



Announcing the First Novel Class of Rapid-Onset Antidepressants in Clinical Practice

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This study was designed with the rational aim/purpose of announcing and discussing the new class of rapid-onset antidepressants that will bring forth significant improvement and positive impact to the management of patients with depression disorders in clinical practice. The class of N-methyl-D-aspartate-glutamatergic ionoceptor blockers represent the first separate novel class of rapid-onset antidepressants with a direct action on the excitatory glutamatergic neurotransmission system but no direct action on the serotonergic, noradrenergic, or dopaminergic neurotransmission systems. It consistently fits into the antidepressants' classification nomenclature, and the pharmacological properties also deemed it appropriate to be accepted and announced as the first separate novel class of rapid-onset antidepressants.

Key words: First separate novel class of rapid-onset antidepressants, glutamatergic neurotransmission blockers, depressive disorders

INTRODUCTION

This study was designed with the rational aim/purpose of announcing and discussing the new class of rapid-onset antidepressants that will bring forth significant improvement and positive impact to the management of patients with depression disorders in clinical practice. Glutamate is the major excitatory neurotransmitter substance found in the central nervous system. Glutamate is a nonessential amino acid neurotransmitter substance that is synthesized from the transamination of glutamine through the enzymatic action of glutamine transaminase. It is synthesized within neuron mitochondria from glucose and several other intermediate precursors. After being synthesized, glutamate is released into the cytoplasm where it accumulates in synaptic vesicles through an energy-dependent process on Mg^{2+} /ATP. The propagation of the nerve impulse toward the axon terminal promotes the release of glutamate from the terminal presynaptic membrane through an exocytotic mechanism that depends on intraneuronal, intra-axonoplasmic influx of Ca^{2+} from the extracellular environment. Glutamate can then interact with

its specific receptors. Glutamate receptors are classified as either metabotropic glutamate receptors (mGluRs), which promote the activation of second intracellular messengers via G-proteins couple mechanisms, or ionotropic receptors. The latter are linked to an ion channel, and their activation allows influx of many different ions, mainly Ca^{2+} and Na^{+} , as well as the efflux of potassium (K^{+}). The class of N-methyl-D-aspartate (NMDA)-glutamatergic ionoceptor blockers (that is, NMDA-glutamatergic ionoceptor antagonist/inverse agonist/partial agonist) also represents the first separate novel class of rapid-onset antidepressants with a direct action on the excitatory glutamatergic neurotransmission system but no direct action on the serotonergic, noradrenergic, or dopaminergic neurotransmission systems. It consistently fits into the antidepressants' classification nomenclature, and the pharmacological properties also deemed it appropriate to be accepted and announced as the first separate novel class of rapid-onset antidepressants. Furthermore, to buttress this point of view, the NMDA-glutamatergic neurotransmission

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blockers such as rapastinel, apimostinel, and ketamine produce their rapid and sustained antidepressant activity through a novel mechanism of action that involves the inhibition/blockade of the NMDA-glutamatergic ionoceptor which is unchallengeable and clinical obvious.¹⁻¹⁰

THE PROPOSED CLASSIFICATION NOMENCLATURE FOR ANTIDEPRESSANTS

The different classes of clinically available antidepressants based on their mechanisms of action are:

1. Tricyclic antidepressants such as amitriptyline, imipramine, desipramine, nortriptyline, clomipramine, trimipramine, protriptyline, and doxepin
2. Monoamine oxidase inhibitors such as phenelzine, nialamide, isocarboxazid, hydracarbazine, tranlycypromine, moclobemide, *bifemelane, *pirlindole, *toloxatone, *selegiline, *rasagiline, and *safinamide
3. Selective serotonin reuptake inhibitors such as fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine
4. Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, desvenlafaxine, duloxetine, *ansofaxine, *nefopam, and *levomilnacipran
5. Norepinephrine-dopamine reuptake inhibitor such as bupropion
6. ++Selective norepinephrine reuptake inhibitors (NRIs) such as *Reboxetine, *viloxazine, *teniloxazine (also known as sulfoxazine or sufoxazine), and *atomoxetine
7. Serotonin receptors' antagonist with serotonin reuptake inhibition such as trazodone, nefazodone, and *vortioxetine
8. ++Serotonin 5-HT_{1A} autoreceptor partial agonist with serotonin reuptake inhibition such as *vilazodone
9. Noradrenergic α_2 -receptor antagonist with specific serotonergic receptors-2 and-3 antagonism such as mirtazapine and ®mianserin
10. ++NRI with serotonin receptors' antagonism (NRISA) such as maprotiline
11. ++Serotonin-norepinephrine reuptake inhibitor and serotonin receptors' antagonism antidepressant with potent antipsychotic D₂ receptor blockade/antagonism (SNRISA with potent antipsychotic D₂ receptor blockade/antagonism) such as amoxapine
12. ++Atypical antipsychotics that exhibit weak D₂ receptor antagonism with potentially strong 5-HT_{2A/2C} receptor blockade such as *olanzapine, *quetiapine, *risperidone, *lurasidone, *aripiprazole, and *brexpiprazole
13. ++NMDA-glutamatergic ionoceptor blockers that exhibit a direct action on the excitatory glutamatergic neurotransmission system such as *ketamine, *CP-101,606 (traxoprodil), *GLYX-13 (rapastinel), *NRX-1074 (Apimostinel), and *Riluzole.

NOTE: ++Emerging antidepressant classes using mechanisms of action-based classification; *Novel/emerging antidepressant drug (s) in a particular class; ®Drug approval was rejected/denied by the United States food drug administration (FDA) due to the submission of fraudulent data regarding its clinical trial by the investigators but had been approved for the treatment of depression disorders long time ago in the European Union and other countries.

THE EMERGING GLUTAMATERGIC HYPOTHESIS OF DEPRESSION

Before thoroughly discussing the NMDA-glutamatergic ionoceptor blockers as the first separate novel class of rapid-onset antidepressants, let us concisely look at the emerging glutamatergic hypothesis of depression disorders in full details. In the central nervous system, glutamate is the major excitatory neurotransmitter and makes functional contributions to more than half of all the synapses in the brain. The glutamate system has an integrated tripartite synapse that consists of: (1) a presynaptic neuron, (2) a postsynaptic neuron, and (3) an astrocyte. Figure 1a showed the tripartite glutamatergic synapse and potential drug targets. The presynaptic neuron releases glutamate in response to action potentials. The released glutamate then binds to various pre- and post-synaptic receptors, as well as to receptors on the surrounding astrocytes. Synaptic glutamate reuptake is performed primarily by astrocytes, specifically, the excitatory amino acid transporter-2 (EAAT-2). Within the astrocyte, glutamate is converted to glutamine (glutamate/glutamine cycle) by glutamine transaminase (synthetase) and then resupplied to the presynaptic neuron where it is used for the synthesis of glutamate. The glutamatergic system consists of two receptor types, namely ionotropic and metabotropic receptors. The ionotropic glutamatergic receptors include NMDA receptors, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate receptors. These ionotropic receptors are ion channels that are permeable to cations (i.e. sodium [Na⁺] and calcium [Ca²⁺]), which in turn depolarize the neuron and/or promote intracellular signaling cascades. There are eight G-protein-coupled mGluRs subtypes (mGluR1-8) that are divided into three distinct groups that are based on their homology and function: Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3), and Group III (mGluR4, mGluR6, mGluR7, and mGluR8). Group I mGluRs are localized on the postsynaptic neuron and are coupled to G_q/G₁₁ subunits; whereas Group II and Group III are localized on the presynaptic neuron and are coupled to G_i/G_o subunits.^{37,49,55} mGluRs can mediate intracellular signaling cascades by activating second messenger pathways and/or through its $\beta\gamma$ subunits. Group I and Group II

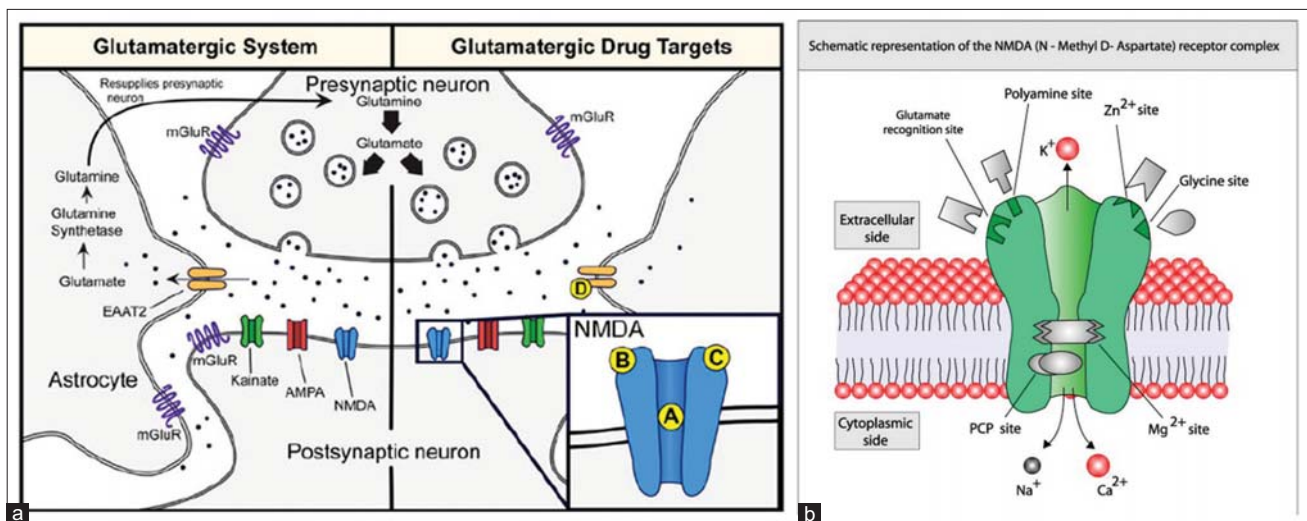


Figure 1: (a) The tripartite glutamatergic synapse and potential drug targets. Left panel: the presynaptic neuron releases glutamate neurotransmitter in response to action potentials. The glutamate neurotransmitter can bind to ionotropic (i.e. NMDA, AMPA, kainate) and metabotropic (i.e. mGluR) receptors located on the presynaptic and postsynaptic neuron as well as on astrocytes. Synaptic glutamate reuptake is performed primarily by the EAAT-2 located on astrocytes. Within the astrocyte, glutamate is converted to glutamine (glutamate/glutamine cycle) via glutamine transaminase (synthetase) and then resupplied to the presynaptic neuron where it is used for the biosynthesis of glutamate neurotransmitter. Right panel: Potential NMDA and EAAT-2 drug targets: (A) Noncompetitive NR2 subunits-unselective NMDA receptor antagonists (e.g. ketamine and memantine) and low-trapping NMDA receptor channel blockers (lanicemine [AZD6765]); (B) NR2B subunit-selective NMDA receptor antagonists (e.g. traxoprodil [CP-101,606] and MK-0657); (C) NR1 subunit-selective NMDA receptor partial agonists (e.g. GLYX-13 [Rapastinel], NRX-1074 [Apimostinel], and D-cycloserine); (D) EAAT-2 reuptake enhancer (e.g. Riluzole). NMDA = N-methyl-D-aspartate; AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; mGluR = Metabotropic glutamate receptors; EAAT-2 = Excitatory amino acid transporter-2. (b) A schematic representation of the N-methyl-D-aspartate-glutamatergic receptor heteromeric complex

mGluRs have been investigated in the pathophysiology and treatment of MDD. Specifically, mGluR5 (e.g., AZD2066 and RO4917523) and mGluR2/3 (RO4995819)-negative modulators have been tested in Phase II clinical trials for treatment-resistant patients, and some compounds (e.g., RO4917523 and RO4995819) have shown promising results.^{48,49,53,55} Assessing all glutamate receptors and their respective implications in MDD are too wide and beyond the scope of this review. Therefore, this present review will primarily focus on NMDA receptors.

Although majority of the clinically available antidepressant drug classes work to produce an immediate increase in the monoaminergic neurotransmitter concentrations, there is still a population of patients that do not respond to these medications. This lends further support for the revised monoaminergic theory which states that depleted monoaminergic neurotransmitters' concentrations or functions may play more of a neuromodulatory role to other neurobiological neurotransmission systems in the central nervous system, rather than a major direct role in MDD.⁵⁶ Thus, more recent research has focused on finding novel, nonmonoaminergic-based, receptor targets for treatment-resistant depression. In particular, the glutamatergic system has become a focal point for drug development research.

Attempts to develop antidepressants that work on other neurotransmitter systems are currently ongoing. One of

such neurotransmitter system is the excitatory glutamatergic neurotransmitter pathway that appears to be important in the pathophysiology of depression disorders. Clinical research has used both indirect and direct measures to evaluate the glutamatergic system in patients suffering from MDD and have found evidence of glutamatergic dysfunction in MDD. For example, clinical studies that have used indirect measures for analysis, such as plasma, cerebrospinal fluid, and serum concentrations, have found differences in glutamate and glutamine in patients diagnosed with MDD as compared to healthy controls. Specifically, several studies have found increased concentrations of glutamate in plasma and increased concentration of glutamine in the cerebrospinal fluid of MDD patients. Furthermore, chronic antidepressant drug treatment has been found to reduce the serum and plasma glutamate concentrations, as well as cerebrospinal fluid glutamine concentrations. Furthermore, antidepressants are known to impact glutamatergic neurotransmission in a variety of ways; for example, chronic antidepressant use is associated with reduction of glutamatergic neurotransmission processes, including a reduction in the presynaptic release of glutamate in the hippocampus and cortical areas. Similarly, the chronic administration of antidepressants significantly reduces depolarization-evoked release of glutamate in experimental animal models. Stress is known to enhance

the release of glutamate in experimental animal models, and antidepressants inhibit stress-induced presynaptic release of glutamate in these models.^{3,4,8} These findings suggest that these monoaminergic systems' selective-acting antidepressant drugs are neuromodulating the functions of the glutamatergic neurotransmission system. In addition, postmortem studies have revealed significant increase in the volume of frontal and dorsolateral prefrontal cortices in depressed patients. Likewise, structural neuroimaging studies have consistently found volumetric changes in other brain areas of depressed patients in which glutamatergic neurons and their connections are most abundant, including the amygdala and hippocampus.³⁷⁻⁴¹

Figure 1b showed a schematic representation of the NMDA-glutamatergic receptor (NMDAR) heteromeric complex. The NMDAR is activated when the endogenous co-agonist neurotransmitters-glutamate (or D-aspartate) and glycine (or D-serine) bind to it. When activated, NMDAR allows non-selective positively charged ions (cations) such as Ca^{2+} , Na^{+} , and K^{+} to flow through the cell membrane. The NMDA receptor is very important for controlling synaptic plasticity, learning, and memory. While the opening and closing of the ion channel is primarily gated by ligand binding, the current flow through the ion channel is voltage dependent. Extracellular magnesium (Mg^{2+}) and zinc (Zn^{2+}) ions can bind to specific sites on the receptor, blocking the passage of other cations through the open ion channel. Depolarization of the cell dislodges and repels the Mg^{2+} and Zn^{2+} ions from the pore, thus allowing a voltage-dependent flow of Na^{+} and small amounts of Ca^{2+} ions into the cell and K^{+} out of the cell. Currently, the NMDAR is a heteromeric complex that has three (3) different subunits with a total of fourteen (14) isoform variants for all of these subunits. The NMDA receptor heteromeric complex interacts with multiple intracellular proteins by these three different subunits, namely GluN1 (NR1), GluN2 (NR2), and GluN3 (NR3). The NR1 subunits have eight different isoform variants generated by alternative splicing from a single-gene *GRIN1*. These different isoform variants of NR1 subunits are NR1-1a (the most abundantly expressed isoform variant), NR1-1b, NR1-2a, NR1-2b, NR1-3a, NR1-3b, NR1-4a, and NR1-4b. In vertebrates, there are expressions of four different isoform variants of NR2 subunits which are NR2A, NR2B, NR2C, and NR2D that are encoded by the *GRIN2A*, *GRIN2B*, *GRIN2C*, and *GRIN2D* genes, respectively. Glutamate binding site and the control of the Mg^{2+} block are formed by the NR2B subunit isoform variant. Furthermore, NR2B is predominant in the early postnatal brain, but the number of NR2A subunits grows, and eventually, NR2A subunits outnumber NR2B. This is called the NR2B-to-NR2A developmental switch and is notable because of the different kinetics each NR2 subunit isoform variant lends to the

NMDA receptor. For instance, greater ratios of the NR2B subunit lead to NMDA receptors which remain open longer compared to those with more NR2A. Unlike NR1 subunits, the NR2 subunits are expressed differentially across various cell types and control the electrophysiological properties of the NMDA receptor. The NR2B subunit isoform variant is mainly present in immature neurons and in extrasynaptic locations. The basic structure and functions associated with the NMDA receptor can be predominantly attributed to the NR2B subunit. The NR2B subunit has been involved in modulating activity such as learning, memory, processing and feeding behaviors, as well as being implicated in number of human pathological derangements such as MDD. Late in the 20th century, the NR3 subunits were discovered with two isoform variants NR3A and NR3B that are encoded by the *GRIN3A* and *GRIN3B* genes, respectively. Furthermore, the family of NR3 subunits (i.e., NR3A and NR3B isoform variants) also possesses a glycine binding site each that exhibit an inhibitory (antagonistic/negative modulatory) effect on NMDA receptor activity/function in contrast to the stimulatory (agonistic/positive modulatory) effect exhibited by the NR1 subunits when they are bound to the co-agonist glycine. This depicts that the co-agonist glycine binds to any of the NR3 subunit isoform variants to inhibit and antagonize (negative modulation) the activation of NMDA receptor activity/function. According to the studies carried out by Das and colleagues in 1998 demonstrating the existence of these two (2) varieties of the NR3 subunits (NR3A and NR3B), which are coded by different genes. The NR3A variant is expressed throughout the CNS, but expression of the NR3B variant is restricted to motor neurons. Unlike the NR2 subunit, NR3 is a regulatory subunit and its presence decreases the ionic currents generated by activation of the NR1/NR2 heteromers. Further studies also showed that the coexpression of NR1/NR3B heteromers forms excitatory glycine receptors that are insensitive to glutamate/D-aspartate/NMDA and Mg^{2+} blockade. Based on this evidence, it has been postulated that these receptors may be involved in the activation of silent NMDA-alone synapses. All the NMDAR subunits share a common membrane topology that is dominated by a large extracellular N-terminus, a membrane region comprising three transmembrane (TM III) segments, a re-entrant pore loop, an extracellular loop between the TM segments that are structurally not well known, and an intracellular C-terminus, which are different in size depending on the subunit and provide multiple sites of interaction with many intracellular proteins. Multiple receptor isoform variants with distinct brain distributions and functional properties arise by selective splicing of the NR1 transcripts and differential expression of the NR2 subunits. The glycine-binding site modules of the

NR1 and NR3 subunits and the glutamate-binding site module of the NR2A subunit have been expressed as soluble proteins, and their three-dimensional structure has been revealed at atomic resolution by X-ray crystallography. The NR1 – NR2 dimer is therefore considered to be the basic functional organization structure in each receptor. It contains various sites for the binding and recognition of different ligands, which may be either physiological or pharmacological. In this way, each ionotropic receptor subunit has a very similar molecular structure, divided into 4 functional domains. These consist of an aminoterminal extracellular N-terminal domain; a ligand-binding domain; a TM region formed by four hydrophobic segments (M1 to M4), with M2 partially entering the membrane to form the ion channel; and a carboxyl tail domain in the intracellular region. In addition to natural glycine and glutamate-binding sites in the NR1–NR2 dimer, the extracellular region of NR2 in particular contains binding sites for endogenous ligands such as polyamines, which are redox sites for protons and Zn^{2+} . They may exert a regulatory effect on NMDA receptor activity by permitting increases or decreases in Ca^{2+} flux through the receptor under physiological and/or pathological conditions. At the same time, exogenous ligands for steroids, ethanol, and ifenprodil, and a few synthetic molecules, act as experimental tools for the study of NMDA receptor properties and aid in the development of therapeutically useful antagonists. Homomers of the NR2 subunit do not generate functional receptors and are only considered as modulators. Homomers of NR1 subunits produce channels that are activated by glutamate, aspartate, or NMDA in the presence of glycine (or D-serine), but they produce very low amplitude currents compared to receptors formed by NR1–NR2 combined.³⁷⁻⁴¹

A functional NMDA-glutamatergic receptor must comprise of a minimum heterotetramer complex with at least two obligatory NR1 subunits and two regionally localized variable NR2 subunits. The NR1/NR2B TM segments are considered to be the part of the receptor that forms the binding pockets for uncompetitive NMDA receptor antagonists. The high affinity sites for glycine antagonist/inverse agonist/partial agonist are also exclusively displayed by the NR1/NR2B subunits of NMDA receptor. It is claimed that the presence of three (3) binding sites within the receptor, namely A644 on the NR2B subunit with A645 and N616 on the NR1 subunit, are important for binding of ketamine, memantine, and other uncompetitive NMDA receptor antagonists. As earlier mentioned, unlike other ligand-gated ion channels, NMDA-glutamatergic receptors require two distinct mechanisms to be activated. First, NMDA-glutamatergic receptor channels require co-agonist binding at the glycine (or D-serine) binding site on the NR1 subunit and at the glutamate (or D-aspartate) binding

site on the NR2 subunit. Thus, if one of these co-agonists (glycine/D-serine or glutamate/D-aspartate) is not bound to their respective binding site, the ion channel will not open. Second, the NMDA-glutamatergic receptor channels are blocked by Mg^{2+} ions during the resting state. Depolarization of the neuron is required to displace the Mg^{2+} ion from NMDA-glutamatergic receptor channels, which is usually achieved by activation of AMPA receptor-mediated depolarization of the postsynaptic membrane, which relieves the voltage-dependent channel block by Mg^{2+} . The NMDA-glutamatergic receptor ion channel is nonselective and will allow both Na^{+} and Ca^{2+} ions to enter and K^{+} ions out of the cell. The influx of Ca^{2+} is associated with the induction of various signaling cascades.^{37-41,48,49,53,55}

Several postmortem studies have also found changes in the expression of NMDA-glutamatergic receptor subunits in MDD patients, which are likely compensatory effects to the changes in glutamatergic substrate concentrations, and appear to be brain region specific. For example, the NR2B and NR2C subunits have been shown to have increased expression in the locus coeruleus in postmortem tissue of MDD patients. In addition, the expression of NR2A subunits has been found to be elevated in the lateral amygdala. Furthermore, MDD patients have shown an increase in glutamate binding in the hippocampus and a greater sensitivity to glutamate as measured by intracellular Ca^{2+} influx. On the other hand, the NR2A and NR2B subunits transcription have been shown to be reduced in the perirhinal and prefrontal cortices in postmortem tissue from MDD patients. Moreover, postmortem studies have found decreased levels of the NR1 subunit in the superior temporal cortex and prefrontal cortex. The NR1 and NR2 subunits are required for functional NMDA-glutamatergic receptor heteromeric complexes, and thus, increase/decrease in the levels of these NR1/NR2 subunits can be interpreted as changes in total number of functional NMDA-glutamatergic receptors. Based on these previous experimental results, it was hypothesized that depression is associated with the hyperfunction of NMDA-glutamatergic receptors in subcortical regions (i.e. hippocampus, locus coeruleus, and amygdala); whereas at the same time, depression is associated with the hypofunction of NMDA-glutamatergic receptors in cortical regions (i.e., prefrontal, perirhinal, and temporal cortices). Moreover, this finding has led to a conclusion that postulates the new “Glutamatergic hypothesis of depression” which is now moving our understanding of the pathophysiology of MDD a step further from the several decades’ old “Monoaminergic theory of depression.”³⁻¹⁰ Collectively, clinical data suggest the involvement of the glutamatergic system in the pathophysiology of MDD or bipolar depression or schizoaffective depression, which includes disruptions in glutamatergic substrate concentrations and NMDA-glutamatergic receptor alterations.

Although the role of glutamatergic systems is yet to be fully elucidated, a “proof of concept” clinical study reported that the noncompetitive NMDA-glutamatergic receptor antagonist ketamine produced rapid-onset and prolonged antidepressant effects in patients suffering from MDD or bipolar depression or schizoaffective depression. Ketamine is a potent, high-affinity, noncompetitive NMDA receptor antagonist that has long been used in anesthesia and is a common drug of abuse in some parts of the world. A number of preclinical and clinical studies have demonstrated rapid antidepressant effects of ketamine. Multiple studies have suggested that a single dose of intravenous ketamine at subanesthetic doses produces rapid relief of depression, even in treatment-resistant patients, that may persist for 1 week or longer. Unfortunately, ketamine is associated with neurocognitive dysfunction, dissociative, and psychotomimetic properties that make it unsuitable as a long-term treatment for depression. Still, this has generated tremendous interest in developing new drugs that will target the glutamatergic neurotransmission mechanisms for the treatment of MDD or bipolar depression or schizoaffective depression. These potential drug targets are the NMDA-glutamatergic receptor as antagonist or inverse agonist or partial agonist; mGluRs as positive or negative modulator; EAAT-2 as a reuptake enhancer; and as a terminal presynaptic glutamate release inhibitor.¹¹⁻¹⁵

Finally, the structure of mGluRs consists of a protein chain that crosses the membrane seven times. To date, the eight units named mGluR1 through mGluR8 that have been cloned, are classified according to the following: (a) the homology of their amino acids (70% homology among members of the same class, and 45% homology between different classes); (b) in response to their agonists, and (c) the signal paths for second messengers. These previously mentioned ionotropic receptors are categorized according to whether their specific agonists have an affinity for NMDA, AMPA, or kainic acid (KA). Ionotropic receptors are heteromers constituted by different subunits, which give the receptors different physiological and pharmacological properties [Figure 2]. The AMPA receptors are structured as combinations of GluA1 (GluR1), GluA2 (GluR2), GluA3 (GluR3), and/or GluA4 (GluR4) subunits which form an ion channel permeable to Na⁺. However, it has been shown that AMPA receptors whose structure does not include a GluA2 subunit are highly permeable to Ca²⁺. This is due to the presence of a residue of arginine (R), an amino acid present in position R586 in the second transmembrane (TM II) region of GluA2. In contrast, subunits GluA1, GluA3, and GluA4 present a glutamine (Q) residue at position Q582 of the GluA1 subunit protein. The kainate receptors are protein heteromers formed by combinations of the GluK1 (GluR5), GluK2 (GluR6), and/or GluK3 (GluR7) subunits, together

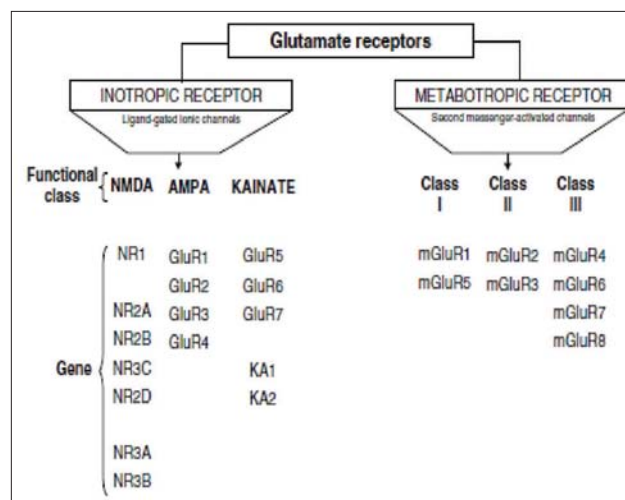


Figure 2: Classification of glutamate receptors

with GluK4 (KA1) and/or GluK5 (KA2) subunits. The combination of GluK5 and GluK1 forms a functional receptor that is permeable to Ca²⁺.^{8,10,16-18,20-36}

N-METHYL-D-ASPARTATE-GLUTAMATERGIC IONOCEPTOR BLOCKERS

The NMDA-glutamatergic ionoceptor blockers are group of drug substances that exhibit either pure antagonist or inverse agonist or partial agonist (mixed agonist-antagonist) pharmacological properties at the NMDA receptors. Their pharmacological mechanism of actions can either be through a direct blockade of the NMDA receptors (such as rapastinel, apimostinel, and ketamine) or via an indirect blockade of the NMDA receptors (such as riluzole).

Selective antagonist or inverse agonist or partial agonist at the NR1 subunit glycine binding-site of N-methyl-D-aspartate receptor (direct-acting NR1 subunit-selective N-methyl-D-aspartate-glutamatergic receptor antagonist/inverse agonist/partial agonist)

Rapastinel (former developmental code names GLYX-13, BV-102) is a novel antidepressant that is under development by Allergan (previously Naurex) as an adjunctive therapy for the treatment of treatment-resistant major depressive disorder. It is a centrally active, intravenously administered (non-orally active) amidated tetrapeptide (Thr-Pro-Pro-Thr-NH₂) that acts as a selective, weak partial agonist (mixed antagonist/agonist) of an allosteric site of the glycine site of the NMDA receptor complex (E_{max} ≈25%). The drug is a rapid-acting and long-lasting antidepressant as well as robust cognitive enhancer by virtue of its ability to both inhibit

and enhance NMDA receptor-mediated signal transduction. The novel compound, GLYX-13 (rapastinel), which is a tetrapeptide (TPPT-amide), was developed for the treatment of MDD with the goal of producing rapid-onset antidepressant effects without producing psychotomimetic side effects. Unlike the NR2B subunit-selective NMDA receptor antagonists and the channel blockers (NR2 subunit unselective NMDA receptor antagonists), GLYX-13 (rapastinel) binds selectively to the NR1 subunit glycine-binding site of the NMDA receptor and acts as a functional partial agonist with this difference in pharmacological action believed to reduce psychotomimetic side effects. Typically, partial agonists will produce agonistic effects at low doses or in the absence of the receptor's site full agonist (glycine) but will produce antagonistic effects at high doses or in the presence of the receptor's site full agonist (glycine). In a Phase II clinical study comprising of 112 MDD patients, GLYX-13 (rapastinel) produced rapid and sustained antidepressant effects following a single infusion (5.0–10.0 mg/kg; 3–15 min infusion), and most importantly, did not produce psychotomimetic effects. Specifically, the antidepressant effects of GLYX-13 (rapastinel) were apparent at the end of day one and persisted until day seven following the single infusion. A Phase II double-blind, placebo control, multi-dose clinical trial has also been done (NCT01684163). GLYX-13 (rapastinel) and its congener compounds do not bind directly to the glycine binding site of the NR1 subunit of NMDA receptor but rather bind to a different regulatory allosteric site on the NR1 subunit of NMDA receptor complex that serves to allosterically modulate the glycine-binding site. As such, rapastinel is technically an allosteric modulator of the glycine site of the NMDA receptor and hence is more accurately described as a functional glycine site weak partial agonist. In addition to its antidepressant effects, rapastinel has been shown to enhance memory and learning in both young adult and learning-impaired, aging rat models. It has been shown to increase Schaffer collateral-CA1 long-term potentiation *in vitro*. In concert with a learning task, rapastinel has also been shown to elevate gene expression of hippocampal NR1, a subunit of the NMDA receptor, in 3-month-old rats. Neuroprotective effects have also been demonstrated in Mongolian Gerbils by delaying the death of CA1, CA3, and dentate gyrus pyramidal neurons under glucose and oxygen-deprived conditions. In addition, rapastinel has demonstrated antinociceptive activity, which is of particular interest, as both competitive and noncompetitive NMDA receptor antagonists are ataxic at analgesic doses, while rapastinel and other glycine subunit ligands are able to elicit analgesia at nonataxic doses.

In addition to GLYX-13 (rapastinel), another novel congener compound NRX-1074 (Apimostinel) has been developed,

which is similar to GLYX-13 (rapastinel) pharmacologically; however, NRX-1074 (Apimostinel) is an orally bioavailable compound and is more potent than GLYX-13 (rapastinel). In a 2014 Phase I clinical trials, NRX-1074 (Apimostinel) was well tolerated. As of 2015, an intravenous formulation of apimostinel is in a phase II clinical trial for MDD, and an oral formulation is concurrently in phase I trials for MDD. Like rapastinel, it is under development as an adjunctive therapy for treatment-resistant depression. Furthermore on NRX-1074 (Apimostinel), clinical trial recruitment for Phase I safety and pharmacokinetic study (NCT01856556) and Phase II multidose single infusion for patients with MDD (NCT02067793) has been done. However, apimostinel is 100 fold more potent by weight and orally stable, whereas rapastinel must be administered via intravenous injection, is orally active. Apimostinel is intended by Allergan as an improved, follow-up drug to rapastinel. Similarly to rapastinel, apimostinel is an amidated tetrapeptide and has almost an identical chemical structure to rapastinel but has been structurally modified via the addition of a benzyl group. The drug has shown rapid antidepressant effects in preclinical models of depression. In addition, similarly to rapastinel, it is well-tolerated and lacks the schizophrenia-like psychotomimetic effects of other NMDA receptor antagonists such as ketamine.^{1,6,15,19}

Unselective antagonist or inverse agonist or partial agonist at the NR2 subunits glutamate binding-site of N-methyl-D-aspartate receptor (direct-acting NR2 subunits-unselective N-methyl-D-aspartate-glutamatergic receptor antagonist/inverse agonist/partial agonist)

Ketamine is a noncompetitive and unselective antagonist for the NR2 subunits of NMDA-glutamatergic receptor (also known as NMDA-ionoceptor channel blocker) that binds to the phencyclidine-binding site inside the ion channel of the NMDA receptor, blocking the channel in a way that is similar to how Mg^{2+} ion blocks NMDA receptors, and is unselective for the NR2A-D subunits of the NMDA receptor channel. Noncompetitive NMDA-glutamatergic ionoceptor antagonists that exhibit a direct action on the excitatory glutamatergic neurotransmission system such as ketamine are now being promoted for off-label use in the treatment of MDD or bipolar depression or schizoaffective depression. Subanesthetic low-dose ketamine has been found to possess a rapid-onset antidepressant action with a minimal dissociative anesthetic effect clinically. Because of this, property clinical psychiatrists are now using this drug as an adjunct or augmenting pharmacotherapeutic agent in the management of major depressive disorder or bipolar

depression or schizoaffective depression so as to facilitate and enhance fast clinical remission. Ketamine is a potent, high-affinity, noncompetitive NMDA receptor antagonist that has long been used in anesthesia and is a common drug of abuse in some parts of the world. A number of preclinical and clinical studies have demonstrated rapid antidepressant effects of ketamine. Multiple studies have suggested that a single dose of intravenous ketamine at subanesthetic doses produces rapid relief of depression, even in treatment-resistant patients, that may persist for 1 week or longer. Unfortunately, ketamine is associated with neurocognitive dysfunction, dissociative, and psychotomimetic properties that make it unsuitable as a long-term treatment for depression. Still, a number of other NMDA-glutamatergic receptor antagonist or inverse agonist or partial agonist; mGluRs positive or negative modulator; EAAT-2 reuptake pump enhancer; and terminal presynaptic glutamate release inhibitor are under investigation as potential antidepressants for clinical use.^{1,6,15,19,45,48}

In the Berman *et al.*'s⁴² study, the noncompetitive NMDA-glutamatergic receptor antagonist ketamine was first used in a "proof of concept" randomized double-blind study to assess the effects of ketamine on MDD in seven patients who received both vehicle (placebo) and ketamine treatment (counter balanced). A single, subanesthetic dose of ketamine (0.5 mg/kg) was intravenously (i.v.) infused over 40 min, and the antidepressant effects of ketamine were assessed using the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventor (BDI). In comparison, an anesthetic dose for ketamine in humans ranges from 1.0 mg/kg to 4.5 mg/kg intravenous and from 6.5 to 13.0 mg/kg intramuscular. In this study, ketamine produced rapid, within 4 h, and prolonged antidepressant effects that lasted up to 72 h as compared to placebo control. This rapid antidepressant effect of ketamine is far superior to the 4–12 week delay with the current antidepressant drugs. The hallucinogenic (or psychotomimetic) effects (e.g., out of body experience and hallucinations) of ketamine subsided (within 2 h) before the onset of the antidepressant effects as measured by the visual analog scales for intoxication "high" high and Brief Psychiatric Rating Scale. This was the first clinical study to demonstrate that glutamatergic drugs may be effective for the treatment of MDD.

In another clinical study conducted by Zarate *et al.*^{50,52} to assess the antidepressant effects of ketamine in patients with treatment-resistant MDD and to determine a better understanding of the duration of the antidepressant effects, following a single low-dose 0.5 mg/kg infusion of ketamine, treatment-resistant patients showed a significant reduction in depression scores at 110 min that lasted up to 7 days as measured by HDRS. Specifically, 71% of the patients achieved

response criteria one day after the infusion, while 29% achieved full remission. In addition, 35% maintained response criteria on day seven. Again, the hallucinogenic (or psychotomimetic) effects diminished before the onset of the antidepressant effects of ketamine (within 2 h). This study confirmed the finding in the Berman *et al.*⁴² study that ketamine produces rapid and prolonged antidepressant effects in the treatment of depression and extended ketamine's efficacy to treatment-resistant MDD.

Another study was conducted by Ghasemi *et al.*⁴³ to compare the effects of ketamine and electroconvulsive therapy (ECT) in patients suffering from MDD. This study found that both ketamine and ECT produced antidepressant effects; however, ketamine produced superior antidepressant effects in terms of fast response onset. For example, ketamine produced rapid antidepressant effects starting at 24 h; whereas, the antidepressant effects of ECT were not expressed until after 48 h. The antidepressant effects of both ketamine and ECT lasted until the completion of the study, which was 7 days. These results suggest that ketamine is as efficacious, if not more efficacious, as ECT for treating MDD.

In addition to these previously mentioned studies, several other clinical studies^{46,54} have found that i.v. infusions of low-dose ketamine produce rapid and sustained antidepressant effects in patients with MDD; a rapid reduction in suicidal ideation but produced some neurocognitive dysfunction in patients with treatment-resistant MDD.

An antianhedonic effect of ketamine treatment in treatment-resistant bipolar depression was recently demonstrated by Lally *et al.*⁴⁴ In a randomized, placebo-controlled, double-blind crossover design, 36 treatment-resistant bipolar depression patients were treated with a single, low intravenous dose of 0.5 mg/kg ketamine. They found that ketamine rapidly reduced anhedonia in these patients within 40 min and that these effects preceded reductions in other depressive symptoms. Furthermore, the decrease in anhedonic symptoms persisted up to 14 days. The authors concluded that these findings demonstrate the importance of glutamatergic mechanisms for the treatment of treatment-refractory bipolar depression and especially for the treatment of anhedonia symptoms.

The nasal spray of esketamine, the S (+) enantiomer of ketamine, acting as a noncompetitive NMDA receptor antagonist has been approved by the FDA in the United States for use in conjunction with other oral antidepressants, for the treatment of treatment-resistant major depressive disorder among adult patients.^{45,59}

Currently, preclinical researches are evaluating the pharmacological and intracellular effects that are responsible for the antidepressant effects of ketamine, which will aid the development of novel glutamatergic antidepressant drugs.³⁷⁻⁵⁹

The postulations from the studies done by Zanos *et al.*⁵⁷ and Wray *et al.*⁵⁸ are new insights into the other possible mechanism of action for NMDA antagonist such as ketamine, but these postulations are yet to be universally accepted. In addition, the postulation from the studies by these two groups of researchers is conflicting and contradictory to each other. Zanos *et al.*⁵⁷ postulated that negative allosteric modulation or selective inhibition of NMDARs localized on GABAergic interneurons with GABA-A receptors containing alpha 5 subunits (alpha 5 GABA-NAMs) in the prefrontal cortex (restricted brain localization) mediate the rapid antidepressant-like actions of ketamine, perhaps via an AMPA receptor-dependent increase in coherent neuronal circuit activity. While Wray *et al.*⁵⁸ hypothesized that ketamine would translocate G α from lipid rafts to non-raft microdomains, similarly to other antidepressants but with a distinct, rapid/fast onset treatment duration of action. Other NMDA antagonists did not translocate G α from lipid raft to non-raft domains. The ketamine-induced G α plasma membrane redistribution allows increased functional coupling of G α and adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP). Moreover, increased intracellular cAMP increased phosphorylation of cAMP response element-binding (CREB) protein, which, in turn, increased brain-derived neurotrophic factor expression. The ketamine-induced increase in intracellular cAMP persisted after knocking out the NMDA receptor indicating an NMDA receptor-independent effect. Furthermore, the ketamine metabolite (2R, 6R) hydroxynorketamine also induced G α redistribution and increased cAMP. These results reveal a novel antidepressant mechanism mediated by acute ketamine treatment that may contribute to ketamine's powerful antidepressant effect. They also suggest that the translocation of G α from lipid rafts is a reliable hallmark of antidepressant action that might be exploited for diagnosis or drug development.³⁷⁻⁵⁹

Selective antagonist or inverse agonist or partial agonist at the NR2B subunit glutamate-binding site of N-methyl-D-aspartate receptor (direct-acting NR2B subunit-selective N-methyl-D-aspartate-glutamatergic receptor antagonist/inverse agonist/partial agonist)

The Pfizer pharmaceutical company developed the potent NR2B subunit selective NMDA receptor antagonist CP-101,606 (traxoprodil) as a neuroprotectant for head injury and stroke, but later, it was evaluated as an adjunctive treatment for patients with treatment-resistant MDD. The selectivity of traxoprodil for NR2B subunits of the NMDA receptor complex was believed to reduce the psychotomimetic effects that have been associated with the nonspecific

NMDA receptor antagonist ketamine. A single 8 h infusion of traxoprodil (0.75 mg/kg/h for 1.5 h, then 0.05 mg/kg/h for 6.5 h) was evaluated as an adjunctive treatment to paroxetine (40.0 mg/day) in a double-blind clinical study. Traxoprodil produced rapid (5 days) antidepressant effects with 60% of the patients meeting response criteria. However, traxoprodil produced psychotomimetic effects in four of the nine patients that met response criteria. Although a Phase II clinical trial was conducted in 2005–2006 to evaluate the effects of monotherapy traxoprodil in patients with treatment-resistant depression (NCT00163059), to date, there are no published results from these clinical trials.^{1,6,15,19}

Recently, another NR2B subunit-selective NMDA receptor antagonist MK-0657, that developed for the treatment of Parkinson's disease, was the first oral formulation of NMDA receptor antagonist to be tested in treatment-resistant MDD patients. This was a double-blind, placebo-controlled study in which the patients received either MK-0657 (4.0–8.0 mg/day) or placebo for 12 days. MK-0657 produced inconsistent antidepressant effects from day 5 to day 12 as measured by both HDRS and BDI. Furthermore, MK-0657 failed to produce a significant reduction in depression symptoms as measured by Montgomery–Asberg Depression Rating Scale (MADRS). MK-0657 did not produce psychotomimetic or adverse side effects. One possible explanation for the inconsistent results is that the study was terminated after only five patients completed both phases of the study. Early termination of the study was due to recruitment challenges.^{1,6,15,19}

Excitatory amino acid transporter-2 reuptake enhancer and terminal presynaptic glutamate release inhibitor (indirect-acting unselective glutamatergic receptors antagonist)

The EAAT-2 glutamate reuptake enhancer and terminal presynaptic glutamate release inhibitor - riluzole, which is approved by the FDA for the treatment of amyotrophic lateral sclerosis, has been evaluated under a number of conditions for the treatment of MDD including monotherapy, adjunctive therapy, and relapse prevention in patients that responded to ketamine treatment. Because of its unique mechanism of action, riluzole is being referred to as an indirect-acting unselective glutamatergic receptors' antagonist due to the fact that its spectrum of pharmacological action extends to affect both the ionotropic (NMDA, AMPA, and kainate) glutamatergic receptors and the metabotropic (mGluR1-8) glutamatergic receptors. Riluzole was evaluated as a treatment for MDD because of its dual pharmacological effects on the glutamatergic system. Specifically, riluzole increases the reuptake of glutamate into astrocytes via EAAT-2 and also inhibits terminal presynaptic glutamate release, which produces

pharmacological actions similar to the effects of the NMDA receptor antagonists such that riluzole can reduce NMDA receptor activation by decreasing the synaptic concentrations of glutamate available to bind to postsynaptic NMDA receptors. The antidepressant effects of riluzole were first evaluated in an open-label clinical study in patients with treatment-resistant MDD. In the open-label clinical study, daily riluzole (mean dose of 169 mg/day) produced antidepressant effects on weeks three through week six as compared to baseline MADRS score. There was not a placebo control in this study by Zarate *et al.*⁵¹ In another small scale clinical study ($n = 10$), adjunctive riluzole (100 mg/day) treatment produced a rapid decrease in depressive symptoms from week one through week six as compared to baseline HDRS scores. There was no placebo control group in this study by Sanacora *et al.*⁴⁷ Two double-blind clinical studies evaluated riluzole as relapse prevention in patients that responded to a single infusion of ketamine; however, both studies found that riluzole was not efficacious than placebo for relapse prevention in patients that responded to ketamine treatment. Moreover, riluzole did not produce antidepressant effects in patients that did not respond to ketamine infusions (i.e., ketamine nonresponders). In general, riluzole was well tolerated in these studies, and psychotomimetic effects were not observed. At the time of this review, two Phase II double-blind, placebo control, adjunctive treatment clinical trial are underway for patients with treatment-resistant (or treatment-refractory) MDD (NCT01204918 and NCT01703039).^{1,6,15,19}

What this review adds to the body of knowledge

- This review remarkably announces the incorporation of NMDA-glutamatergic ionoreceptor blockers as the first separate novel class of rapid-onset antidepressants because of their clinically significant rapid-onset antidepressant activity.

CONCLUSION

This review remarkably announces the incorporation of NMDA-glutamatergic ionoreceptor blockers as the first separate novel class of rapid-onset antidepressants because of their clinically significant rapid-onset antidepressant activity. These rapid-onset antidepressants are rapastinel, apimostinel, ketamine, and riluzole.

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There are no conflicts of interest.

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