

Mini Review

NMDA Receptors at the Interface of Molecular Neurobiology and Therapeutics: A Mini Review

Je'Niece Manning, Melissa Williams, Daya S. Gupta*

South University School of Pharmacy, South University, 709 Mall Blvd, Savannah, GA 31406, USA

*Correspondence: Daya S. Gupta, South University School of Pharmacy, South University, 709 Mall Blvd, Savannah, GA 31406, USA, E-mail: dayagup@gmail.com; DOI: 10.1042/JCTCS.9.3.0065

Received date: August 25, 2026; Accepted date: August 31, 2026; Published date: October 05, 2026

Citation: Je'Niece Manning, Melissa Williams, Daya S. Gupta (2026) NMDA Receptors at the Interface of Molecular Neurobiology and Therapeutics: A Mini Review. J Clin Trial Case Stud, 9:3.

Copyright: © 2026, Daya S. Gupta. All intellectual property rights, including copyrights, trademarks rights and database rights with respect to the information, texts, images, logos, photographs and illustrations on the website and with respect to the layout and design of the website are protected by intellectual property rights and belong to Probe Publisher or entitled third parties. The reproduction or making available in any way or form of the contents of the website without prior written consent from Probe Publisher is not allowed.

Description

The N-methyl-D-aspartate receptor (NMDAR) occupies a distinctive position at the intersection of molecular neurobiology, synaptic physiology, and clinical pharmacology. In The Role of the NMDA Receptor in the Treatment of Psychiatric and Neurological Diseases, Heath et al. (2026) provide a broad overview of NMDAR biology and evaluate its therapeutic relevance across schizophrenia, treatment-resistant depression (TRD), Alzheimer's disease, Parkinson's disease, neuropathic pain, and epilepsy. The central premise is that abnormal NMDAR signaling is shared across numerous neuropsychiatric disorders and that improved understanding of receptor structure, subunit composition, and signaling may enable development of more selective and better-tolerated therapies.

Molecular architecture as the basis for pharmacological selectivity

A particularly useful feature of the review is its progression from receptor biology to therapeutic application. The NMDAR is a heterotetramer assembled from GluN1, GluN2AD, and GluN3A-B subunits. Its component subunits contain amino-terminal, ligand binding, transmembrane, and intracellular C-terminal domains, providing several potential sites for pharmacological modulation. Glutamate interacts primarily with GluN2 subunits, whereas glycine or D-serine acts as a co-agonist through GluN1-containing receptors. Activation ultimately permits Ca^{2+} influx after voltage-dependent Mg^{2+} blockade is relieved.

Glutamate is the principal excitatory neurotransmitter used by many long-range projection neurons in the brain, with rapid excitatory synaptic transmission mediated predominantly through AMPA receptors. As depicted in Figure 2 (of the original article), NMDAR activation requires both ligand binding and sufficient postsynaptic depolarization to relieve the voltage-dependent Mg^{2+} block. This dual requirement enables the receptor to function as a molecular coincidence detector, permitting Ca^{2+} influx when presynaptic neurotransmitter release coincides with postsynaptic neuronal activity.

The resulting increase in intracellular Ca^{2+} activates signaling pathways, including calcium/calmodulin-dependent protein kinase II (CaMKII), that promote AMPA receptor trafficking and insertion into the postsynaptic membrane. This strengthens excitatory synaptic transmission and contributes to long-term potentiation (LTP). NMDARs also participate in long-term depression (LTD), allowing synaptic strength to be either enhanced or reduced depending on the temporal pattern, magnitude, and duration of Ca^{2+} signaling. Relatively modest NMDAR activation is associated with LTD, whereas stronger and more sustained NMDAR activation favors LTP (Lüscher and Malenka, 2012). Through these bidirectional effects, NMDARs serve as key molecular regulators of synaptic plasticity and enable neuronal circuits to adapt dynamically in response to experience.

These NMDAR-dependent changes in synaptic efficacy are fundamental to learning, memory, and adaptive modification of neural networks. By linking coincident neuronal activity to persistent changes in synaptic strength, NMDARs also contribute to the ability of neural circuits to generate behavioral responses that are appropriate to a particular context. Consequently, disturbances in NMDAR function may impair the normal adaptation of neuronal networks and contribute to maladaptive cognitive and behavioral responses. Consistent with this central role, dysregulated NMDAR signaling has been implicated in a broad range of neuropsychiatric and neurological disorders, including schizophrenia, depression, Alzheimer's disease, Parkinson's disease, neuropathic pain, and epilepsy.

Furthermore, NMDAR function is influenced by receptor composition and intracellular domain variability. The intracellular C-terminal

domain (CTD) differs substantially among subunits and regulates receptor trafficking, localization, and protein–protein interactions. Given the hetero-tetrameric structure and variable subunit combinations, distinct NMDAR populations likely serve specialized roles in neuronal circuits underlying cognition. This structural and functional diversity underscores why precise pharmacological targeting of specific receptor domains or subtypes may be necessary to achieve therapeutic selectivity.

From a molecular pharmacology perspective, this structural heterogeneity is highly significant. It explains both the biological versatility of the receptor and the difficulty encountered with earlier nonselective NMDAR antagonists. NMDAR signaling participates in synaptic plasticity, learning, memory, and neuronal development; consequently, indiscriminate inhibition can interfere with normal neuronal function. The review appropriately identifies the inability of existing drugs to discriminate adequately among receptor populations – particularly synaptic versus extra synaptic receptors as an important contributor to adverse effects [1].

Disease-specific therapeutic modulation

One of the most important messages of the review is that NMDAR dysfunction cannot be treated according to a simple paradigm of receptor inhibition. Rather, the required pharmacological strategy depends on the underlying disease biology. Schizophrenia is increasingly conceptualized as a disorder of brain dysconnectivity, in which impaired coordination among distributed cortical and subcortical networks may arise, at least in part, from NMDAR hypofunction and disrupted NMDAR-dependent synaptic signaling. Consistent with this hypothesis, therapeutic strategies in schizophrenia have focused on enhancing, rather than suppressing, NMDAR function. Sarcosine increases synaptic glycine by inhibiting GlyT1, whereas sodium benzoate and luvadaxistat inhibit D-amino acid oxidase and thereby increase endogenous D-serine. The article reports encouraging clinical observations with these approaches while also noting that luvadaxistat improved cognition without producing significant improvement in negative symptoms. This section illustrates an important principle in contemporary neuropsychopharmacology: Modulation of endogenous co-agonist systems may provide a subtler approach than direct receptor agonism.

The therapeutic strategy is nearly reversed in Treatment-Resistant Depression (TRD), where NMDAR antagonism, followed by enhanced AMPA receptor signaling, provides an important mechanistic basis for rapid antidepressant effects. The review highlights esketamine as an established treatment and discusses arketamine, apimostinel, and zelquistinel as emerging therapeutic approaches. Particularly noteworthy is the shift beyond conventional NMDAR channel blockers toward positive allosteric modulators and other agents intended to retain antidepressant and neuroplastic benefits while minimizing psychotomimetic adverse effects.

TRD is defined by an inadequate response to conventional antidepressants, including selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs), which primarily act through monoaminergic neurotransmitter systems. Monoaminergic pathways also play important roles in long-range neuromodulation, influencing the functional state of distributed neural circuits. In contrast, NMDAR-dependent signaling contributes more directly to activity-dependent plasticity within glutamatergic networks by modifying synaptic strength and the processing of excitatory information. The therapeutic efficacy of NMDAR-directed agents in patients who do not respond adequately to monoamine-based treatments therefore underscores the complex and multifactorial pathophysiology of depression. It also highlights glutamatergic signaling and synaptic plasticity as important therapeutic targets that complement, rather than simply duplicate, traditional monoaminergic mechanisms.

In Alzheimer's disease, the therapeutic challenge is still different. Amyloid- β -associated NMDAR hyperactivity can produce excessive Ca^{2+} influx and neuronal injury, whereas physiological synaptic NMDAR signaling remains important for neuronal survival and cognitive function. Memantine addresses this problem through use-dependent antagonism that preferentially affects hyperactivated receptors. The review also discusses memantine nitrate and RL-208 as examples of efforts to improve upon this pharmacological profile. The distinction between pathological and physiological receptor activity is therefore critical and reinforces the need for pharmacological modulation rather than complete receptor blockade.

The sections on Parkinson's disease, neuropathic pain, and epilepsy extend this concept further. Amantadine represents an established NMDAR-modulating approach in Parkinson's disease, although selective GluN2B antagonists such as CP-101606 and MK0657 illustrate the difficulties associated with translating promising receptor-selective pharmacology into meaningful clinical efficacy. In neuropathic pain, gabapentin and pregabalin are presented as indirectly influencing NMDAR signaling through $\alpha 2\delta$ -1 calcium channel interactions, while GluN2B-selective inhibition represents a more targeted investigational strategy. In epilepsy, ketamine becomes particularly relevant during refractory status epilepticus when GABA-A receptor internalization reduces the effectiveness of conventional GABA-enhancing therapy.

Translational and pharmacotherapeutic significance

Table 1 (of the original article) is one of the review's major strengths because it brings together disease indication, molecular target, mechanism, and developmental status. It emphasizes the remarkable diversity of NMDAR-directed approaches: direct antagonists, subunit-selective antagonists, positive allosteric modulators, GlyT1 inhibitors, DAAO inhibitors, and agents that indirectly alter receptor function.

This pharmacological diversity demonstrates that the NMDAR should no longer be viewed simply as a receptor that should either be "blocked" or "activated." Therapeutic success is increasingly likely to depend upon where, when, and how strongly NMDAR signaling is modified. Subunit composition, cellular localization, disease stage, receptor activation state, and interactions with other neurotransmitter systems may ultimately determine clinical response.

This point has particular relevance to pharmacy and molecular biology education because NMDAR pharmacology provides an excellent example of how knowledge at the molecular level translates into drug action, therapeutic indication, adverse effects, and clinical decision-making. The receptor demonstrates why apparently contradictory pharmacological strategies enhancing NMDAR activity in schizophrenia

while inhibiting excessive signaling in AD, depression, pain, or epilepsy, can all be rational when interpreted in the context of disease-specific molecular pathology [2].

Strengths, limitations, and future perspectives

A major strength of the article is its integration of receptor structure and signaling with clinical pharmacology rather than discussing these areas independently. The review also succeeds in showing that emerging therapies increasingly move away from indiscriminate NMDAR blockade toward subunit-selective, allosteric, co-agonist, and indirect modulatory strategies.

The breadth of the review is also a limitation. Because six distinct neurological and psychiatric conditions are covered, individual disease mechanisms and clinical evidence cannot be examined exhaustively. Furthermore, the manuscript functions primarily as a broad narrative synthesis rather than presenting a formal systematic-search and evidence grading framework. Consequently, promising preclinical findings and established clinical therapies must be interpreted at different levels of evidentiary confidence. Drug development status is also inherently dynamic, making periodic reassessment of this therapeutic landscape important.

The most compelling future direction is therefore precision NMDAR pharmacology. The authors appropriately argue that further work is needed to clarify the contributions of individual receptor subunits, determine where NMDAR dysfunction occurs within disease pathways, and establish whether compensatory or redundant mechanisms influence therapeutic responses. Advances in structural biology and molecular pharmacology should facilitate the development of agents capable of selectively modifying pathological receptor populations while preserving physiological NMDAR-dependent synaptic function.

Conclusion

The review presents the NMDAR as considerably more than a conventional ionotropic glutamate receptor; it is a molecular signaling hub whose dysregulation can contribute to fundamentally different neurological and psychiatric phenotypes. Its therapeutic importance arises from this same complexity. Existing drugs such as memantine, amantadine, ketamine, and esketamine demonstrate that NMDAR modulation can yield clinically meaningful effects, while emerging subunit-selective compounds, co-agonist pathway modulators, and allosteric agents point toward a more sophisticated generation of therapeutics. The most important conceptual transition is therefore from global NMDAR antagonism to context-dependent receptor modulation. As structural and molecular understanding of NMDAR subtypes advances, the ability to distinguish pathological from physiological signaling should improve. Such precision offers the prospect of maintaining the therapeutic benefits of NMDAR modulation while reducing the neurological, psychiatric, and behavioral adverse effects that have historically constrained this otherwise highly attractive drug target.

References

- 1) Heath S, Ruzicka M, McLoon T, Gupta D, Emeri O, et al. The role of the NMDA receptor in the treatment of psychiatric and neurological diseases. *Brain Sci.* 2026, 16:786.
- 2) Lüscher C, Malenka RC. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harb Perspect Biol.* 2012, 4:a005710.