

Modulation of the activity of *N*-methyl-D-aspartate receptors as a novel treatment option for depression: current clinical evidence and therapeutic potential of rapastinel (GLYX-13)

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Abstract: Classical monoaminergic antidepressants show several disadvantages, such as protracted onset of therapeutic action. Conversely, the fast and sustained antidepressant effect of the *N*-methyl-D-aspartate receptor (NMDAR) antagonist ketamine raises vast interest in understanding the role of the glutamate system in mood disorders. Indeed, numerous data support the existence of glutamatergic dysfunction in major depressive disorder (MDD). Drawback to this short-latency therapy is its side effect profile, especially the psychotomimetic action, which seriously hampers the common and widespread clinical use of ketamine. Therefore, there is a substantial need for alternative glutamatergic antidepressants with milder side effects. In this article, we review evidence that implicates NMDARs in the prospective treatment of MDD with focus on rapastinel (formerly known as GLYX-13), a novel synthetic NMDAR modulator with fast antidepressant effect, which acts by enhancing NMDAR function as opposed to blocking it. We summarize and discuss current clinical and animal studies regarding the therapeutic potential of rapastinel not only in MDD but also in other psychiatric disorders, such as obsessive-compulsive disorder and posttraumatic stress disorder. Additionally, we discuss current data concerning the molecular mechanisms underlying the antidepressant effect of rapastinel, highlighting common aspects as well as differences to ketamine. In 2016, rapastinel received the Breakthrough Therapy designation for the treatment of MDD from the US Food and Drug Administration, representing one of the most promising alternative antidepressants under current investigation.

Keywords: depression, glutamate, NMDARs, rapastinel, ketamine

Introduction

Psychiatric disorders represent a main source of disability worldwide. The World Health Organization (WHO) Global Burden of Disease Survey estimates that by the year 2020, major depressive disorder (MDD), a serious and at times life-threatening stress-related psychiatric illness, will represent the second cause of disability in the world.¹ Therefore, there is an urgent need for improved therapies of MDD.² Classical monoaminergic antidepressants, although representing at the time of their development a real progress in the therapy of mood disorders, show major drawbacks. These include a delayed onset (of weeks) and often only partial therapeutic response. In addition, these substances do not ameliorate key symptoms of depression, such as cognitive impairment, symptoms that implicate synaptic dysfunction in the pathophysiology of MDD.³ A growing body of evidence indicates that drugs targeting the glutamate system,

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which plays a main role in modulating synaptogenesis and synaptic plasticity, may represent a valuable alternative in treating MDD.⁴⁻⁶

Glutamate is the main excitatory neurotransmitter in the brain. It exerts pleiotropic effects on numerous brain functions, acting on various glutamate receptors. These include ionotropic receptors that include the 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid receptor (AMPA), *N*-methyl-D-aspartate receptor (NMDAR) and kainate receptor (KAR) as well as several classes of metabotropic receptors (mGluR). Several results support the implication of abnormal glutamatergic mechanisms in the pathophysiology of depression. Using microarray gene profiling and electron microscopic stereology, lower expression of synaptic function-related genes and a reduced number of synapses were found in the dorsolateral prefrontal cortex (dlPFC) of individuals with MDD.⁷ Altered expression of synapse- and glutamate-related genes was also reported in the hippocampus of depressed subjects.⁸ Moreover, glutamatergic alterations in depression appear to show sex specificity. In a recent large cohort study of postmortem subjects, significantly higher expression of several glutamate receptor genes was reported in the dlPFC of patients suffering from MDD who committed suicide, with the greatest effects recorded in female subjects.⁹ These results are significant, since the prevalence of depression is higher among women in comparison to men, and the reasons for this difference are still under debate.¹⁰

The results in humans with MDD implicating the glutamate system in the pathophysiology of depression can be corroborated with data obtained in animal models. Acute stress and corticosterone increase glutamate release in the prefrontal cortex (PFC),¹¹ whereas antidepressant treatment prevents the stress-induced neuroplastic changes in the PFC by blocking accumulation of glutamate vesicles and expansion of excitatory synapse function.¹² Chronic stress significantly impairs recognition memory, a cognitive process controlled by the PFC through suppression of glutamate receptor expression and function.¹³ Interestingly, in the hippocampus, chronic stress increases the local expression of NMDAR, an effect that can be influenced by antidepressant treatment.¹⁴

Antidepressive effect of the NMDAR antagonist ketamine

The most convincing clues regarding the implication of the glutamate system in depression come from pharmacological studies. Glutamatergic agents, especially those

targeting the NMDAR, represent promising alternative drugs for treating mood and anxiety disorders. A single, low dose of the NMDAR antagonist ketamine produces a fast (within minutes after administration) and sustained (up to 2 weeks) antidepressant effect.^{15,16} Moreover, ketamine has been reported to have antisuicidal properties¹⁷ and also to be effective in other stress-associated psychiatric disorders, such as posttraumatic stress disorder (PTSD).¹⁸ These results open new avenues in the search for more efficient antidepressant treatments.

The rapid mood-elevating effect of ketamine is intensely studied, and several molecular mechanisms have been proposed to explain it. Ketamine was shown to rapidly activate the mammalian target of rapamycin (mTOR) pathway, leading to an increased number and function of new synaptic spines in the PFC of rats.¹⁹ On the other hand, the blockade of mTOR signaling by rapamycin abolishes synaptogenesis and antidepressant responses induced by ketamine in animal models.¹⁹ Another group reported that the swift antidepressant effect of ketamine depends on the rapid synthesis of brain-derived neurotrophic factor (BDNF), implicating the deactivation of the eukaryotic elongation factor 2 (eEF2) kinase.²⁰ Moreover, inhibitors of eEF2 kinase elicit antidepressant-like effects.²⁰ In addition, it was shown that ketamine inhibits, similar to lithium, brain glycogen synthase kinase-3 (GSK3) in mice and that this inhibition of GSK3 is necessary for a rapid antidepressant-like effect.²¹ Interestingly, the GSK-3 inhibition produced by lithium potentiates the antidepressant, synaptogenic and electrophysiological effects of ketamine.²² Recent scientific works have proposed also an alternative, NMDAR-independent pathway to explain the antidepressant action of ketamine, implying the effect of the ketamine metabolite (2*R*,6*R*)-HNK (hydroxynorketamine) through its action on AMPAR.²³ These new results are of crucial importance involving the activation of AMPAR in the antidepressive mechanism of ketamine and are in agreement with data implicating the GluA1 subunit of AMPAR in the neurobiology of depression.²⁴

Despite the remarkable therapeutic efficacy of ketamine, several major disadvantages deter from its widespread clinical use. Particularly, its notorious psychosis-like²⁵ and addictive potentials²⁶ have been well established for several years and are the greatest causes of reservation regarding its clinical application. Regrettably, these may not be the only deleterious effects precipitated by ketamine. Although serial infusions of ketamine in the short term (of 4 weeks) do not result in significant cognitive impairment,²⁷ recent investigations underline serious cognitive deficits and altered hippocampal

activation in heavy ketamine abusers.²⁸ In addition, ketamine was shown to have several undesired actions in rodent models, inducing cortical neurotoxicity²⁹ and the initiation of abnormal cortical oscillations.³⁰ Alternatives to ketamine with a similar therapeutic profile, but milder side effects, have therefore become a necessity for the advancement of the field of clinical psychiatry. Subunit-specific NMDAR antagonists that do not block all NMDARs in the brain represent one group of potential alternative drugs. NMDARs are tetramers composed of two obligatory GluN1 and two GluN2 subunits, the latter having four possible isoforms, A–D.³¹ In addition, diversity of NMDAR is determined by the presence of GluN3 and the family of heterotrimeric GluN1/GluN2/GluN3 NMDAR.³²

GluN2A and GluN2B represent the main NMDAR subunits in the forebrain. GluN2B-specific antagonists induce similar potent antidepressant effects to global NMDAR antagonists, without triggering detrimental effects.^{33–36} Interestingly, the brain activation pattern differs substantially between the two classes of NMDAR antagonists.³⁷ Nevertheless, GluN2A subunits may also represent potential targets for antidepressant therapies,^{38–40} as is the case with other glutamate receptors that are tightly linked structurally and functionally to NMDAR, particularly mGluR5.^{41–43}

Antidepressant effects induced by enhancing NMDAR activity

One striking discovery following the characterization of the fast antidepressant profile of ketamine was that also increasing, instead of blocking, that same target (the NMDAR) produces antidepressant-like effects. Sarcosine, also known as *N*-methylglycine, acts as an NMDAR coagonist at the glycine binding site.⁴⁴ It was reported that compared to citalopram, patients receiving sarcosine over a 6-week period reported significantly improved mood scores and were more likely to experience relief of their depression symptoms.⁴⁵ In these trials, sarcosine was well tolerated without significant side effects.⁴⁵ In rodent models, chronic sarcosine treatment significantly ameliorates the increased immobility induced by chronic unpredictable stress in the forced swim test (FST), a classical behavioral paradigm for measuring antidepressant action.⁴⁶ In support of these findings, a single injection of sarcosine rapidly activates the mTOR signaling pathway, an effect abolished by rapamycin or AMPAR blockade, indicating that sarcosine exerts antidepressant-like effects by enhancing AMPAR-mTOR signaling pathway activity and by facilitating AMPAR membrane insertion.⁴⁷ Rapastinel (formerly GLYX-13) is a novel synthetic compound that

modulates the NMDAR in a glycine-like fashion when examined pharmacologically and electrophysiologically.⁴⁸ It is a tetrapeptide (Thr-Pro-Pro-Thr-amide) derived from the hypervariable region of a monoclonal antibody, B6B21, that acts as an NMDAR modulator with glycine-site partial agonist properties and possesses the ability to readily cross the blood–brain barrier.⁴⁸ In 2014, it was the only drug with possible use in psychiatric disorders to receive the US Food and Drug Administration (FDA) Fast Track designation in order to allow an expedited review and approval process. In 2016, the Phase III trial received the Breakthrough Therapy designation from the FDA due to the fact that preliminary clinical data had indicated potential improvement over existing therapies in treating depressive symptoms. Similar to ketamine, rapastinel induced significant antidepressant-like effects in rodent experiments. However, a single injection of ketamine induced a longer lasting antidepressant effect in contrast to rapastinel as measured in a social defeat stress paradigm.⁴⁹ Other authors, however, reported sustained antidepressant and pro-cognitive effects of rapastinel extending at least 1 week after single-dose administration.⁵⁰ Unlike ketamine, rapastinel did not induce psychosis-like, sedative and cognitive symptoms in mice.^{51,52} Moreover, rapastinel prevented or reversed the declarative memory deficits induced by sub-chronic treatment with ketamine or another global NMDAR antagonist, phencyclidine.⁵³ Interestingly, rapastinel even enhanced learning in both young adult and aging rats, and the rapastinel-induced enhancement of learning was greater in old than in young adult animals,⁵⁴ suggesting that rapastinel could represent a promising treatment for deficits in cognitive function associated not only with depression but also with aging. Behavioral responses were accompanied by significant enhancement of long-term potentiation (LTP) in both young and aged animals.^{54,55} Importantly, rapastinel has the unique property to reduce hippocampal long-term depression (LTD), differentiating it from similar NMDAR modulators like D-cycloserine.⁵⁵ The difference in LTP/LTD was proposed to result from greater selectivity for GluN2B subunit-containing NMDARs for rapastinel than D-cycloserine or from the fact that because both substances are structurally dissimilar, upon binding to the glycine site each may induce different conformational states of NMDAR, resulting in different effects on NMDAR function.⁵⁵

Adding to its beneficial impact on affect, rapastinel induced anxiolytic effects in rat models of PTSD, significantly decreasing the accompanying elevated serum levels of both corticosterone and its upstream stress hormone adrenocorticotrophic hormone.⁵⁶

Several animal studies have provided additional hints regarding other potential therapeutic applications of rapastinel. It may represent a therapeutic option in autism,^{57,58} due to data showing that it can ameliorate deficits in play-related prosocial ultrasonic vocalizations (USVs) in rats.⁵⁹ Additionally, rapastinel proved to have an antinociceptive effect in tonic and chronic pain models without inducing locomotor or sedative side effects.⁶⁰ Rapastinel also demonstrated neuroprotective properties in an animal model of cerebral ischemia.⁶¹ Finally, suppression of cortical spreading depolarization and stabilization of dendritic spines by rapastinel suggest that it could be an effective new treatment strategy for amelioration of the symptoms of migraine attacks and ischemic or traumatic brain damage.⁶²

Molecular determinants of the antidepressant effect of rapastinel

Current findings provided clues regarding similar mechanism of action of rapastinel and ketamine, but revealed also differences. Similar to ketamine, rapastinel rapidly increases levels of the phosphorylated and activated forms of the extracellular signal-regulated kinase (ERK) and a downstream target of mTORC1 as well as promotes an elevated BDNF release in rat primary cortical culture neurons.⁶³ This induction of BDNF release and stimulation of phospho-ERK could be experimentally blocked by incubation with an AMPAR antagonist.⁶³ In vitro incubation with rapastinel for 24 hours increased the number and length of neuronal branches, suggesting a neuroplastic effect and higher neuronal complexity triggered by this drug.⁶³ In addition, rapastinel was shown to significantly reverse the changes induced by chronic unpredictable mild stress in the expression of several signaling molecules associated with depression, including AKT, mTOR and eEF2 kinase in the hippocampus.⁶⁴ Analogous effects of rapastinel were noticed also with regard to the expression of VGF (nonacronym),⁶⁴ a neuropeptide, which is encoded by a gene that is responsive to BDNF and physical exercise^{65,66} and may be an important mediator of antidepressant response, enhancing neurogenesis in the hippocampus.⁶⁷ Downregulation of hippocampal VGF not only significantly increases the immobility in the FST compared to controls but also blocks the antidepressant-like effects of rapastinel, highlighting the important role of VGF in the mediation of the rapid-acting antidepressant activity elicited by rapastinel.⁶⁴ Beyond the activation of similar molecular pathways when compared to ketamine, the synaptic and behavioral responses reported appear to be distinct from those induced by ketamine.⁶⁸ The differences in the

serotonin-2 receptor-mediated responses may be related to the lack of psychotomimetic side effects of rapastinel when likened to ketamine, whereas regulation of the hypocretin response may contribute to the therapeutic benefits of both these rapid-acting antidepressant substances.⁶⁸

Another engaging aspect regarding the mechanism of action of rapastinel refers to the fact that its enduring antidepressant effects are associated with a metaplasticity process in the medial PFC (mPFC) and hippocampus.⁶⁹ Metaplasticity is induced by synaptic and cellular activity and manifested as a change in the ability to induce subsequent synaptic plasticity, such as LTP, representing therefore in fact a higher-order form of synaptic plasticity.⁷⁰ In the case of rapastinel, this refers to the fact that a single dose of the drug induced a proliferation of mature spines in distal dendrites of the dentate gyrus of the hippocampus and Layer V of the mPFC,⁵⁰ as well as an increase in NMDAR expression seen at 24 hours postadministration, which has been shown to be causally linked to LTP formation.⁷¹ Among NMDAR subunits, GluN2B was studied regarding electrophysiological effects of rapastinel. A single dose increased the proportion of whole-cell NMDAR current contributed by GluN2B-containing NMDARs in the hippocampus 1 week postdosing, then returned to baseline by 4 weeks postdosing.⁵⁰ In rat hippocampal slices, rapastinel has been shown to enhance conductance of GluN2B-containing NMDARs at rat Schaffer collateral-CA1 synapses.⁵⁵ Furthermore, rapastinel significantly increased positive emotional learning in rodents, an effect annulled by the GluN2B receptor-specific antagonist ifenprodil.⁷²

Therapeutic efficacy of rapastinel in clinical trials

To this date, few human trials regarding the potential benefits of rapastinel have been completed and published. Yet, the modest number of clinical studies available supports the therapeutic efficacy of rapastinel in individuals suffering from psychiatric illnesses. In a double-blind, placebo-controlled, proof-of-concept clinical trial, a single intravenous (IV) dose of rapastinel administered to 116 subjects with MDD who had not responded to an adequate trial with at least one antidepressant agent during their current depressive episode showed an improvement in depression scores within hours without presenting psychotomimetic effects.^{52,73} No treatment-related serious adverse events were reported during the study.^{52,73} The results of this study suggest that a dose of 1 mg/kg IV would be minimally efficacious, and a dose of 10 mg/kg would lie at the peak of the dose-response curve.^{52,73} Other clinical

trials are ongoing to investigate the efficacy of rapastinel as adjunctive therapy in MDD ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02932943) Identifier: NCT02932943) or as add-on therapy in the prevention of relapse in patients with MDD ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02951988) Identifier: NCT02951988). Additionally, in a small open-label sample, rapastinel was recently shown to be effective in the treatment of obsessive-compulsive disorder (OCD), displaying acute beneficial effects regarding obsessions, compulsions and symptoms of anxiety and depression.⁷⁴

Discussion

Rapastinel represents a novel promising glutamatergic antidepressant. The lack of psychotomimetic side effects constitutes an important step forward when compared to ketamine or other NMDAR modulators, such as lanicemine.⁷⁵ Although the neurobiological mechanisms underlying the therapeutic efficiency of rapastinel have been intensely studied, there is a need for more clinical studies with larger cohorts to replicate and extend the initial promising results into the clinical context. Rapastinel has rapid efficacy that lasts for ~1–2 weeks after a single injection, opening possibilities for using it in conjunction with standard monoaminergic antidepressants.

Another interesting aspect is the effect of rapastinel on specific NMDAR subunits, ie, the GluN2B-containing NMDAR. This is of potential practical relevance since in a large postmortem study, the expression of the GluN2B subunit was higher in all MDD patients who died by suicide relative to those who did not, suggesting that GluN2B mRNA levels may be a biological marker of suicidality in depression.⁹ Moreover, GluN2B appears to play an important role in metaplasticity⁷⁶ and therefore also in the durable changes triggered by rapastinel. However, these data do not show a preferential effect of rapastinel on GluN2B, and future studies are needed to evaluate the contributions also of other NMDAR subunits in the therapeutic action of rapastinel.

Besides NMDAR, there is increasing evidence that enhancement of AMPAR function may also play a major role in the antidepressant effect of ketamine.²³ Both ketamine and rapastinel led to increases in both GluN2B and GluA1 protein levels.⁵¹ However, the cellular mechanisms and networks implicated in the effects mediated via AMPAR are still unknown. Although the global ablation of GluA1-containing AMPAR produced a depression-like phenotype,²⁴ in mice with inducible ablation of GluA1 in glutamatergic forebrain neurons, no alteration of the emotional behavior was noted.^{77,78} This suggests that AMPAR located onto GABAergic interneurons may be heavily involved in mood disorders. Nevertheless, since

AMPA potentiators represent alternative antidepressants,⁷⁹ the effect of possible combinations and interactions with rapastinel should be determined by subsequent studies. Like ketamine, the rapastinel-induced antidepressant-like effects required AMPAR/KAR activation.⁵¹ Recent studies show a direct effect of rapastinel on AMPAR activation in stress models of depression; however, the results are variable, indicating differences to ketamine. Although the antidepressant effect of rapastinel in the FST required AMPAR activation,⁶⁴ only R-ketamine but not rapastinel significantly attenuated the reduced GluA1 AMPAR expression in the PFC and hippocampus in the social defeat stress model of depression.⁴⁹ Future studies, for example, examining the antidepressive effect of rapastinel in genetic models of AMPAR or NMDAR deletion, are needed to clarify the role of these receptors in its therapeutic action.

In fact, although acting by different mechanisms (agonism vs antagonism of NMDAR), both rapastinel and ketamine may produce rapid antidepressant effects by increased synaptic plasticity, for example, by increasing BDNF release.^{20,64} Whether AMPAR activation represents in this context a point of convergence that in fact underlies the antidepressant effect of both compounds remains to be determined by future studies. Nevertheless, considering the cognitive dimension in depression, it is of importance that rapastinel acts as a cognitive enhancer⁵² and reverses memory deficits induced by ketamine or another NMDAR antagonist in rodent models.⁵³ Therefore, it is important to underlie once more that the effects of rapastinel and ketamine are not identical, and acute administration of rapastinel and ketamine has different, even opposing effects in terms of receptor activation, LTP induction⁵⁵ and learning and memory.⁵³ Finally, another aspect that should be clarified by future studies is whether there are age-specific characteristics in the antidepressant effect of rapastinel. It was shown in animal models that ketamine does not induce any antidepressant-like effects if administered before puberty.⁸⁰ The mechanisms underlying these age-dependent differences are not yet understood. It is, however, known that NMDARs undergo important changes in their constitution and function during transition to adulthood,⁸¹ paralleled by significant changes in the brain activation pattern induced by NMDAR antagonists.⁸² Future studies may establish whether these changes also determine a different therapeutic responsiveness to rapastinel in MDD.

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Disclosure

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