SPECIAL ARTICLE

# Glutamate modulators as novel interventions for mood disorders

# Moduladores de glutamato como novas intervenções em transtornos do humor

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*Abstract*

*Recent evidence suggests that critical molecules in neurotrophic signaling cascades are long-term targets for currently available monoaminergic antidepressants. As chronic and severe mood disorders are characterized by impairments in neuronal resilience, pharmacological strategies that subserve a neuroprotective function might alter disorder pathophysiology and modify disease progression. Several promising approaches involve modulation of the glutamate neurotransmitter system, via post-synaptic receptor blockade or potentiation and presynaptic vesicular release inhibition. A focused review of the extant scientific literature was conducted, with a discussion of 3 compounds or classes of drugs currently undergoing clinical investigation: ketamine, riluzole, and AMPA receptor potentiators. Recent investigations in mood disordered patients suggest that the NMDA receptor antagonist ketamine might demonstrate rapid antidepressant properties. Riluzole has been shown to reverse glutamate-mediated impairments in neuronal plasticity and to stimulate the synthesis of brain derived neurotrophic factor. Open-label trials in treatment-resistant depression have yielded promising results. Likewise, AMPA receptor potentiators favorably impact neurotrophic factors as well as enhance cognition.* ***Conclusions:*** *Pharmacological approaches that modulate components of the glutamate system offer novel targets for severe, recurrent mood disorders. Controlled studies are necessary.*

***Keywords:*** *Mood disorders/drug therapy; Signal transduction/drug effects; Antidepressive agents/therapeutic use; Glutamates/therapeutic use; Ketamine/therapeutic use; Riluzole/therapeutic use; Receptors, AMPA;*

*Resumo*

*Recentes evidências sugerem que as moléculas críticas nas cascatas de sinalização neurotrófica são alvos de longo prazo dos antidepressivos monoaminérgicos disponíveis atualmente. Na medida em que transtornos graves e crônicos são caracterizados por deficiências na resiliência neuronal, estratégias farmacológicas que sejam úteis para uma função neuroprotetora talvez possam alterar a fisiopatologia e modificar a progressão da doença. Vários enfoques promissores envolvem a modulação do sistema neurotransmissor do glutamato, via bloqueio ou potencialização do receptor pós-sináptico e inibição da liberação vesicular pré-sináptica. Foi realizada uma revisão focada da literatura científica existente, com a discussão de três compostos ou classes de drogas que estão atualmente sob investigação clínica: a ketamina, o riluzol e os potencializadores de receptores de AMPA.* ***Discussão:*** *Estudos recentes com pacientes com transtornos de humor sugerem que a ketamina, um antagonista do receptor NMDA, poderia ter demonstrado propriedades antidepressivas rápidas. O riluzol demonstrou reverter deficiências mediadas pelo glutamato na plasticidade neuronal e estimular a síntese de fatores neurotróficos derivados do cérebro. Ensaios abertos com depressão resistente ao tratamento produziram resultados promissores. Da mesma forma, os potencializadores de receptores de AMPA impactam favoravelmente os fatores neurotróficos, assim como melhoram a cognição.* ***Conclusões:*** *Enfoques farmacológicos que modulam os componentes do sistema de glutamato oferecem novos alvos para transtornos de humor recorrentes e graves. São necessários estudos controlados.*

***Descritores****: Transtornos do humor/quimioterapia; Transdução de sinal/efeitos de droga; Antidepressivos/uso terapêutico; Glutamatos/uso terapêutico; Ketamina/uso terapêutico; Riluzol/uso terapêutico; Receptores de AMPA*

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## Introduction

### 1. Pathophysiological models of mood disorders emphasize impairments in cellular plasticity

Current pathophysiological theories regarding the neurobiology of mood disorders, including major depression and bipolar disorder, include alterations in intracellular signaling cascades and impairments of cellular plasticity and resilience.[1-3] There is recent evidence suggesting that critical molecules in neurotrophic signaling cascades such as brain derived neurotrophic factor (BDNF) and mitogen activated protein (MAP) kinases are long-term targets for currently available antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs). New data indicating modulation of specific glutamate receptors as a key component of the mechanism of action of conventional antidepressants suggests an approach to develop a novel class of antidepressants that enhances neuronal plasticity and cellular resilience.[2] One of the underlying themes guiding this work is that agents that enhance cellular plasticity and resilience, rather than solely functioning in limited neurogenesis models, might have particular salience for the treatment of severe, recurrent, difficult-to-treat mood disorders.[1] Thus, the unifying hypothesis of this pharmacological approach is that new treatments for mood disorders, in addition to attenuating the constellation of symptoms that manifest as the complex syndrome of depression (e.g. anergia, hopelessness, insomnia or hypersomnia, suicidal thoughts, anhedonia), would also reverse impairments of cellular resilience, reductions in brain volume, and regional glial and neuronal cell death.

An increasing number of neuroimaging, neuropathological, and biochemical studies consistently suggest that impairments in neuroplasticity and cellular resilience are found in patients who suffer from severe, recurrent mood disorders. Recent morphometric magnetic resonance imaging (MRI) and post-mortem investigations have demonstrated abnormalities of brain structure that correspond to abnormalities of metabolic activity.[4-5] Structural imaging studies demonstrate reduced gray matter volumes in areas of the orbital and medial pre-frontal cortex (PFC), temporal lobe, and enlargement of the third ventricle in patients with mood disorders compared to healthy controls (reviewed in[6-7]). Recent post-mortem neuropathological studies in mood disorder patients are complementary, showing reductions in cortical volume and region- and layer-specific reductions in number, density, and/or size of neurons and glial cells in the subgenual PFC, orbital cortex, dorsal anterolateral PFC, amygdala, and basal ganglia and dorsal raphe nuclei (reviewed in[4,8]). It is important to note, however, that it is not known what the above-noted structural and functional alterations constitute: 1) developmental abnormalities conferring vulnerability to severe mood episodes; 2) compensatory changes to other pathogenic processes; 3) sequelae of recurrent affective episodes; 4) effects of comorbidity or pharmacological treatments; or 5) epiphenoma which lack significance for the clinical phenotype of the disorder. Understanding these issues will partly depend upon experiments that delineate the onset of such abnormalities within the illness course and determine if they antedate mood episodes in high-risk individuals.

## Methods

We conducted a selective literature review of several promising classes of agents that impact the glutamate system. This article reviews the mechanisms and clinical profile of three candidate compounds undergoing large-scale studies in the United States: ketamine, riluzole, and AMPA receptor potentiators, or AMPAkines.

## Discussion

### 1. Overview of the glutamate system

Glutamate is the major excitatory synaptic neurotransmitter in the brain and plays a vital role in the regulation of several important CNS processes, including the regulation of synaptic plasticity, learning, and memory.[9-12] Glutamate is found in greater than 80% of neurons and exists in relatively high concentrations in brain tissue (approximately 8-10 mmol/kg, in contrast to monoamines, which are in the μmol/kg range). Because of the putative role of glutamate in neuronal plasticity and its relative ubiquity, modulation of the glutamatergic system is being investigated in several ongoing clinical studies in neuropsychiatric disorders marked by impairments in mood, concentration, attention, and memory.[13]

Glutamate exerts its action at the presynaptic and postsynaptic level through the stimulation of specific receptors that can be classified by structural characteristics; the first group, "ionotropic glutamate receptors", which include N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate families of receptors, are ion channels, which when stimulated open the channel pore allowing sodium, potassium or calcium to flow freely into the cell. This opening of the pore changes the polarization of the neuronal surface and often activates intracellular signaling pathways. AMPA receptors mediate the majority of excitatory synaptic transmission in the CNS, and the AMPA R channels are comprised of four subunits (GluR1, GluR2, GluR3, and GluR4). The second group, "metabotropic receptors" are G-protein-coupled receptors that exert their actions through second messenger pathways. Therapeutic agents, such as the mGlu receptor agonists, can specifically target these receptors; it is also possible to target the release of glutamate before it binds to either the ionotropic or metabotropic receptors. The most recently described pharmacological target in the glutamate system is the family of excitatory amino acid transporters (EAATs), which serve to remove glutamate from the synapse. Subtypes 1 and 2 in particular, which are localized to astrocytes, appear to play a major role in glutamate reuptake and subsequent conversion into glutamine. Recent groundbreaking work from Johns Hopkins has found that specific classes of antibiotics increase gene expression of subtypes of EAATs, offering a novel mechanism for modulation of synaptic glutamate concentrations and resultant glutamate excitoxicity. Thus, therapeutic agents directed at these different molecular glutamatergic targets may result in complex effects on a wide range of neuropsychiatric symptoms.[2]

Candidate drugs impacting primarily on glutamate receptors include the following: NMDA receptor antagonists, metabotropic glutamate receptor (mGluR) agonists and antagonists, and positive modulators of AMPA receptors. These candidate molecules have demonstrated antidepressant-like properties in preclinical and clinical studies.[3,14-15] For NMDA antagonists in particular, there is now substantial preclinical evidence that these agents have antidepressant properties. Chronic treatment with NMDA antagonists resulted in antidepressant-like behavioral effects in models such as chronic mild stress, learned helplessness, footshock-induced aggression, and olfactory bulbectomy (reviewed in[14]). Chronic,

but not acute treatment with NMDA antagonists also resulted in reductions in density of forebrain β-adrenoreceptors[16-17] and 5-$HT_2$ receptors.[18] In a fashion similar to that of monoamine-based antidepressants, NMDA antagonists given to animals processed in the forced swim test resulted in a rapid down-regulation of forebrain β-adrenoceptors.[19] Finally, repeated administration of conventional antidepressants has been found to alter the expression of mRNA that encodes NMDA receptor subunits,[20] through expression of BDNF.[21]

Perhaps the most robust clinical evidence that modulation of glutamatergic activity may be important in the treatment of mood disorders comes from the extensive clinical utility of the anticonvulsant lamotrigine.[22-23] Many clinicians believe lamotrigine to be particularly effective for treatment resistant mood disorders, and its utility in the depressed phase of bipolar disorder is now well established. While lamotrigine has multiple cellular effects, including inhibition of use-dependent sodium and P-and N-type calcium channels, inhibition of an excessive release of glutamate appears to be an important aspect of its mechanism of action.[24-26] In healthy volunteers given ketamine, an NMDA antagonist, investigators at Yale reported that lamotrigine attenuated the hyperglutamatergic consequences of NMDA receptor dysfunction, namely the cognitive dysfunction and psychomimetic effects of ketamine.[27]

The remaining sections of this paper will discuss 3 drugs (or drug classes) that impact varied components of the glutamate system: ketamine, riluzole, and AMPA receptor potentiators. Based on promising proof-of-concept pilot trials with small sample sizes, these compounds are being actively studied in larger samples for treatment-resistant mood disorders in several centers in the United States.

## 2. The ketamine model for rapid mood elevation

Existing treatments for depression may take several weeks to months to exhibit an antidepressant effect. Given the increased morbidity and mortality resulting from failure to treat depression in a timely fashion, there is clearly a need to develop rapidly-acting and potent treatments in addition to electroconvulsive therapy (ECT), which is generally considered to be the most rapid and potent form of treatment. Ketamine, a high-affinity non-competitive NMDA antagonist, has been used as a standard anesthetic agent for many years in both pediatrics and adults, with doses as high as 2 mg/kg.

There is abundant preliminary evidence that ketamine has anxiolytic and antidepressant effects in animal models[28-31] and may have rapid antidepressant properties. The Yale group reported the first placebo-controlled, double-blind trial investigating the effects of a single dose of intravenous ketamine (0.5 mg/kg) in 9 patients with depression,[32] work recently replicated in a larger sample at NIMH. In the Yale report, investigators[32] administered either the noncompetitive NMDA antagonist ketamine or saline to patients who were unresponsive to conventional antidepressants. Ketamine (0.5 mg/kg, infused over 40 minutes) significantly reduced depression rating scales scores within 3 hours. The reduction in depression scores continued to emerge over time, and persisted beyond 72 hours, the planned duration of the study. At the point the study was terminated (72 hours), the Hamilton scores were significantly reduced (Mean ± SD) 14 ± 10 and 0 ± 12 points in the ketamine and saline conditions, respectively. All subjects relapsed and were within 5 points of their baseline Hamilton scores before the end of the week.

Studies with NMDA antagonists (e.g., ketamine) and other glutamate modulators have been conducted for many years in healthy controls, in patients with schizophrenia, in substance abusers and in patients with major depression in an attempt to better understand the role of the glutamatergic system in neuropsychiatric disorders.[33-34] Since NMDA receptor modulation has a powerful, albeit complex, effect on biogenic amine turnover, it could be argued that the antidepressant-like actions of functional NMDA antagonists result from elevated levels of biogenic amines (e.g., norepinephrine and dopamine). However, the rapid antidepressant action of ketamine[32] indicates that it is the NMDA antagonist properties *per se* that are responsible for these effects since intravenous infusion of biogenic-amine based agents (e.g., an SSRI or tricyclic) will not produce such a rapid improvement in symptoms. However, while study findings are encouraging,[32] it is important to note that this was a serendipitous finding and was not the primary aim of the study. In addition, the study sample size was small. Thus, larger controlled studies are necessary to adequately test this intriguing pilot finding.

## 3. Enhancement of neuroplasticity: the example of riluzole

A significant challenge for depression research is identifying optimal continuation therapy for the prevention of relapse following acute remission of symptoms.[35] As discussed, lamotrigine was found to increase the immediate mood-elevating effects of ketamine in healthy volunteers.[27] An important unanswered question is the relationship between a drug's ability to potentiate the acute response to ketamine and its ability to prevent relapse of symptoms following effective treatment with ketamine. *Could an anti-glutamatergic drug with a similar mechanism of action to lamotrigine be effective for continuation therapy for patients who acutely respond to ketamine?* Recent investigations suggest that the glutamate antagonist riluzole, the only U.S. FDA-approved drug for amyotrophic lateral sclerosis (ALS, or Lou Gehrig's Disease), impacts numerous neurochemical and neuropeptide systems relevant to mood disorders. A recent open-label trial showed significant antidepressant effects of riluzole in nineteen treatment-resistant patients with unipolar depression.[36] Patients showed significant improvement on the MADRS scale for depression and concurrent reductions in comorbid anxiety symptoms (shown by reductions in Hamilton Anxiety Rating score). Riluzole was also beneficial for patients with bipolar depression as an augmenting agent to lithium.[37] In these studies, all patients who responded were remitters, suggesting a subgroup of mood disorder patients who might be particularly appropriate for this intervention. Although the mechanisms of lamotrigine and riluzole appear to be similar, preliminary data from NIMH has also found that patients who had previously failed to respond to lamotrigine subsequently responded to riluzole.

Chemically, riluzole is 2-amino-6- trifluoromethoxybenzothiazole,[38] and easily penetrates the blood-brain barrier.[39] Evidence from a variety of studies with experimental animals and with humans indicates that riluzole is devoid of the psychotomimetic or other behavioral side-effects commonly associated with excitatory amino acid antagonists.[40-41]

In contrast to several glutamate modulating drugs (memantine, ketamine), riluzole does not appear to act directly on the NMDA receptor.[42] Rather, the mechanism of its anti-glutamatergic (and antiepileptic) effect is through the (1) inhibition of voltage-dependent sodium channels in mammalian

CNS neurons[43-44] and the (2) inhibition of glutamate release.[45] However, tetrodotoxin, a sodium channel blocking agent, failed to block the inhibitory effect of riluzole on glutamate, suggesting that the effects of riluzole are not exclusively mediated by its action on sodium channels.[46] The anticonvulsant activity of riluzole may also be due to its effect on neurotransmission mediated by the (3) AMPA/KA receptors,[42,47-50] however, the mechanism by which riluzole interacts with these receptors in brain and spinal motor neurons remains unclear.[51] There is also evidence that riluzole inhibits presynaptic glutamate release through (4) inactivation of P/Q-type calcium channels.[52] This release inhibition may involve a pertussis toxin-sensitive G protein signaling pathway. Recently, we and others have reported riluzole's efficacy in patients with primary anxiety disorders (Mathew et al, in press) and in anxiety associated with MDD.[36] One intriguing mechanism that could explain these findings is evidence that at higher concentrations riluzole strongly (5) potentiated postsynaptic $GABA_A$ receptor function in cultured hippocampal neurons.[53] Commonly used anxiolytics such as benzodiazepines bind to and allosterically interact with $GABA_A$ receptors, which mediate most fast inhibitory neurotransmission in the CNS. Finally, and perhaps most exciting given recent pathophysiological hypotheses regarding mood disorders,[15] a recent report has suggested that riluzole (6) enhances glutamate uptake in rat astrocyte cultures.[54] By acting directly on astrocytic glutamate transporters at low riluzole concentrations, there was a significant increase in the rate of glutamate uptake by astrocytes, which quantitatively are the most important regulators of normal extracellular glutamate concentrations.[55-56] Thus, riluzole appears to confer neuroprotection and anticonvulsant activity through numerous mechanisms (Table 1).

**Table 1 – Reported mechanisms of action of riluzole**

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| 1. Inhibition of voltage-dependent sodium channels in mammalian CNS neurons |
| 2. Inhibition of vesicular presynaptic glutamate release |
| 3. Potentiation of AMPA/KA receptor-mediated neurotransmission |
| 4. Presynaptic inhibition of glutamate release through inactivation of P/Q-type calcium channels |
| 5. Potentiation (in high concentrations) of postsynaptic $GABA_A$ receptor function |
| 6. Enhancement of glutamate uptake into astrocytes |
| 7. Enhancement of brain-derived neurotrophic factor (BDNF) |

Our pilot studies found that 8 weeks of open-label riluzole treatment was effective in 18 patients with generalized anxiety disorder, of whom half had histories of dysthymia or MDD (Mathew et al, in press). Using $^1$H-MRS in the same sample, we also found that riluzole reversed glutamate-mediated impairments in neuronal plasticity by increasing N-acetyl-aspartate (NAA), a neuronal marker, in the left hippocampus. These neuroimaging findings are potentially consistent with preclinical reports of riluzole stimulation of brain derived neurotrophic factor (BDNF) synthesis in cultured mouse astrocytes.

Thus, riluzole might fundamentally alter disorder pathophysiology by enhancing neuronal resilience and plasticity. Inasmuch as a growing body of data suggests that mood and anxiety disorders are also associated with regional volumetric reductions, cell loss, and atrophy,[6] we have hypothesized that riluzole would be efficacious for mood disorders (and associated anxiety symptoms) due to reduced glutamate excitotoxicity and reversal of impairments in neurotrophic markers.[57]

### 4. Beyond NMDA: renewed interest in AMPA receptor potentiators

We have already seen that by increasing synaptic non-NMDA glutamatergic neurotransmission, as is the case with ketamine, rapid antidepressant effects are possible. AMPA receptors, which like NMDA receptors are involved in learning and memory, mediate the fast component of excitatory neurotransmission, and AMPA potentiation may result in rapid as well as subacute antidepressant efficacy. Several classes of compounds can allosterically modulate AMPA receptors. These compounds (so-called AMPA receptor positive modulators or AMPA receptor potentiators, ARPs) do not activate AMPA receptors themselves but slow the rate of receptor desensitization and/or deactivation in the presence of an agonist (e.g., glutamate and AMPA).[58-59] AMPAkines, a subclass of ARPs, are small benzamide compounds that allosterically produce positive modulation of AMPA receptors. Clinically, this drug class has been studied as add-on treatment to clozapine in patients with schizophrenia,[60] with consistent patterns of improvement in performance on tests of attention, memory, and distractibility. Preclinical work has shown that the biarylpropylsulfonamide AMPA receptor potentiators (LY392098 and LY451616) have antidepressant effects in animal models of depression (including the application of inescapable stressors, forced-swim test, and tail-suspension-induced immobility tests), in learned-helplessness models of depression, and in animals exposed to chronic mild stress.[61] In one of these pre-clinical studies, the AMPAkine Ampalex was reported to have more rapid effects (during the first week of treatment) than fluoxetine (after 2 weeks).[62]

There is also evidence that AMPA receptors appear responsive to chronic antidepressant treatment, consistent with neural adaptative mechanisms believed to underlie the therapeutic response to these treatments.[14] One group has reported that chronic antidepressant treatment increases the membrane expression of AMPA receptors in rat hippocampus.[63] In addition, chronic treatment with fluoxetine increased phosphorylation of the $Ser^{831}$-$GluR_1$ and $Ser^{845}$-$GluR_1$ sites of AMPA receptor in extracts of cortex, hippocampus, and striatum.[64] In contrast to traditional antidepressants, this group of compounds does not appear to affect the extracellular concentration of monoamines.[65] However, several studies have demonstrated that AMPA receptor activation can increase expression of BDNF both *in vitro* and *in vivo*.[66-68] In addition, LY392098, an AMPA receptor potentiator, increased BDNF mRNA in primary neuronal culture.[69]

Modulation of neurotrophic factor expression and alteration of the rate of neurogenesis may be critical factors that contribute to the understanding of the therapeutic effects of antidepressants and mood stabilizers in mood disorders.[1] In support of this notion, chronic treatment with the AMPA receptor potentiator LY451646 increased progenitor cell proliferation in the dentate gyrus in a dose-dependent manner. The antidepressant-like activity of ARPs in animals may be attributed, at least in part, to the regulation of cell proliferation in the hippocampus.[70] In summary, abundant preclinical evidence exists in support of AMPA receptor potentiation as a potential therapy for mood disorders. Based on these data, ongoing trials of novel AMPA receptor potentiators in severe mood disorders are underway.

## Conclusions

While the focus of this review has concerned the mood-enhancing aspects of glutamatergic drugs, it should be noted that enhancement of cognitive function is an important additional goal of antidepressant treatment. In that respect, the approaches described, particularly AMPA receptor potentiators, have promise in this area. It is well recognized that significant neuropsychological deficits occur in chronic mood disorders, including alterations in memory, attention, and executive functioning.

The question has been raised: Does allosteric modulation of AMPA receptors promote long-term changes in glutamatergic synaptic signaling and thereby facilitate memory encoding?[71] In humans, early studies showed that administration of pyrrolidinones, a class of AMPA receptor potentiator, improved cognition function in patients with schizophrenia and Parkinson's disease.[72-73] Studies with benzyolgpiperdines, another class of AMPA receptor potentiator, have shown enhanced recall in healthy subjects.[74] Clearly, the next step is to test these compounds in patients with mood disorders, with assessment of cognition after treatment.

Significant advances in psychopharmacology have been limited in the last few decades, likely due to poor understanding of the disease biology. It remains to be determined whether all patients with mood disorders will benefit from these glutamate-based approaches, or rather, only a selected subgroup. Identifying predictors of pharmacological response remains an important and active area of research, and tools from brain imaging and genetics will enable enhanced precision in identifying suitable candidate drugs for the individual patient with depression.

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