NMDA RECEPTOR ANTAGONISTS AND EXPLORING THERAPEUTIC POTENTIAL

Abstract

The N-Methyl-D-Aspartate (NMDA) receptors, a glutamate-gated ion channel in the central nervous system, are essential for excitatory neurotransmission and synaptic plasticity. The dysregulation of its activity has been connected to a variety of neurological and psychological disorders. A class of drugs known as NMDA receptor antagonists affect its function and are being researched for therapeutic uses. These drugs inhibit calcium influx, hence influencing synaptic plasticity, excitability, and neurotransmission, and have applications in anaesthesia, pain management, neuroprotection, psychiatric diseases, substance misuse, and cognitive enhancement. Blocking ion channel pores, preventing glutamate binding, interfering with coincidence detection, binding to alternate locations, and allosteric regulation are some of their methods of action. While these medications have therapeutic potential, they can also cause adverse effects and necessitate a careful balancing of benefits and risks. Recent research looks on the temporal effects, structural interactions, and neuroprotective potential of these compounds. However, issues such as cognitive and psychological impacts, individual variability, selectivity, treatment duration, misuse potential, precision medicine, combination therapies, disease modulation, drug development, and ethical considerations remain. Future research should improve our understanding of NMDA receptor function, resulting in more refined drugs and personalised treatment methods. As pharmaceutical research and neuroscience progress, the possibility for optimising NMDA receptor antagonists in diverse medical situations grows more attractive.

Keywords: NMDA antagonist; Neurological disorder; Psychiatric disorder; Therapeutic implication; Excitatory neurotransmitter.

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I. INTRODUCTION

NMDA receptors are essential glutamate-gated ion channels in the central nervous system (CNS), vital for excitatory neurotransmission [1]. Irregular NMDA receptor activity links to neurological and psychiatric disorders, driving interest in NMDA receptor antagonists as potential therapeutics. These drugs target N-Methyl-D-Aspartate (NMDA) receptors, which are ionotropic glutamate receptors crucial for synaptic plasticity, memory, and neuronal signalling [2]. NMDA receptors comprise subunits: GluN1, GluN2 (A, B, C, D subtypes), and GluN3 [3]. Activation demands glutamate, co-agonists like glycine or D-serine, and depolarizing membrane potential. This enables calcium ions (Ca^{2+}) entry, pivotal for cellular processes. NMDA receptor antagonists bind NMDA receptors, dampening their activity. This curbs calcium influx, impacting synaptic plasticity, excitability, and neurotransmission, having both therapeutic and side effects. Side effects encompass cognitive impairments, hallucinations, dissociation, and psychological effects [4]. Therapeutic balance varies by drug, dosage, and patient characteristics.

1. **Applications Include**

- **Anaesthesia:** Ketamine, an NMDA receptor antagonist, induces dissociative anaesthesia, minimizing respiratory depression risk. It also exhibits rapid antidepressant effects in treatment-resistant depression [5].

- **Pain Management:** NMDA receptor antagonists manage chronic pain by countering pain sensitization and hyperalgesia.

- **Neuroprotection:** These drugs explore neuroprotection in stroke, traumatic brain injury, and neurodegenerative diseases, preventing excitotoxicity and cell death [6].

- **Psychiatric Disorders:** Research examines their role in treating depression, anxiety, and schizophrenia, though complexities require more understanding [7].

- **Substance Abuse:** Investigated for treating substance abuse, especially opioid withdrawal and addiction.

2. **NMDA Receptor Structure and Functions:** NMDA receptors are complex structures composed of subunits called GluN1 and GluN2 (A-D) or GluN3. Activation of these receptors allows calcium to enter the cell, triggering signalling pathways important for synaptic plasticity and learning [1]. The NMDA receptor, an ionotropic glutamate receptor, holds a crucial role in synaptic transmission, learning, memory, and neural plasticity [2]. Its structure and function are closely linked to its function in mediating excitatory neurotransmission and facilitating long-lasting changes in neural connections. Let's explore its structure and function:

- **Structure:** The NMDA receptor consists of different subunits, each playing a distinct role show in Figure1. Key subunits include GluN1 and GluN2 (A, B, C, D) or GluN3. The GluN1 subunit is vital for receptor function and is needed for forming functional NMDA receptors [3]. GluN2 and GluN3 subunits adjust the receptor's properties, including how it binds to specific molecules and conducts ions.Usually, the NMDA

receptor forms a tetramer, composed of two GluN1 and two GluN2 (or GluN3) subunits, creating a working receptor unit. This receptor unit spans the neuron's cell membrane, with parts on the outside that bind to glutamate and co-agonists, and parts on the inside that control the opening and closing of the ion channel and how signals are transmitted within the cell [10].
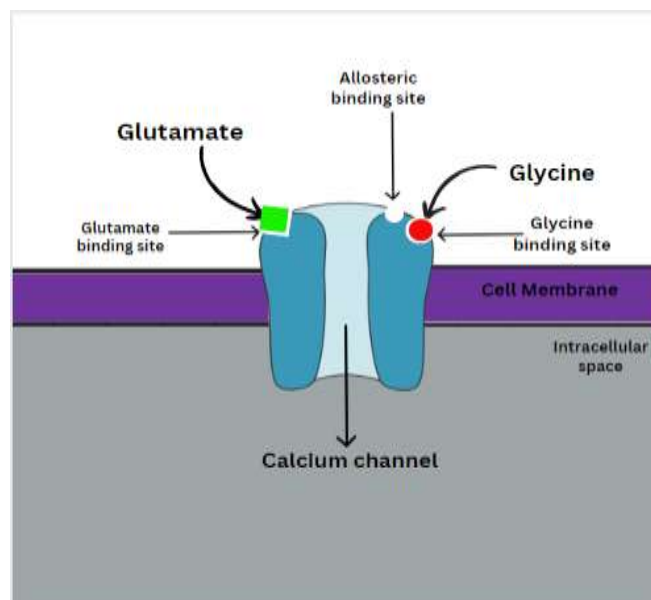

Figure 1: Activated NMDA Receptor

3. **Functions of NMDA Receptor:** The NMDA receptor's function is closely tied to its role in mediating excitatory neurotransmission and synaptic plasticity-

- **Excitatory Neurotransmission:** Glutamate, a major excitatory neurotransmitter in the brain, binds to the NMDA receptor along with co-agonists like glycine or D-serine. Both glutamate and co-agonists are needed for receptor activation. This leads to the opening of a calcium-permeable ion channel, enabling calcium ions (Ca^{2+}) to enter the neuron [8].

- **Synaptic Plasticity:** Long-term potentiation (LTP) and long-term depression (LTD) are two types of synaptic plasticity that can be induced by calcium influx through the NMDA receptor [9]. LTP makes synapses stronger, which may aid with learning and memory. LTD makes synapses weaker, which improves neuronal circuits [9].

- **Coincidence Detection:** The NMDA receptor uniquely requires postsynaptic depolarization to remove a magnesium block from its ion channel. This "coincidence detection" ensures receptor activation when the postsynaptic membrane is somewhat depolarized, serving as a coincidence detector for pre- and postsynaptic activity [10].

- **Neurological Disorders:** Dysregulation of NMDA receptor function links to neurological disorders like Alzheimer's, Parkinson's, epilepsy, and schizophrenia. Overactive NMDA receptors can cause excitotoxicity, contributing to neuron damage and cell death [11].

- **NMDA Receptor Modulation:** Factors like magnesium ion levels, redox state, and phosphorylation modulate NMDA receptors. Their activity can be influenced by natural molecules and various drugs [12].

  The NMDA receptor centrally manages excitatory neurotransmission and synaptic plasticity, vital for learning, memory, and neural network adaptation. Its structure and function are intertwined, enabling it to control complex signalling essential for normal brain operation. Precise regulation is crucial, as both excessive and insufficient NMDA receptor activity holds significant implications for health and disease [13]. NMDA receptor antagonists exert their effects through different binding mechanisms, either competitive or non-competitive. These mechanisms hinder calcium influx, leading to changes in synaptic plasticity and excitatory neurotransmission

4. **Mechanisms of NMDA Receptor Antagonism:** NMDA receptor antagonists interfere with the normal function of ionotropic glutamate receptors, particularly the N-Methyl-D-Aspartate (NMDA) receptor. They modulate the receptor's activity through diverse ways, ultimately resulting in the inhibition of calcium ion entry and subsequent signalling. Here are key mechanisms of NMDA receptor antagonism [14].

- **Blockade of Ion Channel Pore:** These antagonists can physically obstruct the ion channel pore that allows ion passage, including calcium. By doing so, they prevent the opening of the ion channel, stopping the usual ion flow and disrupting the signalling process initiated by NMDA receptor activation.

- **Prevention of Glutamate Binding:** Many NMDA receptor antagonists bind to the receptor's glutamate-binding site located in its extracellular region. By occupying this site, they prevent glutamate, the main excitatory neurotransmitter, from attaching to the receptor. This halts the initiation of receptor activation.

- **Disruption of Coincidence Detection:** NMDA receptors require postsynaptic membrane depolarization to remove a magnesium ion block from their ion channel. This feature allows them to act as coincidence detectors, necessitating both presynaptic glutamate release and postsynaptic depolarization. Antagonists can disturb this mechanism, preventing magnesium block removal even in the presence of depolarization.

- **Binding to Other Sites:** Some antagonists attach to sites other than the glutamate-binding site, like the glycine or co-agonist binding site. These sites are crucial for full NMDA receptor activation. By binding to them, antagonists can interfere with co-agonist interactions, thereby reducing or blocking receptor activity.

- **Allosteric Modulation:** Certain antagonists function as allosteric modulators, binding to distinct locations on the NMDA receptor complex. This alters the receptor's shape and reduces its responsiveness to glutamate and co-agonists. Consequently, channel opening and calcium influx decrease.

- **Regulation of Calcium Influx:** Ultimately, NMDA receptor antagonists diminish the entry of calcium ions into neurons. This reduction has significant implications for neuronal excitability, synaptic plasticity, and various downstream signalling pathways.

- **Effect on Synaptic Plasticity and Learning:** By inhibiting NMDA receptors' normal activity, antagonists impact synaptic plasticity processes such as long-term potentiation (LTP) and long-term depression (LTD), vital for forming memories and learning. Disruption of these processes contributes to the observed behavioural and cognitive effects of NMDA receptor antagonists.

5. **Therapeutic Implications:** NMDA receptor antagonists offer therapeutic potential for various medical and neurological conditions, thanks to their effects on neuronal signalling, neurotransmission, and synaptic plasticity. Here are some of their key therapeutic implications [9].

- **Anaesthesia and Analgesia:** Drugs like ketamine and nitrous oxide are used in anaesthesia for inducing dissociative anaesthesia and providing pain relief. Ketamine's rapid action and potential to reduce opioid use during surgery are notable.

- **Depression Treatment:** NMDA receptor antagonists, particularly ketamine, show promise in rapidly alleviating treatment-resistant depression symptoms. Their effects on synaptic plasticity and neural circuit modulation play a role.

- **Chronic Pain Management:** Memantine and dextromethorphan, NMDA receptor antagonists, are explored for managing chronic pain, including neuropathic pain. They can attenuate pain sensitization and hyperalgesia by modulating glutamatergic transmission.

- **Neuroprotection:** NMDA receptor antagonists are studied for neuroprotection in stroke, traumatic brain injury, and neurodegenerative diseases. By limiting excessive calcium influx and excitotoxicity, they could help preserve neuronal function.

- **Substance Abuse Disorders:** Investigation into NMDA receptor antagonists as treatments for substance abuse disorders focuses on withdrawal symptom management and craving reduction. Their impact on disrupted neural activity is significant [15].

- **Neurological Disorders:** In conditions like epilepsy and Huntington's disease, NMDA receptor antagonists are explored for modulating neuronal excitability and calcium signalling to mitigate symptoms [8].

- **Psychiatric Disorders:** Beyond depression, NMDA receptor antagonists are researched for their potential in anxiety disorders, bipolar disorder, and schizophrenia. Balancing benefits and risks is a challenge due to the complexity of these disorders [16].

- **Cognitive Enhancement:** Some studies suggest NMDA receptor antagonists could enhance cognition by affecting memory and synaptic plasticity. Striking the right balance between cognitive improvement and potential impairment is being investigated [17].

- **Research Tools:** NMDA receptor antagonists are valuable in neuroscience research to understand NMDA receptors' roles in neuronal circuits, synaptic plasticity, and learning.

  It's important to recognize that NMDA receptor antagonists can lead to cognitive impairments, hallucinations, and dissociation [18]. Finding the right balance between therapeutic benefits and side effects is crucial, and individual responses can vary, necessitating personalized approaches. As research progresses, our comprehension of these antagonists' therapeutic potential deepens. Ongoing studies aim to refine their use, develop more selective compounds, and uncover their mechanisms of action for optimized benefits and minimized risks [19].

6. Key NMDA Receptor Antagonist Drugs

- **Acamprosate:** Used to help individuals maintain abstinence from alcohol. While not a direct NMDA receptor antagonist, its mechanism involves interactions with glutamatergic neurotransmission, including NMDA receptors [20].

- **Neramexane:** An investigational NMDA receptor antagonist with potential applications in neuropathic pain and tinnitus.

- **Methoxetamine (MXE):** A synthetic compound that acts as an NMDA receptor antagonist. Structurally related to ketamine, it has been used recreationally, but its use comes with significant risks.

- **Riluzole:** Approved for treating amyotrophic lateral sclerosis (ALS). While its mechanism isn't fully understood, it modulates glutamate transmission, including NMDA receptor activity.

- **D-Cycloserine**: An antibiotic that acts as a partial agonist at the NMDA receptor's glycine site. Studied for its potential to enhance exposure therapy in anxiety disorders.

- **Ro 25-6981:** An experimental compound acting as a highly selective NMDA receptor antagonist, used in research to study NMDA receptors' role in synaptic plasticity.

- **MAD-399:** A novel NMDA receptor antagonist showing potential in preclinical studies for its effects on synaptic plasticity and cognitive enhancement.

- **NMDAR Glycine Site Ligands (Glycine Modulators):** Various compounds targeting the glycine co-agonist site of the NMDA receptor are investigated as potential therapeutic agents. Examples include GLYX-13 (rapastinel) and NRX-1074, showing promise in depression treatment [21].

- **Lanicemine:** An NMDA receptor antagonist explored for its antidepressant effects, similar to ketamine and esketamine.

- **Zenocutuzumab (MCLA-128):** An investigational compound that may act as an NMDA receptor antagonist among other mechanisms, studied for potential use in treating certain cancers.
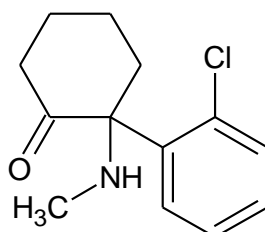
II. NMDA RECEPTOR ANTAGONIST DRUGS

1. **Amantadine:** Amantadine, a primary aliphatic amine and a member of the family of drugs known as adamantanes, is used as an antiviral and antiparkinson's drug as well as a dopaminergic agent, analgesic, an NMDA receptor antagonist, and a non-narcotic analgesic. It is derived from the hydride of an adamantane.
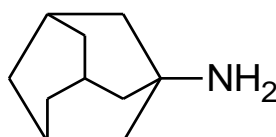

IUPAC Name: adamantan-1-amine

- **Uses:** Antiviral, Antiparkinsonian and Anti-hyperalgesia activities [22-24].
- **Pharmacokinetics:** Amantadine is effectively absorbed by the gastrointestinal tract when taken orally. Most of the total binds to plasma proteins, about 67%. Although traces of an acetyl metabolite have been detected, there is no discernible metabolism. Ten to fourteen hours were the half-life' range [25, 26].

2. **Ketamine:** Ketamine has a strong anaesthetic action and is an NMDA receptor antagonist. It was created in 1963 by Calvin Stevens at Parke Davis Laboratories to replace phencyclidine (PCP).The cyclohexanone class in which ketamine belongs has one hydrogen at position 2 substituted by a 2-chlorophenyl group and the other by a methylamino group. It functions as an NMDA receptor antagonist, analgesic, neurotoxic, environmental pollutant, and xenobiotic in addition to being an intravenous anaesthetic. It is a monochlorobenzene and a member of the cyclohexanone family of secondary amino compounds.


- **IUPAC Name:** 2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one
- **Uses:** Anaesthetic, NMDA Receptor Antagonist, Analgesic, Neurotoxin, Environmental Contaminant and Xenobiotic [27-29].
- **Pharmacokinetics:** Ketamine absorption is extremely rapid, with a bioavailability of approximately 93%. It distributes quickly and has a distribution half-life of 1.95

minutes. Ketamine is primarily metabolised in the liver, and its principal metabolite is norketamine. 85-95% of the given dose is recovered in urine, primarily as metabolites. Ketamine can also be eliminated through bile and faeces [30,31].

3. **Orphenadrine:** The 2-(dimethylamino)ethanol phenyl-o-tolylmethyl ether of orphenadrine is a tertiary amino chemical. It serves as an NMDA receptor antagonist, an H1 receptor antagonist, a parasympatholytic, a muscle relaxant, a muscarinic antagonist, and an antidyskinesia agent in addition to being an antiparkinson's drug. It is a tertiary amino compound as well as an ether.
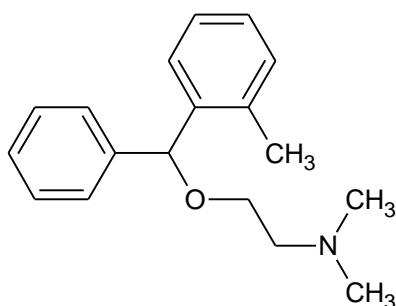

- **IUPAC Name:** *N*, *N*-dimethyl-2-[(2-methylphenyl)-phenylmethoxy]ethanamine
- **Uses:** NMDA Receptor Antagonist, H1-Receptor Antagonist, Anti-Parkinson Drug, Parasympatholytic, Muscle Relaxant, Muscarinic Antagonist and Anti-dyskinesia Agent [32,33].
- **Pharmacokinetics:** Orphenadrine is almost entirely absorbed in the gastrointestinal tract. Orphenadrine binds 95% to plasma protein. Biotransformation happens mostly in the liver [34,35].

4. **Dextromethorphan:** Dextromethorphan is a levorphanol derivative and a codeine analogue that is frequently abused in addition to being used as a cough suppressant. Despite having a structure that is comparable to other opioids, it seldom interacts with opioid receptors. Before December 3rd, 1957, the FDA approved dextromethorphan. It functions as a oneirogen, a prodrug, a neurotoxic, a xenobiotic, an antitussive, and an antagonist of the NMDA receptor. It is similar to a dextrorphan in terms of function. It is a levomethorphan enantiomer.
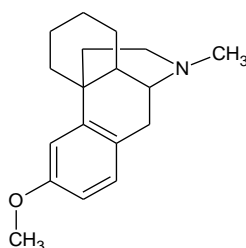

- **IUPAC Name:** (1*S*,9*S*,10*S*)-4-methoxy-17-methyl-17-azatetracyclo[7.5.3.0^{1,10}.0^{2,7}]heptadeca-2(7),3,5-triene
- **Uses:** NMDA Receptor Antagonist, Neurotoxin, Xenobiotic, Environmental contaminant, Antitussive [36].

- **Pharmacokinetics:** Dextromethorphan is absorbed orally. Dextromethorphan is 60-70% protein bound in serum. Dextromethorphan has a half-life of 3-30 hours [37,38].

5. **Meperidine:** Meperidine is a piperidinecarboxylate ester, where piperidine is replaced at positions 1 and 4 by methyl, phenyl, and ethoxycarbonyl groups, respectively. It is an analgesic used to treat moderate to severe pain, such as postoperative pain and discomfort during delivery. It functions as an antispasmodic, a kappa-opioid receptor agonist, a mu-opioid receptor agonist, and an opioid analgesic. It is a piperidinecarboxylate ester, an ethyl ester, and a tertiary amino molecule. It is a conjugate base of a pethidine(1+).
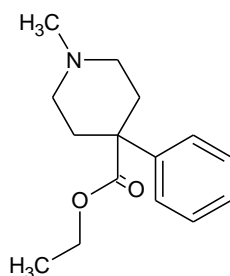

- **IUPAC Name:** ethyl 1-methyl-4-phenylpiperidine-4-carboxylate
- **Uses:** Analgesic, Opioid Analgesic, Antispasmodic drug [39,40].
- **Pharmacokinetics:** Due to substantial first-pass metabolism, the oral bioavailability of meperidine in patients with normal hepatic function is 50–60%. In the liver, meperidine is converted to meperidinic acid by hydrolysis before being partially conjugated with glucuronic acid. It is excreted in the urine [41].

6. **Ifenprodil:** Ifenprodil is an oral NMDA receptor antagonist that may have neuroprotective, anti-inflammatory, and anti-fibrotic effects in addition to its ability to stimulate the central nervous system (CNS). Ifenprodil targets, binds to, and inhibits glutamanergic NMDA receptors (NMDARs), more specifically the glycine-binding NMDA receptor subunits 1 and 2 (glutamate-binding NMDA receptor subunit 2; NMDA-type subunit 2B; GluN2B), inhibiting NMDAR signalling. As a result, neuronal excitotoxicity is inhibited, potentially improving cognitive performance.
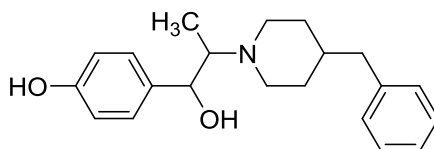
- **IUPAC Name:** 4-[2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl]phenol
- **Uses:** NMDA Receptor Antagonist, Neuroprotective, Anti-Inflammatory and Anti-Fibrotic Activities [42,43].

7. **Tramadol:** A synthetic opioid analgesic with a central effect and SNRI (serotonin/norepinephrine reuptake inhibitor) that resembles codeine and morphine structurally is known as tramadol. Due to its good tolerability profile and multimodal mechanism of action, tramadol is frequently seen as a less dangerous alternative to opioids for the treatment of moderate to severe pain. It is a (R,R)-tramadol(1+) conjugate base. It is a (S, S)-tramadol's enantiomer.
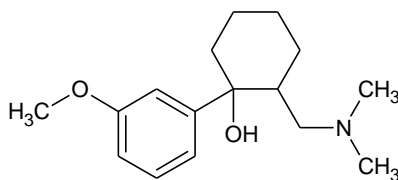
- **IUPAC Name:** (1*R*,2*R*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol
- **Uses**: Adrenergic uptake Inhibitor, Antitussive, Muscarinic Antagonist, Nicotinic Antagonist, NMDA Receptor Antagonist, Opioid Analgesic, Serotonergic Antagonist [44-46].
- **Pharmacokinetics**
  - ➤ Tramadol is given as a racemate, and racemic tramadol is quickly and nearly completely absorbed, having a bioavailability of 75%.
  - ➤ It approximately 20% of the injected dosage binds to plasma proteins.
  - ➤ It extensively demethylated and conjugated in the liver during its first pass metabolism.
  - ➤ It eliminated by the liver, and the metabolites are primarily excreted by the kidneys, accounting for 90% of excretion, with the remaining 10% excreted through faeces [47-49].

8. **Phencyclidine:** The illegal hallucinogen phencyclidine was first used as an anaesthetic in the 1950s and early 1960s but was discontinued in 1965 due to its dissociative hallucinogenic effects, which were sometimes upsetting and occasionally severe and persistent.The family of piperidines that includes phencyclidine is made up of piperidines in which the nitrogen atom has been replaced with a 1-phenylcyclohexyl group. This substance, which was once employed as an anaesthetic, has both hallucinogenic and neurotoxic properties. It functions as an anaesthetic, NMDA receptor antagonist, neurotoxic, and psychotropic substance. It belongs to the benzenes and piperidines families. It comes from a piperidine hydride.
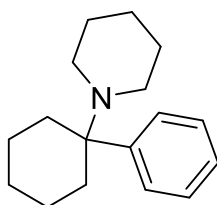

- **IUPAC Name:** 1-(1-phenylcyclohexyl)piperidine
- **Uses:** Neurotoxin, Psychotropic drug, Anaesthetic and NMDA Receptor Antagonist [50,51].

9. **Esketamine:** The S- (more active) enantiomer of ketamine is esketamine. It functions as an intravenous anaesthetic, an NMDA receptor antagonist, and an analgesic. The FDA authorisedesketamine, also marketed under the brand name Spravato (by Janssen Pharmaceuticals), as a nasal spray on March 5, 2019, to treat serious depression that has not responded to treatment. Patients with major depressive disorder who have tried a variety of drugs and therapies without seeing any improvement in their symptoms may find esketamine to be a successful treatment. This medication's simple administration and

quick commencement of action make it stand out from many other antidepressants, which may take several weeks to work. This is due to the intranasal method of administration.
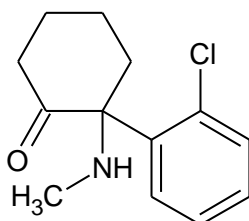
- **IUPAC Name:**(2*S*)-2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one
- **Uses:** NMDA receptor antagonist [52,53].
- **Pharmacokinetics:** Absorption is rapid as drug is administered via nasal spray. Esketamine has a protein binding affinity of 43% to 45%. Esketamine is primarily metabolised to the metabolite noresketamine. Less than 1% of a nasal esketamine dose is eliminated in the urine as unchanged drugs [54].

10. **Methadone:** Methadone is a racemate comprising equimolar amounts of dextromethadone and levomethadone.It is an opioid analgesic that is used to relieve pain and as a heroin substitute in the recovery from heroin addiction. Strong synthetic analgesic methadone functions as both an antagonist of the N-methyl-d-aspartate (NMDA) receptor and a complete agonist of the -opioid receptor (MOR). Methadone replicates the effects of the body's endogenous opioids, endorphins, and enkephalins by releasing neurotransmitters involved in pain transmission. It is a complete MOR agonist.
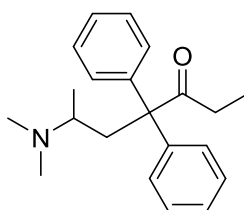
- **IUPAC Name:**6-(dimethylamino)-4,4-diphenylheptan-3-one
- **Uses:** Opioid Analgesic, Xenobiotic, Environmental contaminant, NMDA Receptor Antagonist and Serotonin uptake Inhibitor [55,56].
- **Pharmacokinetics:** Methadone bioavailability ranges from 36-100% when used orally. Methadone's first-pass metabolism is fairly comprehensive. Methadone is eliminated through substantial biotransformation, followed by renal and faecal excretion [57].

III. RECENT DEVELOPMENTS

A study by A Adell examines the temporal mechanisms of NMDA blockade in rats, and it suggests that depending on the initial state of the organism, NMDA receptor antagonists either cause schizophrenia-like or antidepressant-like effects. With NMDA antagonists, depression might get better whereas schizophrenia or healthy patients might get worse [58]. A thorough examination of the conformational alterations and inter-subunit interactions that regulate agonist-gating and subunit-specific competitive inhibition in

NMDA receptors is provided by a work by Liu et al. The modulation of transmembrane ion channel linker tension by GluN1 and GluN2 antagonists via the ligand-binding domain is highlighted by a number of high-resolution structures. With implications for brain physiology, these discoveries expand our knowledge of NMDAR activity [59].The medial habenula (MHb) of adult mice was the area where Otsu et al. studied the operation of the NMDA receptor subunit combination GluN1/GluN3A. When glycine is produced from astrocytes, it activates this particular pair of NMDA receptor subunits in MHb neurons. Activating NMDA receptors on GluN1/GluN3A results in depolarization and enhanced spiking in MHb neurons. Blocking conditioned place aversion requires lowering GluN3A receptor subunit levels in the MHb [60].

By increasing the activation of NMDA receptors in the paraventricular nuclear (PVN), Zhou et al. looked into the connection between prolonged calcineurin inhibitor therapy and enduring high blood pressure. Rats receiving FK506 saw an increase in blood pressure, a decrease in PVN calcineurin activity, and an increase in synaptic density and NMDA receptor phosphorylation. In PVN's pre-sympathetic neurons, calcineurin was discovered. In these neurons, FK506 increased firing, which NMDA antagonists were able to reverse. Giving NMDA blockers in the PVN reduced the sympathetic nerve activity and blood pressure increase brought on by FK506. Hypertension brought on by FK506 was reduced by the therapeutic NMDA receptor antagonist memantine. This reveals the function of PVN calcineurin, which is important for the treatment of calcineurin inhibitor-induced hypertension, in reducing sympathetic activity by way of NMDA receptors [61].According to research by Dore et al., beta-amyloid (Aβ) damages synapses through NMDA receptors. By changing NMDAR structure and protein interactions, elevated PSD-95, a crucial scaffold protein, counteracts the effects of Aβ and protects synapses. Without GluA1, this defence continues to exist. Aβ-induced NMDAR alterations are prevented by enhanced PSD-95, indicating low PSD-95 levels are present in susceptible synapses. Inhibiting depalmitoylation increases PSD-95, reducing the effects of Aβ and providing a potential treatment for Alzheimer's [62].

Alemany et al., examined the effects of continuous low-dose therapy with memantine and a novel NMDA receptor antagonist (UB-ALT-EV) on cognitive function in 6-month-old female 5XFAD mice. Both therapies enhanced cognitive function and decreased calpain-1 activity, as seen by a decline in spectrin breakdown products (SBDP) and the p25/p35 ratio. NMDAR antagonists also reduced tau phosphorylation (AT8), Thioflavin-S plaques, and A deposition. Proteins associated to autophagy changed, indicating that UB-ALT-EV reversed autophagolysosome accumulation. Normal apoptotic indicators (Bcl-2, Bax, and caspase-3) were recovered by UB-ALT-EV. The study underscores the familial AD mouse model's neuroprotective potential [63].Quan et al., synthesized novel tryptamine derivatives targeting GluN2B-NMDA receptors including Z25, exhibiting potent neuroprotective effects ($55.8 \pm 0.6\%$ protection) surpassing positive controls ($41.0 \pm 2.7\%$). Z25 displayed GluN2B-NMDAR antagonist behavior by reducing intracellular Ca2+ influx and enhancing p-ERK 1/2 expression. In vivo, Z25 improved cognitive function in cerebral ischemic injury tests despite its short half-life and low bioavailability ($3.12 \pm 0.01\%$). Promisingly, Z25 could serve as a lead compound for treating cerebral ischemic injury via GluN2B-NMDAR antagonism [64].
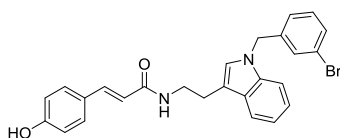
Z25

Yang et al., designed 1-phenyl-pyrrolo[1,2-b]isoquinolin-3-one derivatives act as NMDA receptor antagonists, safeguarding PC12 cells from NMDA-induced damage and apoptosis in vitro. Compound 13b displays potent cytoneuroprotection and dose-dependent prevention, reversing intracellular Ca2+ influx triggered by NMDA. Validated through MST assay, its binding to the NMDA receptor's glycine site remains unaffected by stereochemistry. Molecular docking underscores its efficacy via interactions in the binding pocket. These findings highlight these derivatives as potential neuroprotective agents targeting the NMDA receptor's glycine binding site [65].
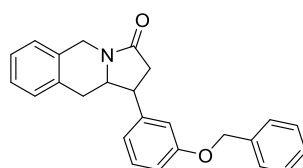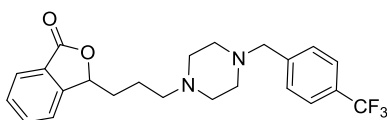

Compound 13b

Bardaghi et al., investigated the protective effect of memantine, an NMDA receptor antagonist, on sepsis-induced brain damage in mice. Memantine was administered before and after sepsis induction. It reduced inflammation and oxidative stress in the brain, as shown by decreased NF-κB, TNF-α, IL-1β expression, and increased antioxidant activity. Post-sepsis, mice exhibited memory impairment and anxiety-like behaviors, which were mitigated by memantine treatment. This suggests memantine could potentially counteract sepsis-related brain issues and prevent long-term behavioral consequences [66].
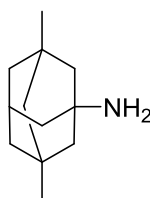

Memantine

Maolanon et al., devised a flexible stereoselective pathway for synthesizing novel 2′-(S)-CCG-IV analogs, allowing late-stage customization and yielding various cyclopropyl glutamate analogs. Assorted analogs were assessed using electrophysiology, displaying GluN2 subunit-tailored potency and efficacy. A GluN2A agonist binding domain crystal structure with 2′-butyl-(S)-CCG-IV was also revealed, illuminating (S)-CCG-IV agonist binding site configuration and efficacy determinants. This synthesis strategy facilitates facile creation of diverse analogs, aiding subtype-specific NMDA receptor agonist development and beyond [67].Xu et al., synthesized a novel series of brain-penetrant GluN2B NMDAR antagonists by combining 3-*n*-Butylphthalide (NBP) and GluN2B ligand structures. Several

compounds showed enhanced neuroprotective activity against NMDA-induced neurotoxicity in hippocampal neurons, with 45e and 45f comparable to ifenprodil, a GluN2B-selective antagonist. Notably, 45e displayed potent binding affinity (Ki = 3.26 nM) and inhibition (IC50 = 79.32 nM) for GluN1/GluN2B receptors, alongside favorable selectivity. In a rat MCAO model, 45e matched ifenprodil's efficacy, demonstrating good bioavailability, brain exposure, and safety profile, suggesting promise as an anti-stroke agent [68].
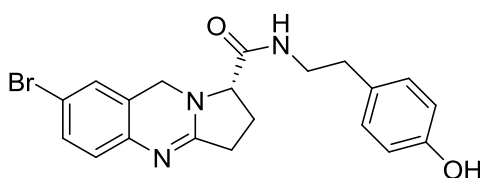

Compound 45e

Pérez-Areales et al., have developed novel compounds by combining an NMDA receptor antagonist with a potent acetylcholinesterase inhibitor, targeting Alzheimer's disease. These compounds demonstrate enhanced efficacy against AChE, butyrylcholinesterase, and NMDA receptors compared to individual parent compounds. The hybrids exhibit increased potencies and potential brain permeability, showing promise for improved therapeutic effects in Alzheimer's treatment. Among all hybrids, 13b exibits best results with IC_{50} of 0.89 mM, 2-fold increased potency over the parent benzohomoadamantanamine and memantine [69].Zhang et al., synthesied novel 1-benzyl-5-oxopyrrolidine-2-carboximidamide derivatives and tested for neuroprotective effects against NMDA-induced cytotoxicity. Compound 12k exhibited potent neuroprotection, surpassing the reference compound ifenprodil. It mitigated Ca2+ influx, suppressed NR2B upregulation, and displayed favorable binding within the NR2B-NMDA receptor site. Compound 12k also demonstrated remarkable metabolic stability and significantly improved learning and memory in behavioral tests. There findings highlight 12k as a promising neuroprotective candidate, targeting the NR2B-NMDA receptor [70].
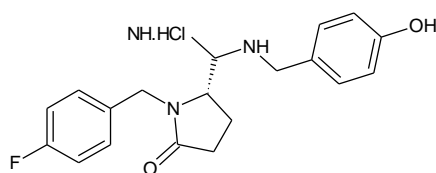
Compound 12k

Zhang et al., Designed, synthesized new 1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylic acid derivatives and screened for neuroprotective potential against NMDA-induced cytotoxicity. Compound 5q displayed remarkable neuroprotection, reducing Ca^{2+} influx, suppressing NR2B up-regulation, and enhancing p-ERK$_{1/2}$ expression. Molecular docking indicated favourable binding to relevant pockets. Compound 5q also demonstrated acceptable metabolic stability. There findings highlight 5q as a promising candidate for developing potent, orally available NR2B-selective NMDAR antagonists with potential therapeutic applications [71].

Compound 5q

Rajan et al., performed synthesis of GluN2A-selective NMDA receptor antagonists with an electron-rich aromatic B-ring. Inhibition was evaluated using GluN2A-containing NMDA receptors in Xenopus oocytes. Compounds 21c, 31a, 37a, and 37b effectively inhibited ion channels. Isoxazole derivative 37b was a potent negative allosteric modulator, displaying 40% of TCN-201 activity at 10 μM concentration [72].
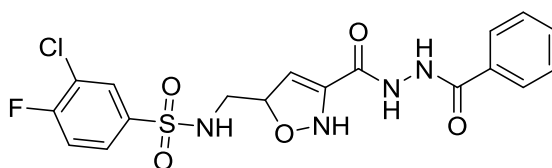
Compound 37b

Baumeister et al., synthesized and evaluated thiophene bioisosteres of potent GluN2B receptor negative allosteric modulators were. Hydroxymethyl derivatives 15 and 16 were designed as phenol bioisosteres. Compounds with 3-phenylpropylamino or 4-phenylbutylamino moieties (5c;11d) exhibited high GluN2B affinity. Relationships between structure, GluN2B affinity, and σ affinity were observed, with preference for GluN2B binding.
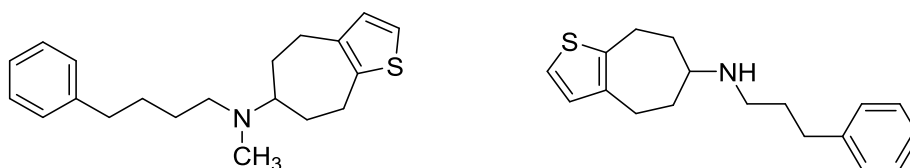
Compound 11dCompound 5c

IV. CHALLENGES AND FUTURE DIRECTIONS [7]

1. **Cognitive and Psychological Effects:** NMDA receptor antagonists like ketamine and PCP can lead to cognitive impairments, hallucinations, and dissociative experiences. Balancing therapeutic effects with psychological and cognitive side effects is a challenge.

2. **Individual Variability:** Responses to NMDA receptor antagonists vary widely among individuals due to genetic factors and neurobiological differences. Optimizing treatment outcomes in light of this variability is important.

3. **Selectivity and Side Effects:** Developing NMDA receptor antagonists that target specific subunits or sites while minimizing off-target effects is challenging. Some antagonists cause unwanted side effects like cardiovascular issues and behavioural changes.

4. **Treatment Duration and Long-Term Effects:** Optimal treatment duration and dosing for various disorders treated with NMDA receptor antagonists are unclear. Understanding long-term effects on neuronal function and brain health is essential.

5. **Abuse Potential:** Certain NMDA receptor antagonists have abuse potential due to dissociative and euphoric effects. Developing safer alternatives without abuse potential is a priority.

6. **Precision Medicine:** Personalized treatment approaches based on genetic and neurobiological profiles could enhance efficacy and minimize adverse effects. Tailoring treatment to individual needs is a future direction.

7. **Combination Therapies:** Combining NMDA receptor antagonists with other drugs, like antidepressants or cognitive enhancers, may improve outcomes and mitigate side effects. Identifying optimal combinations is important.

8. **Neuroplasticity and Disease Modulation:** Understanding how NMDA receptor antagonists affect synaptic plasticity and neural circuits is crucial. Leveraging their effects to treat neurological and psychiatric disorders effectively is a focus.

9. **Drug Development and Optimization:** Developing novel NMDA receptor antagonists with improved selectivity and reduced side effects is challenging. Expanding available compounds can offer clinicians more treatment options.

V. ETHICAL CONSIDERATIONS

Using NMDA receptor antagonists off-label or without supervision raises ethical concerns. Responsible and evidence-based use while safeguarding patient well-being is essential.In the future, research will likely uncover more about NMDA receptor function and antagonism, leading to refined therapies and personalized treatment approaches. Advances in drug development, neuroimaging, and our understanding of the brain will contribute to optimizing NMDA receptor antagonists' use for various medical conditions.

VI. CONCLUSION

In conclusion, the intricate role of NMDA receptors in the central nervous system underscores their significance in synaptic plasticity, learning, memory, and various neurological processes. The development of NMDA receptor antagonists as potential therapeutics has opened doors to innovative treatments for an array of conditions, from chronic pain management and depression treatment to neuroprotection and substance abuse intervention. However, the path to harnessing their benefits is not without challenges. Striking a delicate balance between therapeutic effects and cognitive or psychological side effects remains a significant concern, especially given the individual variability in responses. As recent progresses, a deeper understanding of NMDA receptor mechanisms, combined with advances in precision medicine and drug development, offers promise for refining these

treatments. The pursuit of tailored approaches, optimal dosages, and potential combination therapies could pave the way for more effective and safer treatments. Ethical considerations and responsible use will also guide the integration of NMDA receptor antagonists into medical practice. Ultimately, the continued exploration of NMDA receptor function and antagonist interventions holds the potential to transform the landscape of neurological and psychiatric care, providing new avenues for improving brain health and enhancing patients' lives.

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