 5EDU) by docking studies. Studies demonstrated that the hydroxamic acid-based compound with an aromatic linker (9a) possesses easy penetration in the blood-brain barrier, a good ADME profile, and protection of PC-12 cells from H_2O_2-induced cytotoxicity compared to Belinostat (PXD101), a novel and potent hydroxamate-type histone deacetylase inhibitor and memantine combination, but the results are not significant, and the EC_{50} was reported as 0.94 μM (He et al., 2020).

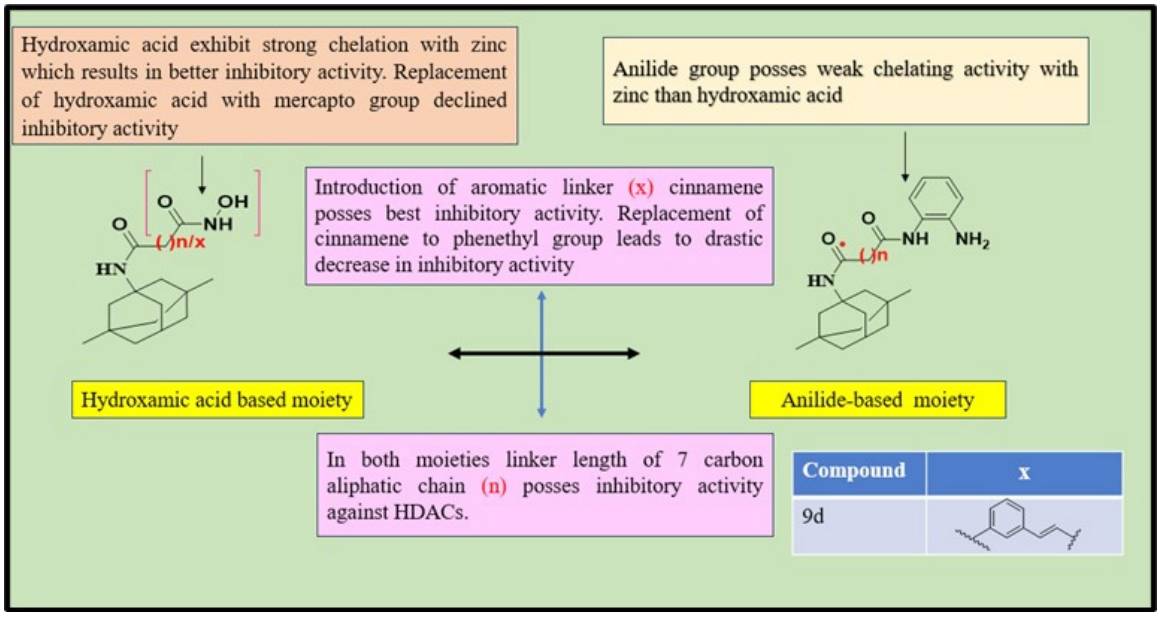


Figure 5. SAR of NMDAR-HDAC dual-target inhibitors for Alzheimer's disease

b) Makhaeva et al. (2015) developed and synthesized a series of γ-carboline (derived from dimebon) and phenothiazine (derived from methylene blue) conjugates using 1-oxo- and 2-hydroxypropylene linkers (Figure 6.). These conjugates were designed to target the cholinesterase family and glutamatergic receptors. Their inhibitory effects were tested against human erythrocyte acetylcholinesterase (AChE), equine serum butyrylcholineaterase (BChE), and porcine liver carboxylesterase (CaE). Overall, the compounds exhibited stronger inhibition of butyrylcholinesterase compared to acetylcholinesterase and carboxylesterase, showing higher activity than dimebon. Among the synthesized molecules, compounds C-1e and C-1f, which feature a carboline nucleus with an ethyl substituent (R_2–C_2H_5) connected via a 1-oxopropylene linker, demonstrated the highest inhibitory activity with IC_{50} values of 0.52 ± 0.01 μM and 0.58 ± 0.06 μM, respectively. Additionally, compound C-2c, incorporating a 2-hydroxypropylene linker with substitutions at R1 = CH_3O and R2 = CH_3, showed the most potent activity with an IC50 of 0.39 ± 0.02 μM. Previous studies have indicated the neuroprotective effects of dimebon and methylene blue in in vitro models of Amyotrophic Lateral Sclerosis when administered together (Atamna & Kumar, 2010; Cano-Cuenca, Solís-García del Pozo, & Jordán, 2013; Oz, Lorke, & Petroianu, 2009; Steele & Gandy, 2013). The synthesized conjugates were also assessed for their binding affinity to the MK-801 (dizocilpine) and ifenprodil sites of the NMDA receptor. Compounds containing 1-oxopropylene linkers exhibited approximately tenfold higher affinity for the MK-801 site compared to dimebon. Conversely, the 2-hydroxypropylene spacer series exhibited reduced affinity towards both binding sites (Makhaeva et al., 2015).

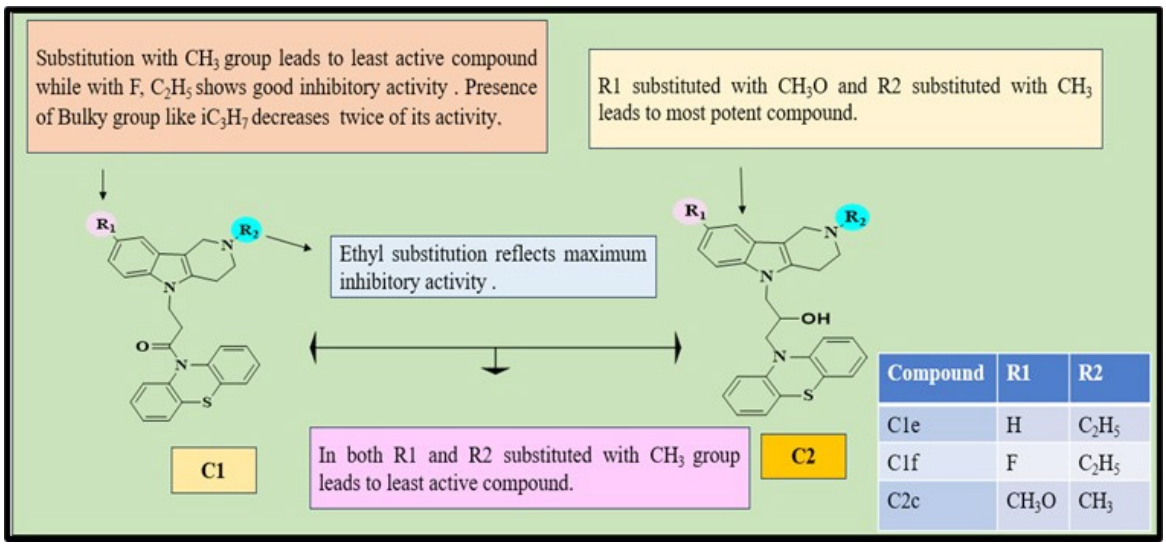


Figure 6. SAR of γ-carbolines and phenothiazine derivatives

c) Currently approved classes of drugs used in AD are NMDAR antagonists and cholinesterase inhibitors (Makhaeva et al., 2018; Rosini et al., 2008). Their clinical efficacy has been established in a fixed combination dose, and this suggests a promising direction for Pérez-Areales et al. (2019) to design and synthesize novel hybrid molecules by incorporating the pharmacophore moieties of benzohomoadamantanamine, a potent NMDA receptor antagonist, and 6-chlorotacrine a cholinesterase inhibitor hybrid utilizing two different lengths of linker and linkage position (Figure 7.) (Simoni et al., 2012). SAR analysis revealed that 13b, 18a, and 18b hybrid compounds exhibited good inhibitory activity, and their inhibitory activity was evaluated using various *in vitro* assays like the Ellman method, Fura-2 imaging These compounds showed favorable results and were found to be more potent than the parent drug (Pérez-Areales et al., 2019).

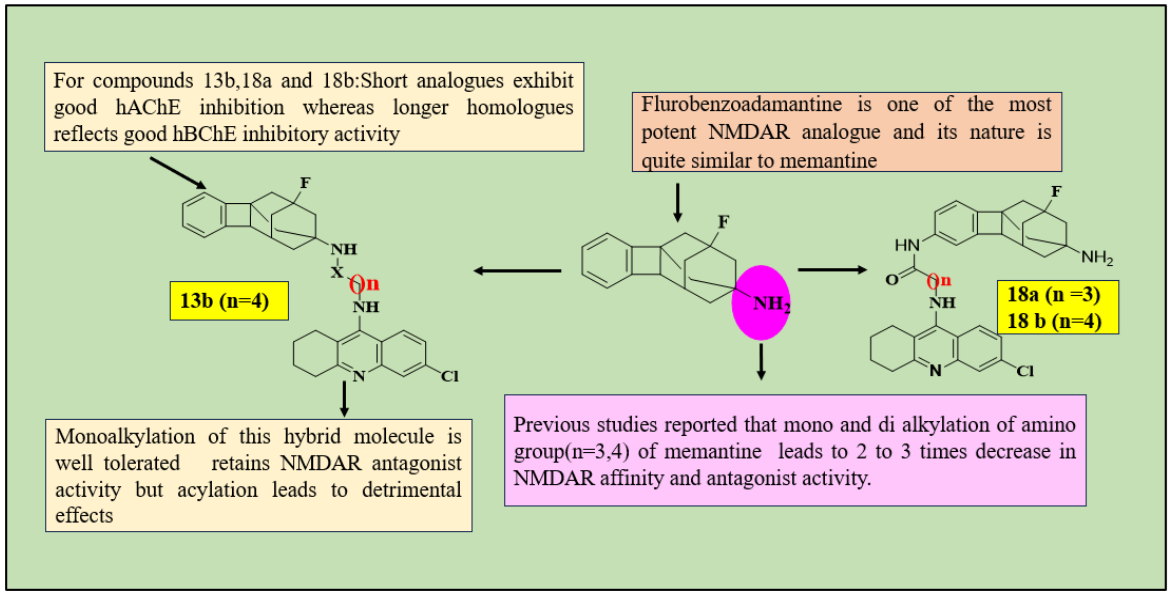


Figure 7. SAR of benzohomoadamantane-chlorotacrine hybrids

d) Banerjee et al. (2010) investigated various piperidine derivatives of dioxadrol (Figure 8.), in which the 4th position of the piperidine ring was fluorinated, and assessed for their pharmacological activity by using the selective radioligand [3H]-(+)-MK-801, pig brain cortex membrane. Structure activity analysis reveals that an axial proton in the 4th position of 1,3-dioxolane is vital for the activity, and ring junctions, which include the 4th position of 1,3-dioxane and piperidine ring, should be in the same configuration to attain higher receptor affinity. Substitution at the 4th position of the piperidine derivative of α-dioxolane was well tolerated. On insertion of fluorine atoms in compounds 8c and 12d, they exhibited high affinity towards σ1 and σ2 receptors as well as the polyamine binding site of NR2B receptors, with Ki values of 81 nM and 27 nM (Banerjee, Schepmann, & Wünsch, 2010).

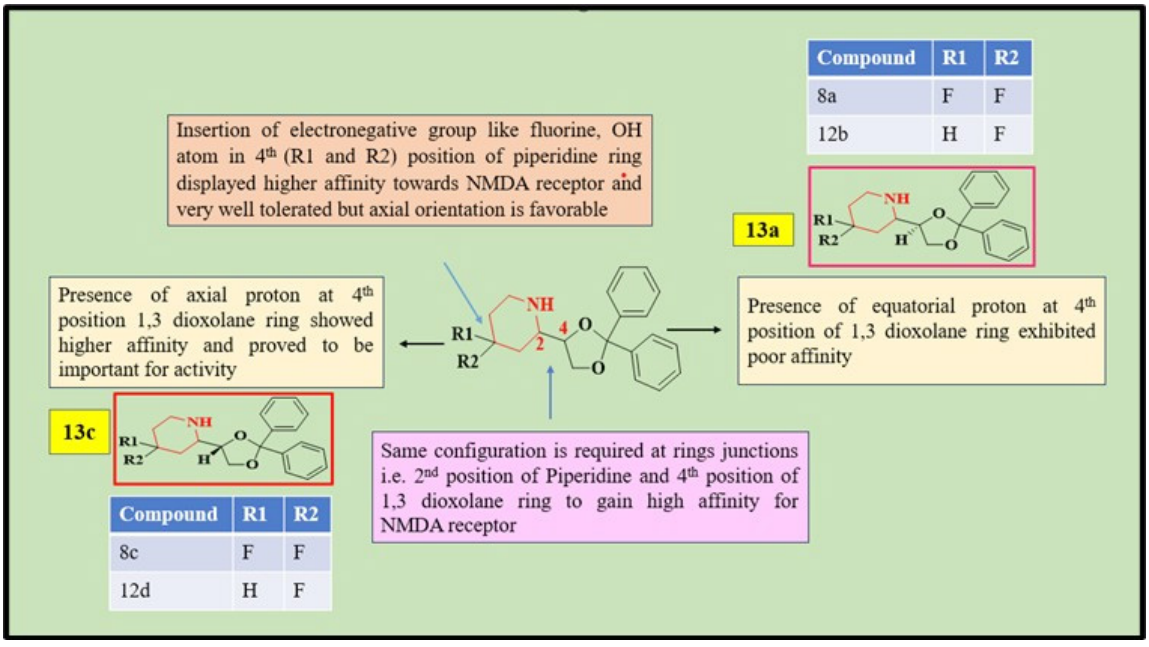


Figure 8. SAR of different fluorinated dioxadrol analogues

e) NMDA receptor offers a key role in cognitive functions, but its overactivation leads to several neurodegenerative disorders (Pochwat, Nowak, & Szewczyk, 2019; Reiner & Levitz, 2018). Considering this underlying process, it can be a relevant target for therapeutic interventions for CNS disorders. Espadinha et al. (2020) have synthesized and screened NMDAR antagonism for a pool of eighteen 1-aminoindan-2-ol tetracyclic lactams (Figure 9.), which were safe and displayed good brain permeability in an in-vitro PAMPA-BBB assay, out of these 11 compounds established good activity and showed IC_{50} values to the same extent as the clinically approved drug memantine in the Ca^{2+} entry-sensitive fluo-4 assay. Docking studies also showcased their binding affinity against the NMDA receptor (Espadinha et al., 2020)

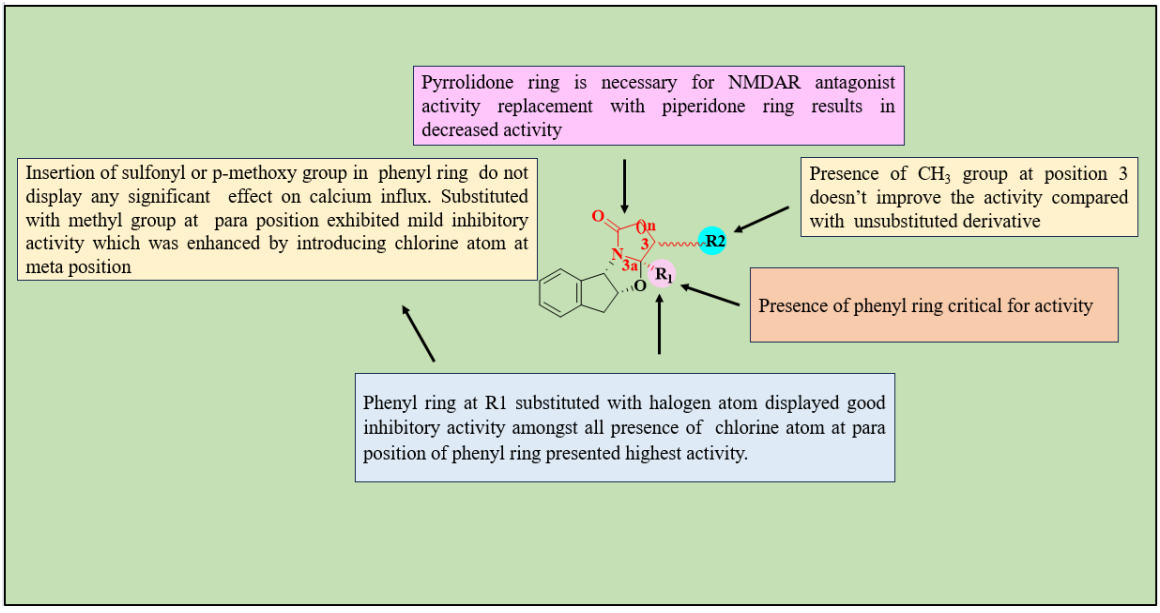


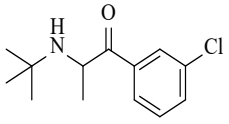
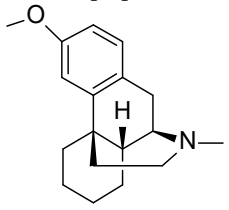
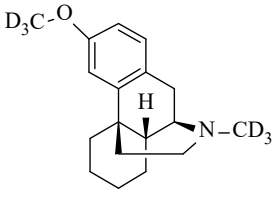
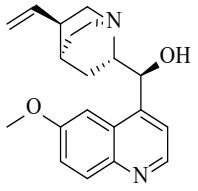
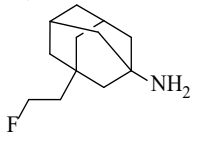
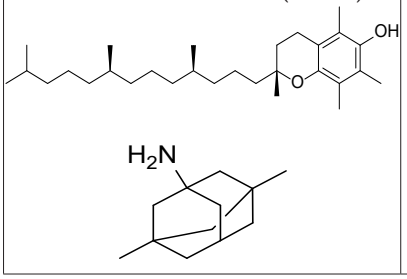
Figure 9. SAR of 1-aminoindan-2-ol tetracyclic lactams

CURRENT STATUS OF NMDA RECEPTOR TARGETING AGENTS UNDER CLINICAL TRIALS

All the data collected from ClinicalTrials.gov, Table 2 provides the information about therapies under clinical trial across the globe. It is a more extensive and widely used resource. The reference date for this review is November 20, 2025, and the information presented is registered at ClinicalTrials.gov (Benarroch, 2011; Cummings et al., 2023; Danysz & Parsons, 2003). AXS-05 is a novel, investigational medicine approved for the treatment of major depressive disorder and currently under Phase 3 of clinical studies to treat AD agitation. It is a combination of dextromethorphan (DM) and bupropion, in which dextromethorphan has the potential to modulate the NMDA receptor, which has a pivotal role in neurological disorders, while bupropion helps to enhance the bioavailability of dextromethorphan and inhibit serotonin and norepinephrine transporters, contributing to multimodal activity. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial results showed good tolerability among patients and also reduced the risk (Grossberg, Cummings, Andersson, Streicher, & Tabuteau, 2024; Ward & Citrome, 2022). AVP-786 proved to be clinically efficacious, well-tolerated, and demonstrated good activity by decreasing agitation in patients with dementia of the Alzheimer's type. Dextromethorphan can be a promising candidate, as it has a high affinity for SERT. Leveraging its pharmacokinetic profile, it is deuterated and combined with quinidine, which is an inhibitor of CYP P50. These results encouraged the FDA to pursue AVP786 to evaluate its long-term safety and efficacy (Carrarini et al., 2021; Tampi, Joshi, Marpuri, & Tampi, 2020). Fluoroethylnormemantine, a novel derivative of memantine, demonstrated good CNS effects in preclinical studies. To further assess its clinical potential, a first-in-human trial, Phase 1, single ascending dose (SAD) study was planned to evaluate its pharmacokinetic parameters in adult healthy volunteers. The study was withdrawn in May 2024 before any participants were enrolled, and the clinical development of the compound remains on hold, awaiting updates from the sponsor. Separately, the US Department of Veterans Affairs conducted a clinical trial involving 613 veterans with mild to moderate AD who were receiving anticholinesterase therapy. Participants were randomly assigned to receive either 2000 IU/day of alpha-tocopherol, 20 mg/day of memantine, a combination of 2000 IU/day alpha-tocopherol plus 20 mg/day memantine, or a placebo, given the critical role of oxidative stress and glutamate overstimulation in neurodegeneration. Vitamin E delayed progression by six months. The study's primary outcome was the assessment of AD cooperative activities of daily living,

while the secondary outcome measured the dependence scale, evaluating the level of assistance patients required for daily activities. Results indicated that treatment with vitamin E alone led to a 3.15-point decline in Alzheimer's cooperative activities of daily living compared to the placebo group. Memantine and a combination of vitamin E and memantine did not show any significant effects, but infection occurred more often; their overall safety was generally acceptable (Dysken et al., 2014).

Table 2. List of agents targeting the NMDA receptor under clinical trial

Compound name and structure	Condition	Target	NCT Number	Sponsor
AXS-05 (dextromethorphan-bupropion) (Phase-3)  **Bupropion**  **Dextromethorphan**	Agitation in Patients with Dementia of the Alzheimer's Type Alzheimer Disease Agitation, Psychomotor	NMDA receptor Antagonist, sigma1 receptor agonist, serotonin and norepinephrine transporter inhibitor	NCT04797715	Axsome Therapeutic, Inc.
AVP-786 (Phase-3)  **Deudextromethorphan**  **Quinidine**	Agitation in Patients with Dementia of the Alzheimer's Type	NMDA receptor Antagonist, sigma1 receptor agonist, serotonin and norepinephrine transporter inhibitor, cytochrome P450 and CYP2D6 inhibitor	NCT03393520	Otsuka Pharmaceutical Development & Commercialization, Inc.
Fluoroethylnormemantine (Phase I) 	Agitation in Patients with Dementia of the Alzheimer's Type Alzheimer Disease Agitation	NMDA receptor Antagonist	NCT05921929	ReST Therapeutics
Vitamin E and Memantine (Phase 3) 	Patients having mild to moderate dementia with Alzheimer's disease	Antioxidant and NMDA receptor Antagonist	NCT00235716	US Department of Veterans Affairs

LIMITATIONS OF CURRENT NMDA-TARGETING AGENTS

Memantine is used for moderate-to-severe Alzheimer's disease, which helps reduce glutamate-induced excitotoxicity that leads to nerve cell death. Although memantine is not completely selective, it preferentially inhibits pathological extrasynpatic NMDA receptor activity while largely sparing normal synaptic signaling. While extrasynpatic NMDARs drive excitotoxicity and neurodegeneration, synaptic NMDARs are essential for neuronal survival, plasticity, and normal cognitive processes. This lack of selectivity limits memantine's overall therapeutic efficacy, and non-selective binding on the receptor underscores the need for more precise development of selective NMDA receptor antagonists that can selectively inhibit excitotoxic extrasynpatic receptors while preserving synaptic signaling. In addition, research aimed at modulating receptor function by targeting kinases and phosphatases is being investigated to enable more precise and efficacious therapeutic interventions (Lipton, 2004b).

MULTI-TARGET DRUGS OUTPERFORMING SINGLE-TARGET THERAPIES

AD is a multifactorial disorder characterized by several pathological mechanisms, including amyloid-beta aggregation, tau hyperphosphorylation, excitotoxicity, oxidative stress, and neuroinflammation. Single-target therapies often provide limited benefit, as they act on specific pathways and mainly offer symptomatic relief. Combination therapies, such as Namzaric, which contains donepezil and memantine, have shown synergistic effects and are used to manage moderate to severe Alzheimer's disease. However, their overall therapeutic efficacy is reduced due to poor bioavailability, drug–drug interactions, suboptimal pharmacokinetics, and potential drug resistance (Wang et al., 2019). To overcome these challenges, multi-target directed ligands (MTDLs) are being explored; these compounds are designed to interact with multiple pathological targets simultaneously, producing diverse pharmacological effects. Its aim is to improve bioavailability, enhance patient compliance, reduce toxicity, and limit overexcitation of specific pathways, offering a more strategic and comprehensive therapy for AD (Pathak & Kabra, 2024).

PATENT LANDSCAPE

In recent years, numerous patents have been filed emphasizing the development of small molecules, biologics, and highly selective NMDA receptor modulators, particularly GluN2B subunit-targeted agents for the treatment of AD, psychiatric disorders, ischemia, and other central nervous system conditions. All patent data were collected from publicly available repositories, including Google Patents and Justia, to provide verified information (Ahmed, Haider, & Ametamey, 2020).

Table 3. Patents on NMDA receptor modulators

Year	Patent No.	Inventors	Compound type	Therapeutic focus
2024	US11993587B2	Dvorak & Coate, 2024	Substituted pyrazolo-pyrazines, GluN2B-selective	NR2B-selective NMDA antagonists with neuroprotective potential
2019 (filed)/ 2020 issued	US10500205B2	Anderson, Volkmann, Menniti, & Fanger, 2019	Thienopyrimidinone NMDA receptor modulators	Broad modulators for neurological use
2020	US20200095200A1	Scully, King, & Worthen, 2020	Diindole compounds for nervous system disorders	NMDA-targeted; potential neuroprotective application
2019	US20190314358A1	King et al., 2019	Selective NR2B antagonists	Neurodegeneration, mood
2018	US2018119374A1	Anderson, Volkmann, Menniti, & Fanger, 2018	NMDA receptor modulators (non-specific)	Cognitive and mood disorders
2017	US20190216753A1	Wang & Axerio-Cilies, 2019	Allosteric modulators (GluN1/ GluN2A & GluN2B)	Stroke recovery, neuronal protection
2015	WO2019191424A1	Liotta, Traynelis, & Jing, 2019	GluN2C/D-selective antagonists	Epilepsy, neurodegeneration
2014	WO2014025942A1	Traynelis, Mullasseril, Garnier, Liotta, & Zimmerman, 2014	NMDA receptor modulators (Subunit-selective)	Broad neurological disorders
2013	WO2013036835A1	Upasani et al., 2013	Neuroactive steroids (NMDA modulators)	Neurological disorders (mood, cognition)

CONCLUSION

The NMDA glutaminergic receptor signaling transduction pathway is crucial for maintaining synaptic signaling and neuronal health at ambient concentrations of glutamate. However, overactivation results in excitotoxicity, which causes synaptic plasticity impairment and neuronal cell death. Maintaining the balance between normal stimulation and overstimulation of the NMDA receptor is crucial. Postsynaptic neurons and astrocytes form the tripartite glutaminergic synapse, which helps regulate glutamate signaling, and dysregulation of this system is significant in the pathophysiology of AD. The NMDA receptor antagonism can act as an upstream therapeutic barrier against neurodegeneration, making it a prominent research target area for unveiling potent innovative drugs alongside therapeutic interventions. However, it is a big challenge to prevent overstimulation and preserve normal physiological function.

FUTURE PROSPECTS

NMDA receptor antagonists have a key role in preventing excitotoxicity-induced neurodegeneration and have emerged as a promising target for divergent signaling pathways concerned with neurodegeneration, which piques fascination for future development and the discovery of novel therapeutic potential. This review highlights the bright future outlook for NMDA receptor antagonists as a potent therapeutic modality supported by clinical evidence showcasing their effectiveness. Research efforts are currently directed towards harnessing their potential for addressing neurological disorders, with hope for future breakthroughs in Alzheimer's disease. Progress in NMDA receptor antagonist development is currently constrained by several unresolved challenges. One of the most significant barriers is the lack of validated biomarkers capable of reliably measuring NMDAR activity in vivo. Such biomarkers are crucial for analyzing therapeutic responses, optimizing dosing, confirming target engagement, and detecting adverse effects during clinical development. Recent advancements, including PET imaging probes for GluN2B-containing receptors and fluid biomarkers such as cerebrospinal fluid neurofilament light chain and glutamate/glutamine ratios, offer promising tools to address this gap. Additionally, genetic and molecular factors, particularly APOE4 carrier status, can significantly influence glutamatergic signaling, excitotoxic vulnerability, and patient responses to NMDA receptor antagonists. As a result, personalized medicine is emerging as a critical frontier in NMDA receptor–targeted therapies, leveraging biomarker-guided approaches and combination or multi-target strategies. Future clinical trials that stratify patients based on genetic and biomarker profiles will be essential to improve treatment outcomes and reduce variability in drug response.

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AUTHORCONTRIBUTION STATEMENT

MM: Conceptualization, Writing-original draft preparation. CST: Writing-Reviewing and Editing. RS: Methodology. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AMPA-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA-N-methyl-D-aspartate, AD-Alzheimer Disease, NR2B-N-methyl D-aspartate receptor subtype 2B, MK-801-Dizocilpine, HDACs-Histone Deacetylases, AQ343-Anthraquinone Spermine, SERT-Serotonin Transporter, BChE-Butyrylcholinesterase, AChE-Acetylcholinesterase, CaE-Carboxylesterase

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