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Chapter

Perspective Chapter - NMDA Treatments for CNS Disorders

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Abstract

The N-methyl-D-aspartate receptor (NMDAR), a glutamate-gated ion channel, mediates various physiological functions, such as synaptic plasticity, learning, and memory. Any homeostatic dysregulation of NMDAR may cause central nervous system (CNS) disorders, such as Alzheimer's disease, depression, and schizophrenia. The involvement of NMDA dysfunction promotes advanced research on developing NMDAR pharmaceutics for treating CNS disorders. NMDAR enhancers, by direct or indirect potentiating NMDAR functions, have been used to recover NMDAR functions for treating schizophrenia. Interestingly, NMDAR blockers, by direct or indirect inhibiting NMDAR functions, have also been utilized for CNS disorders, such as Alzheimer's disease and depression. In this chapter, the current strategy of NMDAR modulation for CNS disorders are elaborated on to discern underlying neurophysiological mechanisms of how homeostatic regulation of NMDAR plays a vital role in the normal and pathological states, respectively.

Keywords: NMDAR, CNS pathology, agonism, antagonism, homeostasis

1. Introduction

Glutamatergic signaling plays a critical role in the CNS function under physiological and pathophysiological states via two major types of receptor: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) [1]. mGluRs consist of three subgroups (Group I-III), while iGluRs comprise four subgroups (AMPARs, KARs, Gluδs, and NMDARs). Among all GluRs, NMDARs play a crucial role in brain development, mediating the physiological functions, such as synaptic plasticity, learning, and memory. NMDARs are voltage-dependent glutamate- or aspartate-gated cation channels with two prerequisites for channel opening: 1) depolarization-induced unblockage of magnesium ions; 2). concomitant binding of glutamate (or aspartate) and glycine (or D-serine). When the NMDARs are either aberrantly enhanced or encumbered opening, various CNS symptoms/disorders may develop, such as depression, psychosis, and cognitive impairment.

CNS disorders still loom over many people's health with limited effective treatment. The role of NMDARs playing in CNS disorders has been gaining attention owing to the finding of ketamine as an antidepressant [2]. This new therapeutic mechanism promotes NMDARs as an emerging therapeutic target. Ketamine, a NMDAR antagonist, exerts rapid and robust antidepressant effects in depressed patients [3]. On the contrary, a NMDAR agonist, D-serine, could alleviate schizophrenic and depressive symptoms in the clinical trial [4]. These contrary

modulations on NMDAR further support the importance of NMDAR homeostasis leveraged by NMDAR modulators [5].

NMDAR modulators, with positive or negative modulation, have been designed to alleviate various symptoms of CNS through distinct mechanisms. Positive NMDAR modulators elevate NMDARs via direct and indirect approaches. Direct NMDAR enhancers fit into the glutamate site or glycine site of NMDARs, or they bind the allosteric pockets of the glutamate/glycine sites. In contrast to direct enhancement, several NMDAR enhancers improve NMDAR functions by modulating indirect pathways, for example, by inhibiting glycine transporter or D-amino acid oxidase (DAAO). Negative NMDAR modulators, on the contrary, work as competitive antagonists to directly occupy the glycine site, or bind an allosteric site (known as non-competitive antagonists), or block NMDAR channel pore (known as uncompetitive antagonists) [6]. All above modulators have shown potential for clinical use in CNS disorders but without one-size-fits-all approach.

2. CNS disorders alleviated by NMDAR modulators

2.1 Neurological disorders

The excitatory neurotransmission of mammalian CNS is largely dictated through glutamate and its receptors, particularly NMDAR. Because its critical roles in mediating synaptic plasticity related to learning and memory formation, the dysfunction of the NMDAR-based signaling is implicated in the neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), as described below.

2.1.1 Alzheimer's disease

AD is the most common cause of dementia to induce not only cognitive impairments in memory and thought, but also behavioral and psychiatric symptoms [7]. Current understanding to AD relies on two main histopathological abnormalities: (1) amyloid plaques composed of amyloid ß (Aß) peptides cleaved from amyloid precursor proteins in the brain tissue, and (2) the formation of intraneuronal neurofibrillary tangles due to phosphorylated and aggregated tau proteins. Although Aß and tau serve as the most discussed mechanisms through which cause AD, no effective treatment was developed successfully. Coincidently, the neurotransmitter systems, including cholinergic, adrenergic and glutamatergic pathways are considered critical in AD progression and development [8]. In this chapter, we focus on the discussion of how NMDAR involves in AD.

NMDAR is the major regulator associated with long-term synaptic plasticity. Studies have reported that AD brains contain neurotoxins consisted of soluble Aß oligomers. The binding of Aß 42 oligomers to forebrain synaptosomes is associated with post-synaptic density complexes containing NMDAR subunits NR1 and NR2B [9]. Consistently, Aß oligomers were found to ablate long-term potentiation in hippocampal brain slices and the cortices of AD brains via overactivating extrasynaptic NMDAR containing NR2B [10]. The over-activation of extrasynaptic NMDAR linked to neurodegeneration in AD has also been supported by the pharmacotherapeutic use of NMDAR inhibitor memantine [11].

Indirect modulation of NMDAR via glutamate release or glycine transporter-1 (GlyT1) are considered feasible for AD. An escalated stimulation via glutamatergic signaling causes glutamate excitotoxicity that results in damaged nerve cells, and such neuronal toxicity is coined "excitotoxicity". In AD, glutamate uptake and

recycling systems are severely impaired [12], which therefore increases glutamate availability, resulting in excessive NMDAR stimulation. Additionally, Aß peptides may increase glutamate availability by weakening glutamate uptake and recycling systems [13] that may contribute to AD pathology. On the other hand, at glutamatergic synapses, glycine is transported by GlyT1, a Na^+/Cl^--dependent carrier protein playing a major role in maintaining glycine concentration below saturation at postsynaptic NMDAR, sculpturing GlyT1 as an intriguing target for NMDAR modulation.

Overall, direct and indirect NMDAR inhibition strategies through the discussed mechanisms to attenuate the overactivation of NMDA function have shown rationale for developing medicine for late-stage AD to attenuate the neuronal death.

2.1.2 Parkinson's disease

PD, the second most common neurodegenerative disease, is a progressive disorder with symptoms of onset gradually, motor disturbances and cognitive impairment. Due to the rapidly aging population worldwide, PD also receives increasing attention from communities [14]. The pathophysiology of PD is due to the degeneration of pigmented dopaminergic neurons, resulting in functional changes to the circuitry of basal ganglia nuclei. Accordingly, levo-dopa, a precursor of dopamine, and dopamine receptor agonists have been serving as the standard treatments for PD. However, long-term use of these standard therapies contribute to the loss of efficacy and development of disfiguring motor complications [15]. Novel PD treatments based on different mechanism is long awaited.

Regulating glutamatergic receptors, particularly NMDAR, has been found to be altered in the basal ganglia of PD where NMDAR is widely expressed. Specifically, NR2B-containing NMDARs may significantly influence the PD pathology while NR2B was found to be substantially distributed in the striatum and other basal ganglia areas. An increasing body of literature has reported that not only experimental PD models but also PD patients present substantially elevated NMDA-sensitive glutamate binding in the striatum [16]. In levo-dopa-treated rodent and primate, GluN2A and the ratio of GluN2A/GluN2B are increased. The findings are also reported in PD patients [17], suggesting that attenuated NMDAR activity may help halt the progression of PD.

Alternately, reshaping synaptic connections for PD patients via brief activation of NMDAR can increase axonal growth rate and axonal branching. The brief NMDAR activation can be achieved through inhibiting GlyT1 to increase levels of extracellular glycine [18]. In addition, activating NMDAR via weak NMDAR glycine binding agonists can also achieve similar effects. This hypothesis remains to be investigated.

2.1.3 Huntington's disease

HD is a progressive CNS disorder due to a single defective gene on chromosome 4 that encodes the protein huntingtin. The defect is hereditary and will eventually develop symptoms in lifetime. At the beginning of symptom onset, patients often have subtle abnormalities in mood, usually followed by a lack of coordination and unsteady gaits [19].

Since the altered function of huntingtin induces neuronal cell death, research focuses on mechanisms towards regulation of such cell death. It has been revealed that the formation of the nuclear protein aggregates, oxidative stress, and mitochondrial dysfunction are associated with neuronal cell death in HD [20]. NMDARs have also been found to regulate neuronal cell death of HD, and by modulating

NMDAR activity, psychotic symptoms of HD due to low NMDA function can be alleviated simultaneously. In this chapter, we focus on the discussion of NMDAR in HD.

Animal studies have shown that neuroexcitatory agonists kainic or quinolinic acids can induce lesions similar to those in HD, indicating that excitotoxicity from NMDAR over-activation could contribute to the progression of the disease [21]. Post-synaptic density protein 95 (PSD-95), a scaffolding protein, can bind huntingtin and the NR2 subunit of NMDAR. At the molecular level in HD, the presence of abnormal huntingtin protein causes the interruption of PSD-95 binding onto NMDAR. The unbinding of PSD-95 results in excitotoxicity and neuronal cell death consistent with HD [20]. Therefore, among the known mechanisms inducing HD progression, NMDAR remains a primary target to develop therapeutic intervention.

2.2 Psychiatric disorders

Existing high concentration of post-synaptic NMDAR in limbic structures [22] highlights the homeostasis of NMDAR activity as be of uttermost significance in behavioral regulation of the brain. The dysfunction of NMDAR can cause a variety of psychiatric disorders such as depression, schizophrenia, bipolar disorder (BD), and anxiety disorder [23].

2.2.1 Depression

Depression is a chronic mental disorder characterized by persistent low mood, loss of interest/pleasure, lack of appetite, sleep disturbance, low energy, and poor concentration. Depression can affect people irrespective of age, ethnicity, and gender. Major depressive disorder (MDD) is the most studied type of depression characterized by one or more major depressive events, that is, the presence of low mood and/or loss of interest for at least 14 days in company with depression symptoms. MDD leads to suicide that takes 2160 self-harm deaths per day in US [24]. Decades of research on depression have yielded several mechanisms that may explain its pathophysiology, including biogenic amine (e.g., monoamine) hypothesis, abnormal endocrine factors, genetic and environmental factors, neurogenesis, and the dysregulation of second messenger systems, which have been extensively reviewed elsewhere [25]. Among them, monoamine-based mechanisms were the most studied with successful development of antidepressants.

Although monoamine treatments are available for MDD, they have not been optimal. Currently, standard monoamine antidepressants require one month or more to exert antidepressant effects [26]. Such time lag has put MDD patients at risk of suicide and other self-harm acts. In recent decades, the NMDAR has emerged as a central player in MDD research, resulting in a paradigm shift from the monoamine-based to the NMDAR-based hypothesis. The NMDAR-based hypothesis of depression originated from early findings in the 1990's that NMDAR antagonists exerted quick antidepressant-like action [27]. Subsequently, many studies have reported abnormal glutamate levels in frontal and occipital cortices in MDD; however, these findings infer the complex role of NMDAR in the brain of MDD patients. The regionally decreased glutamate level in the brain demonstrates an association with the pathophysiology of MDD [28]; on the contrary, the elevated glutamate levels occurs in medication-free MDD patients during an active depressive episode, in remission, and in young people [29]. Since glutamate is a major excitatory neurotransmitter dictating the neural plasticity and process of learning and memory, the alteration to NMDAR causes region-specific maladaptive neurocircuitry in depression and decreases in cognitive controls over negative emotion.

At the molecular level, postmortem brain analyses from MDD patients show alterations in the NMDAR subunit profile, such as reduced GluN2A and GluN2B subunits in locus coeruleus, and decreased GluN1 and GluN2A expression levels but no changes to those of GluN2B, GluN2C and GluN2D subunits in dorsolateral prefrontal cortex of MDD subjects [30]. Further studies have found that biologically, the activation of NMDAR requires both the binding of glycine and glutamate onto their binding sites, and therefore, modulating the release of the two amino acids into synapses are considered feasible. At glutamatergic synapses, glycine is transported by GlyT1, maintaining glycine concentration below saturation at postsynaptic NMDAR. Accordingly, GlyT1 has become an intriguing target for NMDAR activity modulation [31]. Alternatively, inhibiting glutamate levels at synapses renders reduced glutamate binding to NMDAR [32]. In summary, the above findings provide a solid basis for developing chemotherapeutics for treating MDD via modulating NMDA.

2.2.2 Schizophrenia

Schizophrenia is a psychotic illness presenting symptoms with processing thoughts and contents, and develops positive, negative and/or cognitive symptoms. Concurrently, depression and suicidal thoughts and attempts happen often in people suffering from schizophrenia. Because schizophrenia patients require lifelong treatment, early intervention may improve the long-term outlook. Conventional therapies for schizophrenia are developed based on a dopamine hypothesis which has been prevailing to explain symptoms associated with the positive symptoms. However, these treatments have not been optimal and often induce substantial adverse side effects [33].

Glutamate hypofunction hypothesis of schizophrenia has been supported by several lines of studies. Low level of glutamate in cerebrospinal fluid was reported in patients with schizophrenia [34]. The worsening of schizophrenic symptoms was observed in patients treated with NMDAR inhibitors such as ketamine. Healthy people administered with similar inhibitors were reported to develop symptoms of schizophrenia [35]. Building on these data, upregulating NMDA function serves as a promising target for treating schizophrenia [36].

Although NMDAR is a focus for antipsychotic drug development for schizophrenia, direct activation of the NMDAR via targeting the glutamate site is reported to cause excitotoxicity. The finding suggests the demand for targeting the glycine site as an alternative, but direct approach. To reduce glycine site vacancy, a number of studies have synthesized amino-acid derivatives to occupy it [37]. Alternatively, enhancing the glycine levels through GlyT1 inhibition has also shown promise, which is used as an adjunct to conventional therapies [38].

2.2.3 Bipolar disorder

BD, as its name suggested, causes extremes of mood fluctuations that a person will be either in emotional highs (mania or hypomania) or lows (depression). BD is a lifelong disease that episodes of mood swings may occur infrequently or several times in a year. Typically, BD patients spend more time in depressive mood than mania or hypomania. Currently, treatments for BD are limited to symptom reduction and prevention of the occurrence of mood episodes [39].

Neuroimaging [40] and genetic findings [41] have revealed that glutamatergic abnormality is associated with the pathophysiology of BD, indicating NMDAR may play a role in the disease. The use of NMDAR inhibitor further evidences the role of NMDAR in the regulation of BD. Ketamine has shown to improve depressive

symptom. One of possible mechanisms of ketamine in regulating BD symptoms is to increase presynaptic levels of glutamate which in turn binds to AMPAR instead of NMDAR. The increased ratio of AMPAR-to-NMDAR neurotransmission is implicated to induce the antidepressant effects of ketamine [42].

At the molecular level, postmortem findings suggest that BD is associated with a reduced expression of NR1 subunit in the prefrontal cortex [30]. The genetic polymorphisms in the 3'UTR region of GRIN2B gene that encodes for the NR2B subunit has been found to play a role in BD etiology, although its expression level is not significantly different from the control [43]. Together, these studies suggest NMDAR is associated with BD.

2.2.4 Anxiety disorder

Having occasional anxiety is a normal part of life. However, intense, excessive, and persistent worries and fear about specific situation would be in the category of anxiety disorder that needs intervention. Types of anxiety disorders include panic attack, generalized anxiety disorder, and separation anxiety disorder. An anxiety patient may experience one or more of them and can experience anxiety at very young age [44].

Benzodiazepine and selective serotonin reuptake inhibitors (SSRIs) or selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are recommended as first line drug treatment, because of their more favorable profile than tricyclic antidepressants and monoamine oxidase inhibitors. Nevertheless, some SNRIs are also antagonists of metabolic enzyme cytochrome P450, therefore causing drug–drug interactions [45]. In addition, discontinuation of SSRIs or SNRIs may experience withdrawal reactions [46]. These unwanted outcomes suggest an essential for developing next generation anxiolytic treatments based on novel mechanisms.

Fear often occurs together and share similar stress responses with anxiety, and therefore, both are often put into the same context when discussing the underlying mechanisms. Currently, studies have found that the neuronal modulatory systems in brain areas contributing to fear and anxiety share a high degree of overlap [47]. In particular, regulating extinction learning of fear through NMDAR within amygdala, medial prefrontal cortex, and hippocampus is considered critical among the neuronal modulatory systems [48]. Hippocampus and amygdala of the medial temporal lobe situate at the interface between cognition and emotion, which is believed to be potential sites where NMDAR inhibitors exert anxiolytic effects [49]. NMDAR regulates emotionality and cognition, and its antagonists have shown promising effects on them. In contrast to NMDAR antagonism, partial activation of NMDAR facilitates fear extinction in rodents. In clinical setting, partial agonists used as an adjuvant increase psychotherapeutic effects in patients suffering fear-related disorders [50]. These finding suggest that a balanced modulation of NMDAR activity can bring benefits for the patients with anxiety disorder.

3. NMDAR modulators for CNS disorders

3.1 Positive NMDAR modulators

In this section, positive NMDAR modulators for CNS disorders will be discussed (**Figures 1** and **2**, **Table 1**). To enhance NMDAR function, two approaches could achieve: direct or indirect modulation. For direct modulation, three types of enhancers are categorized according to their binding sites: glutamate site, glycine site, and allosteric site of NMDAR.

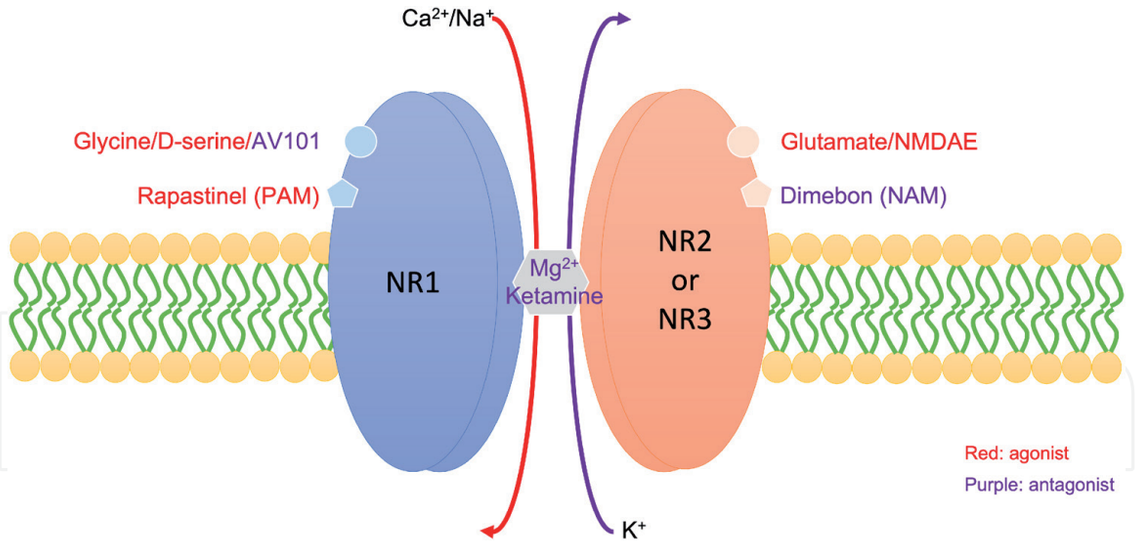

Figure 1.
Scheme of direct agonism/antagonism via various binding sites of NMDAR. NAM, negative allosteric modulators; PAM, positive allosteric modulators.

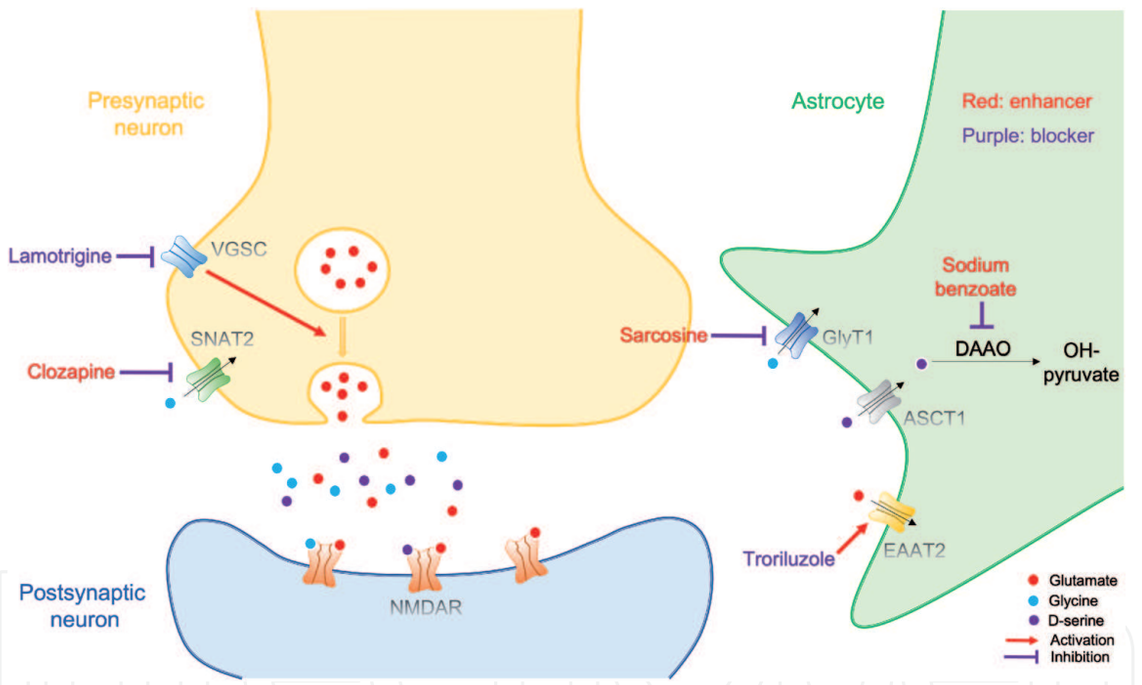

Figure 2.
Indirect NMDAR agonism/antagonism through activation or inhibition on diverse channels or transporters or enzymes. ASCT-1, alanine/serine/cysteine transporter-1; DAAO, D-amino acid oxidase; EAAT2, excitatory amino acid transporter-2; GlyT1, glycine transporter-1; NMDAR, N-methyl-D-aspartate receptor; SNAT2, sodium-coupled neutral amino-acid transporter-2; VGSC, voltage-gated sodium channel.

3.1.1 Direct NMDAR enhancers

3.1.1.1 NMDAR glutamate site agonists

Cognitive deficits occur often in elderly MDD patients, hardly to be relieved with the existing treatment. NMDA enhancement via the glutamate site has been proved to enhance cognitive functions in previous studies [81]. NMDA enhancer (NMDAE), binding the NMDAR glutamate site as an agonist, has been offered for the elderly (>55 years) and adults (18–55 years) with MDD. To testify the efficacy, safety, and the cognitive improvement of NMDAE in those patients, the NMDAE

Drug	Mechanism	Disease	Study
Positive NMDAR modulators			
NMDAE	glutamate site agonist	MDD	NCT03414931 NCT04637620
Glycine	glycine site agonist	Schizophrenia	[53]
D-alanine	glycine site agonist	Schizophrenia	[54]
D-serine	glycine site agonist	MDD Schizophrenia	NCT04721249 NCT00322023
D-cycloserine	glycine site partial agonist	AD MDD Schizophrenia BD Anxiety	[55] NCT00408031 [56] NCT01833897 NCT00515879
Rapastinel (GLYX-13/BV-102)	PAM	MDD	NCT01684163
Apimostinel (NRX-1074)	PAM	MDD	NCT02067793
Clozapine	Indirect enhancer (SNAT2 inhibitor)	PD MDD Schizophrenia BD	NCT00004826 [57] [58] [59]
BI 425809	Indirect enhancer (GlyT1 inhibitor)	AD Schizophrenia	NCT02788513 NCT02832037
Bitopertin (RO-4917838)	Indirect enhancer (GlyT1 inhibitor)	Schizophrenia	NCT01235585
Sarcosine	Indirect enhancer (GlyT1 inhibitor)	PD MDD Schizophrenia	NCT01785628 NCT00977353 [60]
D-Amino acid oxidase inhibitor	Indirect enhancer (D-serine retention)	AD MDD Schizophrenia	[61] [62] NCT01908192
Negative NMDAR modulators			
AV-101 (L-4-chlorokynurenine)	glycine site antagonist	PD MDD	NCT04147949 NCT02484456
Dimebon (Latrepirdine)	NAM	AD HD	NCT00377715 NCT00497159
Dextromethadone (D-methadone/ REL-1017)	NAM	MDD	NCT04688164
Rislenemdaz (CERC-301/MK-0657)	NAM	MDD	NCT01941043
Amantadine	Uncompetitive antagonist	PD HD	NCT00632762 [63]
Memantine	Uncompetitive antagonist	AD PD MDD Schizophrenia BD Anxiety	[64] [65] [66] [67] [68] [69]
Dextromethorphan	Uncompetitive antagonist	MDD BD	NCT04226352 [70]

Drug	Mechanism	Disease	Study
Nuedexta (Dextromethorphan+ Quinidine)	Uncompetitive antagonist	MDD BD	NCT01882829 [71]
AVP-786 (Dextromethorphan+ Quinidine + Deuterium)	Uncompetitive antagonist	AD MDD Schizophrenia	NCT03393520 NCT02153502 NCT03896945
AXS-05 (Axsome, Dextromethorphan+ Bupropion)	Uncompetitive antagonist	AD MDD	NCT04797715 NCT02741791
(R,S)-Ketamine	Uncompetitive antagonist	MDD BD Anxiety	[72] [73] [74]
(S)-Ketamine (Esketamine)	Uncompetitive antagonist	MDD BD	[75] NCT03965871
(R)-Ketamine (Arketamine)	Uncompetitive antagonist	MDD	NCT04108234
Neramexane	Uncompetitive antagonist	AD	[76]
Nitrous oxide (N_2O)	Uncompetitive antagonist	MDD Anxiety	[77] NCT02243826
Lamotrigine	Indirect blocker (glutamate release inhibitor)	MDD Schizophrenia BD	[78] [67] [78]
Riluzole (BHV-0223)	Indirect blocker (glutamate release inhibitor)	AD MDD BD Anxiety	[79] [52] [52] [80]
Troriluzole (BHV-4157)	Indirect blocker (glutamate uptake activator)	AD Anxiety	NCT03605667 NCT03829241

AD, Alzheimer's disease; BD, bipolar disorder; GlyT1, Glycine transporter-1; HD, Huntington's disease; MDD, major depressive disorder; NAM, negative allosteric modulators; PAM, positive allosteric modulators; PD, Parkinson's disease; SNAT2, sodium-coupled neutral amino-acid transporter-2.

Table 1.
NMDAR modulators for CNS disorders [6, 51, 52].

treatment results were compared with sertraline (SSRI) and placebo. The results of those clinical studies are not disclosed as of August 2021 (NCT03414931 and NCT04637620). The potential risk of this approach is the excitotoxicity caused by overactivation through the glutamate-binding site.

3.1.1.2 NMDAR glycine site agonists

Another ligand binding site on NMDAR is the glycine site, which can also be targeted to modulate the NMDAR activation for the treatments of psychiatric disorders [82]. Glycine, acting as an agonist via binding the glycine site, can ameliorate negative symptoms in schizophrenia patients [53]. This preliminary finding encourages the development of other endogenous co-agonists, such as D-alanine. D-alanine, working as an add-on antipsychotic medication, improved schizophrenic symptoms without significant side effects, which further supports that the pathophysiology

of schizophrenia is due to the hypofunction of NMDA neurotransmission [54]. D-serine, an NMDAR co-agonist without psychotomimetic effects, emerges as a novel glutamatergic antidepressant as an adjuvant therapy in MDD patients (NCT04721249). On the other hand, the therapeutic effects of D-serine at low dose (30 mg/kg/d) in schizophrenic patients are inconsistent. Some clinical studies showed significant improvement in positive, negative, and cognitive symptoms [83], whereas others presented no significant improvement [84]. Interestingly, high doses of D-serine (≥60 mg/kg/d) could possess consistent significant improvement in negative symptoms, strongly suggesting a therapeutic dose–response of D-serine for the treatment of schizophrenia (NCT00322023).

D-cycloserine (DCS), a partial agonist of NMDAR with agonism at low doses but antagonism at high doses depending on the intrinsic tone of NMDA function [85], exhibits controversial therapeutic effects on CNS disorders. In some AD studies, a dose as high as 100 mg/d could improve the cognitive symptoms, while a low dose of 15 mg/d could improve memory deficits [55, 86]. However, other studies presented no cognitive improvement from low (10 mg/d) to high dose (500 mg/d) in AD patients [87].

When the high dose of DCS (≥ 500 mg/d) was employed in MDD patients, depressive symptoms could be improved (NCT00408031) [88]. These observations implied that NMDAR antagonism might be a potential target for the development of novel antidepressant. The clinical studies of DCS at a dose of 50 mg/d is argumentative, some claimed to possess significant clinical improvement [89], while the others found no clinical improvement [90]. In the dose finding phase, the dose of 100 mg/d of DCS seemed to be more effective than 50 or 250 mg/d in improving schizophrenic symptoms [56]. In combination with ketamine, DCS could ameliorate depression symptoms in BD (NCT01833897). Cognitive behavioral therapy with DCS also reduced social anxiety (NCT00515879) and PTSD [91]. Overall, the dose selection of DCS determines its agonistic vs. antagonistic effects on NMDAR, hence modulating its therapeutic efficacy for a variety of CNS disorders.

3.1.1.3 NMDAR allosteric site enhancers (positive allosteric modulators (PAM))

Rapastinel (GLYX-13/BV-102), an amidated tetrapeptide acting as a NMDA allosteric glycine site partial agonist, is administered intravenously to treat MDD in clinical trial (NCT01684163). Rapastinel infusion achieved antidepressant effects without psychotomimetic properties and serious adverse events, therefore acquiring FDA Fast-Track and Breakthrough Therapy designations for adjunctive treatment of MDD. However, rapastinel failed to meet primary and key secondary endpoints in three acute studies (RAP-MD-01, −02, −03 by Allergan).

Apimostinel (NRX-1074), a chemical structure like rapastinel with an additional benzyl group, is administered intravenously and orally under the studies of efficacy and safety evaluation for MDD patients and healthy individuals (NCT02067793 and NCT02366364). Benefiting from its molecular weight and orally stability, apimostinel is 100-fold more potent than rapastinel and is also well tolerated without psychotomimetic symptoms [92]. The findings of the studies are not available yet.

3.1.2 Indirect NMDAR enhancers

To enhance NMDAR function, "consolidating" amino acids (e.g., glycine or D-serine, glutamate, and aspartate) in the synaptic cleft could achieve that goal. With the use of inhibitors of amino acid transporters or degrading enzymes, the concentration of those specific amino acids could sustain in the synaptic cleft to boost NMDAR function [58]. Clozapine, a modest inhibitor of sodium-coupled neutral amino acid

transporter-2 (SNAT2), indirectly activates NMDAR via augmenting synaptic glycine levels. Clozapine could also improve symptoms of psychosis, tremor, and dyskinesias in PD patients (NCT00004826) [58]. In addition to reducing the risk of hospital re-admission for MDD patients, clozapine administration also demonstrated higher efficacy than quetiapine by ameliorating depressive symptoms [57]. As approved by Food and Drug Administration (FDA) of the USA, clozapine is utilized to treat treatment-resistant schizophrenia and symptoms of self-harm in patients with schizophrenia. Clozapine is also more effective than other antipsychotics in improving treatment-resistant bipolar disorder [59]. However, clozapine can cause potentially lethal agranulocytosis.

Other than SNAT2 inhibitor, GlyT1 inhibitor could also increase synaptic glycine level by blocking the GlyT1 to enhance NMDAR function. BI 425809, a selective GlyT1 inhibitor, emerges as a potential treatment of cognitive impairment of AD and schizophrenia. Although BI 425809 failed to improve cognition in AD study (NCT02788513), it improved cognition in patients with schizophrenia (NCT02832037). Bitopertin (RO-4917838), a selective and potent GlyT1 inhibitor, modulates both glutamatergic and dopaminergic neurotransmission in animal models of schizophrenia [93]. In six active treatment arms across three clinical studies, only one of them proved improvement in symptoms of schizophrenia (NCT01235585) [94]. However, the magnitude of improvement was small. Because of its strong antagonism, bitopertin induces NMDAR internalization, counterproductive to improve the NMDA function.

Sarcosine, a potent endogenous non-selective GlyT1 inhibitor, was applied in cognitive- and mood-related clinical studies. In PD patients, sarcosine improved depression and neuropsychiatric symptoms, especially in patients with mild–moderate severity (NCT01785628). Both in animal models and in depressed patients, sarcosine improved depression-like behaviors, further strengthening GlyT1 inhibitor as a novel class of promising antidepressant (NCT00977353) [31]. In most clinical studies of sarcosine in patents with schizophrenia, improvement in schizophrenic symptoms were reported [60]. However, when being adjunctive with clozapine, sarcosine could not produce improvement in schizophrenic patients [95]. This phenomenon may be explained by the "ceiling effect": additional NMDAR activation may not be induced due to maximal NMDAR enhancement achieved by clozapine administration alone. In contrast, the combination therapy of sarcosine and sodium benzoate (a D-amino acid oxidase (DAAO) inhibitor) enhances the cognitive function of patients with schizophrenia [96].

DAAO, a flavoenzyme for D-amino acids (e.g., D-serine and D-alanine) degradation, could be strategically inhibited to increase endogenous D-serine levels at the synaptic cleft, resulting in strengthening NMDAR functions. In post-mortem studies, patients with schizophrenia possessed higher expression and activity of DAAO in the cortex and cerebellum [97]. Thus, DAAO inhibition provides a good rationale to be a novel therapeutic target for schizophrenia treatment. Sodium benzoate, a prototype competitive DAAO inhibitor, generated antipsychotic effects in the phencyclidine-induced model of schizophrenia [98]. In some clinical studies, sodium benzoate adjunctive therapy improved symptomatology of patients with schizophrenia [99], and a larger scale clinical trial is undergoing (NCT01908192). In patients with early-phase AD, sodium benzoate predominantly enhanced cognitive and universal functions [61]. Sodium benzoate may enlarge gray matter via synaptogenesis and neurogenesis in MDD treatment [62].

3.2 Negative NMDAR modulators

NMDAR antagonism has been a therapeutic strategy for a variety of CNS disorders [100]. To achieve NMDAR antagonism, several negative NMDAR modulators

have been offered to treat patients with CNS disorders through distinct underlying mechanisms: direct blocking in competitive, non-competitive, and uncompetitive ways, and indirect blocking. All negative NMDAR modulators are introduced in this section (**Figures 1** and **2**, **Table 1**).

3.2.1 Direct NMDAR blockers

3.2.1.1 Competitive NMDAR glycine site antagonists

AV-101 (L-4-chlorokynurenine), a pro-drug of 7-Chlorokynurenic acid (7-CKA), is able to cross the blood–brain barrier and transform to 7-CKA in astrocytes [101]. 7-CKA is a potent and selective NMDAR glycine site antagonist [102]. In preclinical studies, AV-101 demonstrated dose-dependent antidepressant-like effects in animal models [103]. However, AV-101 monotherapy failed to produce the anti-depressant effects in the clinical study (NCT02484456) [104]. On the other hand, AV-101 treatment for patients with PD will be conducted (NCT04147949).

3.2.1.2 Non-competitive NMDAR antagonists (negative allosteric modulators (NAM))

Dimebon (Latrepirdine), an NAM at the polyamine-binding site of NMDARs, was originally used as an antihistamine [51]. Assessed in clinical trials, dimebon significantly improved the neuropsychiatric symptoms of patients with mild-to-moderate AD (NCT00377715) [105]. In patients with HD, short-term administration of dimebon is beneficial for cognitive improvement (NCT00497159) [106]. Dextromethadone (D-methadone/REL-1017), a non-competitive NMDAR antagonist, provided antidepressant activity via mTORC1-mediated synaptic plasticity in the mPFC in animal models [107]. As dextromethadone performs as a rapid-acting treatment for depression in clinical studies (NCT03051256), it gained FDA Fast-Track designation as an adjunctive treatment for MDD. A phase III clinical trial of dextromethadone is currently ongoing (NCT04688164). Rislenemdaz (CERC-301/MK-0657), a NMDAR NR2B-selective antagonist, induced antidepressant properties in patients with treatment-resistant MDD [108]. Nevertheless, in a phase II study, no obvious antidepressant effects were produced by rislenemdaz (NCT01941043).

3.2.1.3 Uncompetitive NMDAR antagonists (NMDAR channel blockers)

Amantadine, a low-affinity uncompetitive NMDAR antagonist with rapid blocking channel kinetics, could ameliorate several clinical symptoms in PD, and the long-term efficacy of chronic treatment with amantadine might improve apathy and fatigue in PD patients (NCT00632762) [109]. For Huntington chorea, amantadine treatment delivered no beneficial effects but brought subjectively better feelings to patients [63]. Memantine, an adamantane derivative like amantadine, is an uncompetitive, moderate affinity, open-channel NMDAR blocker with strong voltage dependency and rapid blocking and unblocking kinetics [110]. Despite being approved by the US FDA for treating moderate-to-severe AD with safe and well tolerated profile, the efficacy of memantine is inconsistent at best. Some studies proved the clinical improvement of memantine in patients with moderate to severe AD [64], while other studies showed little clinical benefits of memantine towards AD treatment [111]. Several clinical results of memantine treatment in PD were also contradictive [65]. In MDD and BD clinical studies, memantine failed to show antidepressant effects in patients [66, 68]. As treatment for schizophrenic

symptoms, adjunct memantine uncovered a beneficial effect in ten studies, but no effects in two studies [67]. One study of memantine revealed minimal improvement in seven patients with anxiety [69].

Dextromethorphan, an uncompetitive NMDA receptor antagonist, is used as a cough suppressant with sedative and dissociative effects. In recent research, dextromethorphan and dextromethorphan-based compounds are considered as potential rapid-acting antidepressants, and therefore its therapeutic effect in MDD is evaluated in the clinical study (NCT04226352). In a BD study, dextromethorphan had no significant antidepressant effects compared with placebo group. This might be due to DRD2/ANKK1 TaqIA polymorphism [70]. Nuedexta, an FDA approved treatment for the pseudobulbar affect, was also utilized to treat MDD and BD. The purpose of adding dextromethorphan with quinidine in this combination is to inhibit the cytochrome P450 2D6 (CYP2D6) isoform, a dominant metabolic pathway of dextromethorphan, hence augmenting the bioavailability of dextromethorphan in CNS [112]. A proof-of-concept clinical trial demonstrated that after Nuedexta treatment, the response and remission rates in the patients with treatment resistant depression were 45% and 35%, respectively (NCT01882829). In a retrospective chart review, Nuedexta induced significant improvement in Clinical Global Impression (CGI) in depressed patients with treatment resistant bipolar disorder, implying its possible effectiveness in the BD treatment [71].

AVP-786, another dextromethorphan-based compound, is in conjunction with quinidine and deuterium to decrease the metabolism of dextromethorphan in the liver and hence increase its blood exposure. Following FDA Fast-Track designation for agitation in AD [113], four AD-related clinical studies of AVP-786 are underway (NCT02442765, NCT02442778, NCT02446132, and NCT03393520). In patients with MDD and schizophrenia, the efficacy, safety, and tolerability of AVP-786 were evaluated in the clinical studies (NCT02153502 and NCT03896945). AXS-05 (Axsome) is in combination with dextromethorphan and bupropion, which acts as an inhibitor of CYP2D6 to enhance the bioavailability of dextromethorphan [114]. In the AXS-05 treatment of agitation in patients with AD, the efficacy and safety of AXS-05 will be compared to placebo (NCT04797715). Three phase III clinical studies on the safety and efficacy of AXS-05 in patients with MDD were conducted without results posted to date (NCT02741791, NCT04019704, and NCT04039022).

(R,S)-Ketamine, an anesthetic and analgesic via intravenous administration, and its derivates (S)-ketamine (esketamine) and (R)-ketamine (arketamine) open a new era for glutamatergic rapid-acting antidepressant. At high doses (1-2 mg/kg), ketamine inhibits NMDAR as an uncompetitive antagonist to produce anesthesia, while at low doses, ketamine induces analgesia against both acute and chronic pain (0.25–0.5 mg/kg). Importantly, rapid-acting antidepressant effects of ketamine at moderate doses (0.5 mg/kg) have been proved in preclinical and clinical studies [3]. In most clinical studies of MDD, (R,S)-ketamine administration decreased depression severity with robust and rapid antidepressant effects [72], in accordance with studies of BD [73] and anxiolytic effects in anxiety disorders [74]. The (S+) enantiomer of ketamine was approved by FDA for adults with MDD with acute suicidal ideation or behavior. Esketamine improved depressive symptoms and delayed relapse in many studies [75], but did not demonstrate significant improvement as an adjunctive therapy with oral antidepressants in elderly patients with treatment-resistant depression [115]. In the study of treatment-resistant bipolar depression, the efficacy, safety, and pharmacokinetics of inhaled esketamine are still being evaluated (NCT03965871). Another enantiomer of ketamine, arketamine, is a less potent NMDAR uncompetitive antagonist, but displays greater and longer antidepressant effects than esketamine without psychotomimetic side effects [116]. In an open-label pilot study, intravenous arketamine generated fast-onset and sustained

antidepressant effects in depressed patients [117], and the larger study is underway (NCT04108234).

Neramexane, a moderate-affinity NMDAR open-channel blocker, possesses similar kinetics and voltage-dependency to memantine. Although it was well tolerated at all administered doses in clinical studies, phase II/III clinical trials for moderate-to-severe AD yielded contradictory results [76]. Nitrous oxide, an uncompetitive NMDAR antagonist, is an inhaled anesthetic often used in obstetrics or dentistry [118]. One recently published research demonstrated that compared with 50% nitrous oxide, 25% nitrous oxide provides comparable antidepressant effects with a markedly lower rate of adverse effects [77]. Other studies are underway to evaluate the efficacy and safety of nitrous oxide in MDD (NCT03869736 and NCT03932825). Nitrous oxide acted as a pharmacologic treatment for lumbar puncture/other procedure-related anxiety (NCT02243826).

3.2.2 Indirect NMDAR blockers

Lamotrigine, inhibiting voltage-dependent Na^+, Ca^{2+}, and K^+ channels, acts as a presynaptic glutamate release inhibitor [119]. FDA approved lamotrigine for the maintenance treatment of BD. Lamotrigine failed to achieve clinical improvement in five clinical studies of MDD, while it induced higher response rate than placebo in BD studies [52]. In a comprehensive meta-analysis, lamotrigine performed better than placebo in improving unipolar and bipolar depressive symptoms [78]. Five of nine clinical trials of lamotrigine in schizophrenia revealed clinical improvement in a range of outcome measures [67].

Riluzole (BHV-0223), a glutamate release inhibitor, was approved by the US FDA for the treatment of amyotrophic lateral sclerosis. The mechanisms that reduce extracellular glutamate by riluzole includes reduced glutamate release through presynaptic inhibition of voltage-gated sodium channels (VGSCs), increased glutamate uptake by astroglial cells, and enhanced AMPA trafficking [120]. In a current clinical study of AD, riluzole decreased the reduction in cerebral glucose metabolism, a positive correlation with cognitive measures [79]. Additionally, riluzole only ameliorated depressive symptoms in one of four placebo-controlled MDD studies, and failed to reach clinical improvement in a BD study [52]. In one trial of anxiety disorders, eighty percent subjects responded positively to riluzole [80], and the following functional neuroimaging studies proved the alterations in hippocampal N-acetylaspartate (NAA) concentrations and volumes were in correlation with riluzole-induced improvement on anxiety scales [121]. Troriluzole (BHV-4157), a tripeptide prodrug conjugate of riluzole, has been developed to improve the bioavailability, safety, and dosing of riluzole. As a glutamate modulator, troriluzole decreases the level of synaptic glutamate via strengthening glutamate uptake, mainly through excitatory amino acid transporters (i.e., EAAT2) located on glial cells. Both in clinical studies of AD and anxiety, the clinical efficacy of troriluzole is under assessment (NCT03605667 and NCT03829241).

4. Conclusions

Not only does the discovery of ketamine to act as a novel rapid-acting antidepressant trigger a strong interest in developing novel NMDAR-modulating agents by a variety of proof-of-concept studies for CNS disorders, but also, after exploring the potential pathological mechanisms for the major CNS disorders as described above, the aberrant NMDAR activity shows to play a pivotal role in regulating clinical symptoms, hence facilitating the development of positive and negative NMDAR

modulators against those pathological aberrances in NMDAR activity. Interestingly, but not surprisingly, monotherapy of single NMDAR modulators often failed in clinical studies, boosting the prosperity of combination treatment with multiple modulators, or even with the standard treatments, further implying the intricate mechanisms underlying the CNS pathology.

To date, numerous clinical studies of NMDAR modulators are still underway. With more successful clinical improvement by NMDAR modulators in clinical studies, the mysterious puzzles of CNS disorders could be dissolved gradually, further refining the utilization of NMDAR modulators as optimal treatment with less undesirable side effects for the sophisticated CNS disorders that involve vulnerability in NMDA homeostasis.

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Conflict of interest

The corresponding author is the CEO of SyneuRx International Corp., which is developing CNS therapeutics.

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