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REVIEW ARTICLE

Glutamate system as target for development of novel antidepressants

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Depression is a common psychiatric condition characterized by affective, cognitive, psychomotor, and neurovegetative symptoms that interfere with a person's ability to work, study, deal with interpersonal relationships, and enjoy once-pleasurable activities. After the serendipitous discovery of the first antidepressants, for years the only pharmacodynamic mechanisms explored in the search of novel antidepressants were those related to the 3 main monoamines: serotonin, norepinephrine, and dopamine. New-generation monoaminergic antidepressants, such as selective-serotonin and dual-acting serotonin/norepinephrine reuptake inhibitors, improved treatment and quality of life of depressed patients. Nevertheless, there are still important clinical limitations: the long latency of onset of the antidepressant action; side effects, which can lead to early discontinuation; low rate of response; and high rate of relapse/recurrence. Therefore, in the last several years, the focus of research has moved from monoamines toward other molecular mechanisms, including glutamatergic (Glu) neurotransmission. This review provides a comprehensive overview of the current knowledge on the Glu system and on its relationships with mood disorders. Up to now, N-methyl-D-aspartate (NMDA) receptor antagonists, in particular ketamine, provided the most promising results in preclinical studies and produced a consistent and rapid, although transient, antidepressant effect with a good tolerability profile in humans. Although data are encouraging, more double-blind, randomized, placebo-controlled trials are needed to clarify the real potentiality of ketamine, and of the other Glu modulators, in the treatment of unipolar and bipolar depression.

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FOCUS POINTS

- Current monoaminergic antidepressants have relevant clinical limitations, such as presence of side effects which can lead to early discontinuation, persistence of residual symptoms, low rates of remission, frequent relapses and long time for the onset of the antidepressant effect with increased suicide risk.
- There is preclinical and clinical support for glutamate involvement in the pathophysiology of depression.
- The high-affinity noncompetitive NMDA receptor antagonist Ketamine has shown rapid and consistent antidepressant and anti-suicidal effect.

Introduction

Depression is a common psychiatric condition characterized by affective, cognitive, psychomotor and neurovegetative symptoms, which more frequently include depressed mood; feelings of hopelessness, guilt, and worthlessness; irritability; restlessness; fatigue and decreased energy; anxious or empty feelings; difficulty concentrating and making decisions; alterations of sleep and appetite; and persistent aches, pains, and headaches. These symptoms interfere with a person's ability to work, study, deal with interpersonal relationships, and enjoy once-pleasurable activities.

New-generation antidepressants, and in particular selective serotonin (5-HT) reuptake inhibitors (SSRIs) and 5-HT norepinephrine (NE) reuptake inhibitors (SNRIs), are currently considered the first line pharmacological agents for the treatment of depression and are preferred to the older antidepressants.[1,2] Although the introduction of SSRIs and SNRIs has allowed us to improve the quality of life of depressed patients, especially in terms of side effects and tolerability, there are still relevant clinical limitations. Future-generation antidepressants should lack the side effects that more commonly lead to discontinuation, e.g., sexual dysfunctions and weight gain, and they should also have a faster onset of action, especially to avoid early discontinuations due to lack of efficacy and to more promptly reduce the risk of suicide.[3] Further, a subset of depressed patients does not respond to the available antidepressants or relapses after the initial response or

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remission, even if the drug is continued. In fact, although the treatment of depression has consistently improved during the last three decades, the prognosis of the disorder is far from being satisfactory, and depression remains one of the major causes of morbidity and disability worldwide.[4,5]

A number of strategies have been proposed recently in order to treat depressed patients who do not adequately respond to the standard treatment protocols, including augmentation or combination with lithium or atypical antipsychotics, combination of two antidepressants with different pharmacological actions, electroconvulsive therapy, transcranial magnetic stimulation, and deep brain stimulation. However, in some cases the results are promising, and in others they are disappointing.[6]

In parallel to the aforementioned novel treatment strategies, new lines of pharmacological research have been developed in order to discover novel antidepressant agents. For years, the only pharmacodynamic mechanisms that have been explored in the search of new antidepressants were those related to the 3 monoamines: 5-HT, NE, and dopamine (DA).[7] However, given the difficulties in finding strong evidence to support the postulated depression-related monoamine alterations, the focus of research moved from monoamines toward other molecular mechanisms, including glutamate (Glu) and melatonin neurotransmission, neuropeptide system (substance P, corticotrophin-releasing factor, neuropeptide Y, vasopressin and oxytocin, galanin, and melanin-concentrating hormone), glucocorticoids, opioid and cannabinoid receptors, and inflammatory and neurodegenerative pathways, as well as the intracellular processes involved in the signal transduction cascades.[8–12]

Among these new approaches, research on the Glu system, which is involved in several central nervous system (CNS) physiologic functions, including cognition, memory and learning, and in the modulation of neurogenesis and neurodegeneration, has led to the development of novel compounds that have been evaluated in both preclinical and clinical studies with different results.[13,14] N-Methyl-D-aspartate (NMDA) antagonists, for example, which are thought to be neuroprotective through the inhibition of voltage-gated cation channels and through the subsequent decrease of neurotransmitter release enhancing astrocyte uptake of extracellular Glu, seem to be very promising. Unfortunately, although the NMDA receptor antagonists have shown rapid and consistent antidepressant action, the presence of relevant psychomimetic side effects limits their use.[15] This narrative review aims to provide a comprehensive overview of the current knowledge on the relationships between the Glu system and mood disorders with a particular focus on preclinical and clinical implications. MEDLINE and PubMed databases were searched for English language articles using the keywords glutamate (Glu), antidepressants, depression, N-Methyl-D-aspartate (NMDA) antagonists, riluzole, and ketamine.

Glutamate Synthesis and Localization

The most abundant neurotransmitters in the CNS are two amino acids: Glu, which is the major excitatory neurotransmitter in the mammalian brain, and gamma-aminobutyric acid, which serves as the principle neurotransmitter for inhibitory transmission.[13] In the human brain, Glu is ubiquitous and is present at levels of 8–10 mmol/kg of brain tissue. Glu neurons project within the cortex and to subcortical regions, such as locus coeruleus, raphe nucleus, and substantia nigra, where they modulate monoaminergic systems. The Glu system is involved in several physiologic functions, including memory, learning and other cognitive tasks, modulation of neurogenesis/neurodegeneration, and induction of neuronal plasticity.[13]

Glu acts through the so-called tripartite glutamatergic synapse—an integrated neuronal-glial synapse that allows pre- and postsynaptic neurons and glia to interact with each other (Figure 1).[16] In particular, upon depolarization of the presynaptic neuron, vesicular Glu is released in a calcium-dependent manner into the synaptic cleft where it can bind to its receptors. Glu is removed from the extracellular space by excitatory amino acid transmembrane transporters (EAATs), which are located on glial cells and are responsible for protecting neurons from the detrimental effects of excessive synaptic levels of Glu. Within glial cells, Glu is recycled through a Glu/glutamine (Gln) metabolic cycle by the enzyme Gln synthetase into Gln, which, in turn, is transferred to the presynaptic neurons. Here, Gln is converted back into Glu and packaged into the presynaptic vesicles. In fact, within neurons, there are two primary kinds of Glu production: synthesis ex novo from glucose through transamination of the tricarboxylic acid cycle intermediate alpha-oxoglutatrate, and the conversion of Gln into Glu by glutaminase located in neuronal mitochondria (Figure 1).

Glutamate Receptors

Glu can bind two different kinds of receptors: ionotropic and metabotropic. Ionotropic receptors, which include α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), NMDA, and kainate receptors, are ligand-gated, nonselective cation channels that allow the flow of K^+, Na^+, and Ca^{2+}. The NMDA receptors play an important role in memory formation and neuroprotection. In particular, those located in the synapse modulate synaptic efficacy and promote pro-survival events, whereas the extrasynaptic NMDA receptors

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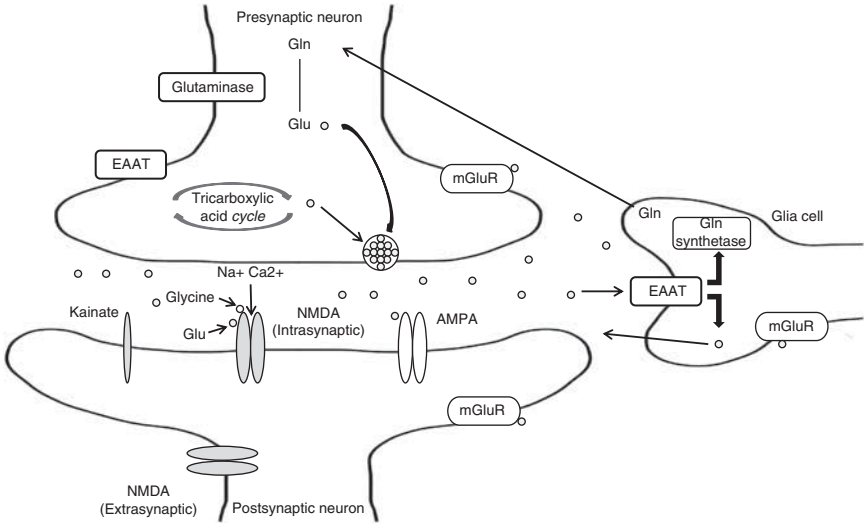

Figure 1. Glutamatergic synapse. **Glu:** Glutamate; **Gln:** glutamine; **mGluR:** metabotropic glutamate receptor; **EAAT:** excitatory amino acid transporter; **NMDA:** Nmethyl-D-aspartate; **AMPA:** α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; **Na+:** sodium; **Ca2+:** calcium ion.

are coupled to cell death pathways.[17,18] Under physiological conditions, Glu activates synaptic NMDA and AMPA receptors, with subsequent activation of intracellular signal transduction, which involves trophic downstream effectors, such as cyclic adenosine monophosphate response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF), and preserves neuronal viability. On the contrary, when Glu is overproduced, the activation of extrasynaptic NMDA receptors antagonizes the activated pathway by the synaptic receptors, and inhibits CREB and BDNF. The overstimulation of NMDA receptors leads to neurodegeneration through a process called excitotoxicity. In fact, in the presence of excessive levels of Glu, the overactivation of NMDA receptors, including the extrasynaptic ones, causes an excessive influx of Ca^{2+} into the postsynaptic neuron.[19] The excessive cytosolic Ca^{2+} concentrations, in turn, activate a number of cellular degradation processes, including proteases, lipases, nitric oxide synthase, and other enzymes that lead to cell death.[20] Excitotoxicity triggered by overstimulation of glutamate receptors also contributes to intracellular oxidative and nitrosative stress.[21]

Metabotropic Glu receptors (mGluR), which belong to the family of G protein-coupled receptors, are divided into three groups, with a total of eight subtypes. These receptors indirectly activate ion channels on the plasma membrane and can both increase or decrease the excitability of the postsynaptic neurons. In particular, group II mGluRs, which are present in pre- and postsynaptic neurons, are able to decrease NMDA receptor activity and the risk of cellular excitotoxicity.

Evidence Linking the Glutamate System to Mood Disorders

Since its identification as a neurotransmitter in 1959, Glu has been hypothesized to be involved in the pathophysiology of a number of neurological disorders, including epilepsy, stroke, Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's disease.[22] More recently, it has been suggested that alterations of Glu homeostasis may induce a generalized brain dysfunction that underlies various psychiatric conditions, including mood disorders.[23] The involvement of Glu in the pathophysiology of mood disorders was first hypothesized after the early reports describing the action of antidepressants on Glu receptors and the presence of elevated Glu concentrations in serum, plasma, and cerebrospinal fluid from patients with major depressive disorder (MDD).[24–28] However, other authors reported decreased Glu levels in cerebrospinal fluid of MDD subjects, or did not find alterations in the baseline Glu levels.[29–31] Controversial data have also come from neuroimaging studies, which have observed complex and regional differences in Glu neurotransmission. In fact, while increased Glu levels have been reported in the occipital cortex of 29 medication-free MDD patients,[32] decreased Glu levels in the anterior cingulate cortex of MDD patients were reported as well.[33–35] It seems that the MDD-related dysfunctions of Glu neurotransmission are more complex than the simplistic view of increase or decrease of the overall activity of the system.

Recent data from postmortem studies have supported the hypothesis that mood disorders are characterized by altered Glu receptor expression.[36]

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In fact, increased Glu levels and decreased mGluR2 or mGluR3 receptor levels have been observed in the prefrontal cortex of MDD patients,[37,38] and in the dorsolateral prefrontal cortex (DLPFC) of bipolar patients.[39] The glycine binding site, measured with [3H]CGP-39653, was found to be reduced in suicide victims.[40] Similarly, a significant decrease in the NMDA receptor density was reported in both bipolar and unipolar depression.[41,42] In particular, it seems that overstimulation with upregulation of the NMDA NR2A receptor subtype could play a relevant role in the pathophysiology of MDD.[43,44] However, whether these alterations are primary disturbances, epiphenomena, or consequences of the presence of the disorder remains to be clarified.

Other postmortem studies have shown decreased expression of Glu transporters EAAT1 and EAAT2 and of Glu synthetase in the frontal areas of MDD patients.[45,46] Similarly, decreased levels of EAAT3, EAAT4, and mRNA expression have been described in the striatum of patients with mood disorders.[47] Cortical glial cell loss and reduced glial density have been well-documented in patients with mood disorders.[48] The impairment of glial cell activity can lead to increased Glu system activation and neural toxicity, especially at extrasynaptic sites.[49] The excessive levels of extracellular Glu may trigger excitotoxicity processes and neurodegeneration; under conditions of Glu spillover, the activation of extrasynaptic group II mGlu receptors pathologically dampens the stimulated presynaptic release of Glu. The decreased synaptic availability of Glu, in turn, will cause lowered CREB activity and BDNF expression, with subsequent decrease of neuroplasticity and cellular resilience.[20,50]

Glutamate Receptor Ligands in the Treatment of Unipolar and Bipolar Depression

The involvement of the Glu system in the pathophysiology of mood disorders is also supported by preclinical and clinical evidence that has demonstrated that Glu receptor ligands have consistent and rapid antidepressant effects.[23]

Preclinical studies

Compounds that primarily impact Glu receptors such as NMDA receptor antagonists, mGlu receptor agonists and antagonists, and positive modulators of AMPA receptors have demonstrated antidepressant properties, with a potential common trophic downstream mechanism of action.[36,51,52]

NMDA receptor antagonists are a class of anesthetics that bind and inhibit the NMDA receptors, and that are used as inductors of dissociative anesthesia for animals and, less commonly, for humans. They have been classified into four categories: competitive antagonists, which block the binding site of the neurotransmitter Glu; glycine antagonists, which block the glycine site; noncompetitive antagonists, which inhibit NMDA receptors by binding to allosteric sites; and uncompetitive antagonists, which block the ion channel by binding to a site within it. NMDA receptor antagonists have shown antidepressant-like effects in animal models of depression, such as chronic mild stress, learned helplessness, footshock-induced aggression, and olfactory bulbectomy.[51] Although, in rodents, NMDA receptor antagonists have been found to cause neurotoxicity and brain damage (Olney lesions), such damage has never been reported in primates such as humans.[53]

In rats exposed to chronic mild stress, memantine, a low-affinity NMDA receptor antagonist, was reported to reverse anhedonia and increase adrenal gland weight, corticosterone levels, and BDNF protein concentrations in the prefrontal cortex.[54] In forced-swimming and open-field tests, both memantine and imipramine significantly reduced immobility time of rats, as compared to the control group, without affecting locomotor activity.[55]

Other preclinical studies using animal models of depression involved ketamine, a high-affinity, noncompetitive NMDA receptor antagonist. In rats exposed to chronic mild stress, treatment with ketamine reversed anhedonia-like behavior and increased adrenal gland weight, promoted regain of body weight, and normalized corticosterone and adreno cortico tropic hormone (ACTH) levels.[56] In addition, acute administration of ketamine and imipramine were compared in forced-swimming and open-field tests. Both ketamine and imipramine reduced immobility time, as compared to the control group, without affecting locomotor activity.[57] In another study, the co-administration of imipramine with ketamine was found to induce a more pronounced antidepressant effect than treatment with each antidepressant alone. In addition, ketamine induced stronger increases of CREB and BDNF protein levels in the prefrontal cortex, hippocampus, and amygdala, and a greater PKA and PKC phosphorylation in the hippocampus, amygdala, and prefrontal cortex.[58] The acute administration of ketamine at a high dose, but not imipramine, was found to increase BDNF levels in the rat hippocampus, which is considered crucial for the rapid onset of the antidepressant action induced by ketamine.[57] Other studies seem to show that the effect of ketamine is dependent on the activation of the BDNF/TrkB signaling pathway.[59] In particular, the fast antidepressant action of ketamine requires a rapid protein translation, which is the crucial step preceding the increase of dendritic BDNF levels. The eukaryotic

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elongation factor 2 kinase (eEF2K), a Ca2+/calmodulin–dependent serine/threonine kinase that phosphorylates eEF2 and modulates protein translation, has been proposed as the main molecular substrate involved in the rapid antidepressant effect of ketamine. In fact, the inhibition of NMDA receptors induced by ketamine leads to inhibition of eEF2 kinase and consequent dephosphorylation of eEF2 and increase of BDNF synthesis.[59]

As far as mGlu receptors ligands are concerned, there is evidence that mGlu receptor agonists have anxiolytic, antidepressant-like, and neuroprotective properties in animal models of depression.[60,61] Interesting results have also come from the research on group II mGlu receptor antagonists. In particular, MGS0039 was effective in the learned helplessness model of depression and led to enhanced hippocampal proliferation in mice.[62,63] In addition, LY341495, another group II mGlu receptor antagonist, was found to have antidepressant-like effects in a rat forced-swim test and in a mouse tail-suspension test.[64] Interestingly, the antidepressant-like effect of LY341495, as in the case of ketamine, seems to be related to the activation of the BDNF/TrkB signaling pathway. In fact, pre-treatment with K252a, a TrkB tyrosine kinase inhibitor, was found to block the sustained (more than 24 hours) antidepressant-like effect of LY341495.[65]

AMPA receptor-positive modulators are a novel class of drugs that includes a number of compounds, such as CX-516, cyclothiazide, piracetam, aniracetam, and LY392098. They do not activate AMPA receptors themselves, but decrease the rate of receptor desensitization and deactivation in the presence of an agonist.[66,67] These compounds have demonstrated antidepressant-like effects, either in monotherapy or as adjunctive treatment, in animal models of depression, including exposure to inescapable stressors, the forced-swim test, the tail-suspension/induced-immobility test, and learned helplessness models.[68]

Clinical studies

In humans, ketamine has shown consistent and rapid, although transient, antidepressant effect after a single intravenous injection (0.5 mg/Kg) in two placebo-controlled studies carried out in MDD patients (Table 1).[69,70] In fact, the antidepressant effect occurred within 110 minutes after injection and lasted for about 1 week.[70] Euphoria and psychotomimetic side effects were observed acutely, but were temporally distinct from the improvement of depressive symptoms, which persisted for 1 week. In another study, carried out in 10 treatment-resistant MDD patients who received between 1 and 6 injections of ketamine over a 12-day period, the response criterion [a decrease of 50% or more from the baseline total score of the Montgomery-Asberg Depression Rating Scale (MADRS)] was met by 90% of patients after the first infusion, and it remained stable up to the end of the treatment.[71] The decrease of MADRS scores after the last ketamine infusion was of 85%. After the end of the treatment, 8 of 9 patients relapsed after 19 days (mean), ranging between 6 and 45 days, but 1 patient remained antidepressant-free for >3 months.

In addition, there is evidence that ketamine can be useful in the treatment of bipolar depression (Table 1).[72–75] In a randomized, placebo-controlled, double-blind, crossover, add-on study, 18 treatment-resistant, bipolar depressed patients treated with mood stabilizers received an intravenous infusion of either ketamine or placebo; depressive symptoms significantly improved in subjects who received ketamine, as compared with placebo, and the improvement of depression, which occurred within 40 minutes from the intravenous infusion of ketamine, remained significant up to the third day.[72] Ketamine was generally well tolerated; the most frequent adverse effect was dissociative symptoms at the 40-minute point. This result was replicated by subsequent work of the same group of researchers, which involved 15 bipolar I or II depressed patients treated with mood stabilizers. A single intravenous infusion of ketamine led to a rapid (within 40 minutes) and robust improvement of depressive symptoms, which was also accompanied by the resolution of suicidal ideation.[73] Similarly, in another study, which was carried out in 33 MDD patients, a single ketamine infusion was able to dramatically reduce suicidal ideation within 40 minutes, and the improvement lasted for up to 4 hours post-infusion.[76] In a more recent study, 25 bipolar depressed subjects taking mood stabilizing drugs were treated with a single ketamine infusion. More than 50% of subjects responded to treatment, and about 50% achieved remission after 14 days. These data support the potential of ketamine infusion as add-on therapy to mood stabilizers in bipolar depression resistant to current antidepressants.[74] In addition, a report has recently been conducted on two patients with bipolar II disorder who responded to intramuscular (i.m.) ketamine augmentation.[75] The first patient was treated with 50 mg i.m. every 4 days for 5 months until she relapsed; then, the dose was increased to 70 mg every 4 days, and she remained asymptomatic for another 4 months. Similarly, the second patient showed a long-term good response to i.m. ketamine, which remained effective for several months and was well tolerated; the main adverse effects were moderate anxiety, irritability, dissociative feelings, and headache.

Other data supporting the antidepressant properties of ketamine come from research regarding

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Table 1. *Summary of open-label and randomized-controlled trials on the efficacy of ketamine in the treatment of depression*

Author	Design of the study	Diagnosis	Subjects N	Ketamine	Main findings
Berman *et al* (2000)[69]	Double-blind, randomized, placebo-controlled	MDD	7	Single dose 0.5 mg/kg i.v.	Significant improvement of depressive symptoms within 72 h after ketamine but not placebo.
Zarate *et al* (2006)[70]	Double-blind, randomized, crossover, placebo-controlled	Treatment-resistant MDD	18	Single dose 0.5 mg/kg i.v.	Significant improvement of depression within 110 min after ketamine, as compared with placebo. Of the 17 subjects treated with ketamine, 71% met response and 29% met remission criteria the day following ketamine infusion. 35% of subjects maintained response for at least 1 week.
Okamoto *et al* (2010)[77]	ECT, open-label, vs propofol	Treatment-resistant MDD	31	Single dose 0.8 mg/kg i.v.	Significantly earlier and greater improvement of depression in patients where ketamine was used as anesthetic.
aan het Rot *et al* (2010)[71]	12 days, open-label	Treatment-resistant MDD	10	Repeated doses 0.5 mg/kg i.v.	90% of patients responded after the first infusion and remained stable up to the end of the treatment. After the end of treatment, 8 of 9 patients relapsed after 19 days (mean), ranging between 6 and 45 days, but 1 patient remained antidepressant-free for >3 months.
Diazgranados *et al* (2010)[72]	Double-blind, randomized, crossover, placebo-controlled, add-on	Bipolar disorder	18	Single dose 0.5 mg/kg i.v.	Significant improvement of depressive symptoms within 40 min in subjects receiving ketamine, as compared with placebo. The improvement of depression remained significant up to the third day. Most frequent adverse effect was dissociative symptoms at the 40-min point.
DiazGranados *et al* (2010)[76]	Open-label	MDD	33	Single dose 0.5 mg/kg i.v.	Suicidal ideation decreased significantly on the SSI within 40 min; the decrease remained significant through the first 4 h post-infusion. Depression, anxiety, and hopelessness were significantly improved at all time points.
Ibrahim *et al* (2011)[91]	4-week, double-blind, riluzole vs placebo after ketamine i.v.	Treatment-resistant MDD	42	Single dose 0.5 mg/kg i.v.	Significant improvement of depression from baseline after ketamine infusion. 27% of responders had not relapsed by 4 weeks with an average time to relapse of 13.2 days. No difference was detected between the riluzole and placebo treatment groups.
Zarate *et al* (2012)[73]	Double-blind, randomized, crossover, placebo-controlled, add-on	Bipolar I or II disorder	15	Single dose 0.5 mg/kg i.v.	Significant improvement of depressive symptoms within 40 min in subjects receiving ketamine as compared with placebo. The improvement remained significant through day 3. Rapid improvement of suicidal ideation. The most common side effect was dissociative symptoms at the 40-min time point.
Wang *et al* (2012)[78]	ECT, double-blind, randomized, vs propofol	Treatment-resistant MDD	48	Single dose 0.8 mg/kg i.v.	Patients where ketamine was used as anesthetic, alone or in combination, showed an earlier and higher improvement of the HDRS total scores, as compared with those treated with propofol alone

MDD: Major Depressive Disorder; i.v.: intravenous; ECT: electroconvulsive therapy; HDRS: Hamilton Depression Rating Scale; SSI: Scale for Suicide Ideation.

electroconvulsive therapy (ECT) (Table 1). In one study, 31 inpatients with treatment-resistant MDD were assigned to receive propofol or ketamine as anesthetic and underwent 8 ECT sessions. The Hamilton Depression Rating Scale (HDRS) scores, which were evaluated before ECT and after the second, fourth, sixth, and eighth ECT sessions, improved significantly earlier in the ketamine group, which suggests the possible contribution of ketamine in the resolution of depression.[77] In a more recent ECT study, 48 MDD patients were randomly divided into 3 groups: a propofol group, a ketamine group, and a propofol plus ketamine group. Patients treated with ketamine, alone or in combination, showed an earlier and higher improvement of the HDRS total scores, as compared with those treated with propofol alone.[78] In addition, in 30 patients with treatment-resistant MDD, a significant positive correlation was found between the baseline pattern of slow wave activity of the first two non-REM episodes (as revealed by the delta sleep ratio) and the improvement of depression after a single open-label infusion of ketamine.[79]

Among the other NMDA receptor antagonists, the low-affinity noncompetitive memantine (oral dose) did not show any antidepressant effect.[80] In fact, it seems that the extent of the affinity for NMDA receptors, as well as the method of administration, are fundamental for the antidepressant action of NMDA antagonists.

Riluzole (2-amino-6-trifluoromethoxy benzothiazole) is a neuroprotective drug that is the only FDA-approved medication for amyotrophic lateral sclerosis. In open-label studies, riluzole has shown antidepressant efficacy in patients with treatment-resistant MDD[81,82] and bipolar depression.[83,84] More recently, among 26 drug-free MDD patients who received a single ketamine injection, 17 (65%) met the response criteria (50% reduction from baseline on the MADRS) after 24 hours and 14 patients (54%) met the response criteria after 72 hours. These latter patients were enrolled in a 32-day, randomized, double-blind, placebo-controlled, flexible-dose continuation trial of riluzole (100–200 mg/d). Unfortunately, no significant differences in the time-to-relapse between riluzole and placebo groups were detected.[85]

Conclusion

The pharmacological treatment of MDD is far from being satisfactory, and its optimization remains one of the major challenges worldwide for researchers in the field of psychopharmacology. Current monoaminergic antidepressants have relevant clinical limitations, including the presence of side effects that can lead to early discontinuation, persistence of residual symptoms, low rates of remission, frequent relapses, and long time for the onset of the antidepressant effect with increased suicide risk.

Glu is the major excitatory neurotransmitter in the mammalian brain, where it is involved in several physiologic functions, including cognition, memory, and learning, and in the modulation of neurogenesis and neurodegeneration. While Glu system abnormalities have been found in mood disorders, a number of compounds acting at this level, including NMDA receptor antagonists, mGlu receptor agonists and antagonists, and positive modulators of AMPA receptors, have been produced and tested in animals and in humans.

The high-affinity noncompetitive NMDA receptor antagonist ketamine, which has shown rapid and consistent antidepressant action with a good tolerability profile in both preclinical and clinical studies, is the compound that showed the most promising results. The preferential blockade by ketamine of extrasynaptic NMDA receptors, which promotes excitotoxicity and decreases cellular resilience, may account for its neuroprotective and antidepressant action.[86] However, several factors need to be considered in interpreting the clinical data on the use of NMDA receptor antagonists, in particular ketamine, in the treatment of unipolar and bipolar depression. Although there are several case reports[75,87,88] and some open-label studies,[71,76,77] the number of double-blind, randomized, placebo-controlled trials (Table 1) is scarce and presents several limitations. First, the sample sizes of most of these studies, which are relatively small, limited the statistical power of the analyses and the strength of the results. Second, the transitory dissociative disturbances developed by patients treated with ketamine may have compromised the study blinding, potentially confounding the results. Future studies should take into account the difficulty in maintaining the study blinding, and both raters and patients should be evaluated in order to clarify the strength of the blinding. Another factor that needs to be considered is that the patients involved in these studies are usually affected by treatment-resistant mood disorders, and the results may not be generalizable to patients with different forms of depression.

Overall, the clinical data on the effectiveness of ketamine in the treatment of unipolar and bipolar depression are promising. A single dose (0.5 mg/Kg i.v.) of ketamine seems to produce a rapid and consistent antidepressant and anti-suicidal effect that has not been reported with the current antidepressant. However, the length of mood improvement after a single dose of ketamine remains to be clarified, as well as the efficacy and tolerability of repeated administrations for the long-term maintenance of recurrent unipolar and bipolar depression. Further double-blind, randomized, placebo-controlled/active comparator studies, involving larger samples of patients possibly in long-term treatment, are needed to better understand the real

clinical potential of ketamine and the other NMDA receptor antagonists in the treatment of mood disorders.

In addition, given their acute psychotomimetic side effects, selective subtype NMDA receptor antagonists, such as those binding the NR2B receptor subtype, deserve to be investigated.[89] The NR2B receptor antagonist Ro 25-6981, for example, showed antidepressant-like properties in the forced swim test with good tolerability.[90] From a safety perspective, this compound has not been associated with brain damage (vacuolization) in rodents, in contrast to the reversible vacuolization at high doses observed with other NMDA receptor antagonists, such as ketamine and dizocilpine.[53]

Finally, preclinical neurobiological data demonstrated that the rapidity of the antidepressant action of ketamine may be linked to the activation of the BDNF/TrkB signaling pathway with subsequent increase of BDNF levels in the hippocampus.[59] In particular, a rapid protein translation, which results in the increase of hippocampal BDNF levels, seems to be crucial to having the fast antidepressant action. The main molecular substrate involved in this effect is the eEF2K, which phosphorylates eEF2 and modulates protein translation. This molecule, as well as other intracellular substrates involved in the BDNF/TrkB signaling pathway and in the physiology of the tripartite Glu synapse, may provide molecular targets for the development of novel fast-action antidepressants.

References

1. Davidson JR. Major depressive disorder treatment guidelines in America and Europe. *J Clin Psychiatry*. 2010; **71**: e04.
2. Gelenberg AJ. A review of the current guidelines for depression treatment. *J Clin Psychiatry*. 2010; **71**(7): e15.
3. Stahl MS. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 3rd ed. New York: Cambridge University Press; 2008.
4. Kessler RC, Berglund P, Demler O. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003; **289**(23): 3095–3105.
5. World Health Organization. Data and Statistics. http://www.who.int/research/en. Accessed September 16, 2010.
6. Vieta E, Colom F. Therapeutic options in treatment-resistant depression. *Ann Med*. 2011; **43**(7): 512–530.
7. Kintscher U. Reuptake inhibitors of dopamine, noradrenaline, and serotonin. *Handb Exp Pharmacol*. 2012; **209**: 339–347.
8. Catena-Dell'Osso M, Marazziti D, Rotella F, Bellantuono C. Emerging targets for the pharmacological treatment of depression: focus on melatonergic system. *Curr Med Chem*. 2012; **19**(3): 428–437.
9. Paschos KA, Veletza S, Chatzaki E. Neuropeptide and sigma receptors as novel therapeutic targets for the pharmacotherapy of depression. *CNS Drugs*. 2009; **23**(9): 755–772.
10. Marazziti D, Catena Dell'Osso M, Consoli G, Baroni S. Second messenger modulation: a novel target of future antidepressants? *Curr Med Chem*. 2009; **16**(35): 4679–4690.
11. Catena-Dell'Osso M, Bellantuono C, Consoli G, *et al*. Inflammatory and neurodegenerative pathways in depression: a new avenue for antidepressant development? *Curr Med Chem*. 2011; **18**(2): 245–255.
12. Marazziti D, Catena-Dell'Osso M. The role of oxytocin in neuropsychiatric disorders. *Curr Med Chem*. 2008; **15**(7): 698–704.
13. Coyle JT, Leski ML, Morrison JH. The diverse roles of L-glutamic acid in brain signal transduction. In: Davis KL, Charney D, Coyle JT, Nemeroff C, eds. *Neuropsychopharmacology: The Fifth Generation of Progress*. Nashville, TN: American College of Neuropsychopharmacology/Lippincott Williams & Wilkins; 2002: 71–90.
14. Zarate CA, Machado-Vieira R, Henter I, *et al*. Glutamatergic modulators: the future of treating mood disorders? *Harv Rev Psychiatry*. 2010; **18**(5): 293–303.
15. Preskorn SH, Baker B, Kolluri S, *et al*. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J Clin Psychopharmacol*. 2008; **28**(6): 631–637.
16. Machado-Vieira R, Manji HK, Zarate CA. The role of the tripartite glutamatergic synapse in the pathophysiology and therapeutics of mood disorders. *Neuroscientist*. 2009; **15**(5): 525–539.
17. Manev H, Favaron M, Guidotti A, Costa E. Delayed increase of Ca2+ influx elicited by glutamate: role in neuronal death. *Mol Pharmacol*. 1989; **36**(1): 106–112.
18. Markowitz AJ, White MG, Kolson DL, Jordan-Sciutto KL. Cellular interplay between neurons and glia: toward a comprehensive mechanism for excitotoxic neuronal loss in neurodegeneration. *Cellscience*. 2007; **4**(1): 111–146.
19. Dubinsky JM. Intracellular calcium levels during the period of delayed excitotoxicity. *J Neurosci*. 1993; **13**(2): 623–631.
20. Hardingham GE, Bading H. The yin and yang of NMDA receptor signalling. *Trends Neurosci*. 2003; **26**(2): 81–89.
21. Vanhoutte P, Bading H. Opposing roles of synaptic and extrasynaptic NMDA receptors in neuronal calcium signalling and BDNF gene regulation. *Curr Opin Neurobiol*. 2003; **13**(3): 366–371.
22. Javitt DC, Zukin SR. The role of excitatory amino acids in neuropsychiatric illness. *J Neuropsychiatry Clin Neurosci*. 1990; **2**(1): 44–52.
23. Machado-Vieira R, Salvadore G, Ibrahim I, Diaz-Granados N, Zarate CA. Targeting glutamatergic signaling for the development of novel therapeutics

for mood disorders. *Curr Pharm Des*. 2009; **15**(14): 1595–1611.
24. Kim JS, Schmid-Burgk W, Claus D, Kornhuber HH. Increased serum glutamate in depressed patients. *Arch Psychiatr Nervenkr*. 1982; **232**(4): 299–304.
25. Altamura CA, Mauri MC, Ferrara A, *et al*. Plasma and platelet excitatory amino acids in psychiatric disorders. *Am J Psychiatry*. 1993; **150**(11): 1731–1733.
26. Mauri MC, Ferrara A, Boscati L, *et al*. Plasma and platelet amino acid concentrations in patients affected by major depression and under fluvoxamine treatment. *Neuropsychobiology*. 1998; **37**(3): 124–129.
27. Levine J, Panchalingam K, Rapoport A, *et al*. Increased cerebrospinal fluid glutamine levels in depressed patients. *Biol Psychiatry*. 2000; **47**(7): 586–593.
28. Mitani H, Shirayama Y, Yamada T, *et al*. Correlation between plasma levels of glutamate, alanine and serine with severity of depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; **30**(6): 1155–1158.
29. Frye MA, Tsai GE, Huggins T, Coyle JT, Post RM. Low cerebrospinal fluid glutamate and glycine in refractory affective disorder. *Biol Psychiatry*. 2007; **61**(2): 162–166.
30. Francis PT, Poynton A, Lowe SL, *et al*. Brain amino acid concentrations and Ca2+-dependent release in intractable depression assessed antemortem. *Brain Res*. 1989; **494**(2): 315–324.
31. Maes M, Verkerk R, Vandoolaeghe E, Lin A, Scharpe S. Serum levels of excitatory amino acids, serine, glycine, histidine, threonine, taurine, alanine and arginine in treatment-resistant depression: modulation by treatment with antidepressants and prediction of clinical responsivity. *Acta Psychiatr Scand*. 1998; **97**(4): 302–308.
32. Sanacora G, Gueorguieva R, Epperson CN, *et al*. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry*. 2004; **61**(7): 705–713.
33. Auer DP, Putz B, Kraft E, *et al*. Reduced glutamate in the anterior cingulate cortex in depression: an in vivo proton magnetic resonance spectroscopy study. *Biol Psychiatry*. 2000; **47**(4): 305–313.
34. Mirza Y, Tang J, Russell A, *et al*. Reduced anterior cingulate cortex glutamatergic concentrations in childhood major depression. *J Am Acad Child Adolesc Psychiatry*. 2004; **43**(3): 341–348.
35. Hasler G, van der Veen JW, Tumonis T, *et al*. Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch Gen Psychiatry*. 2007; **64**(2): 193–200.
36. Zarate CA Jr, Du J, Quiroz J, *et al*. Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: role of the glutamatergic system. *Ann N Y Acad Sci*. 2003; **1003**: 273–291.
37. Scarr E, Pavey G, Sundram S, MacKinnon A, Dean B. Decreased hippocampal NMDA, but not kainate or AMPA receptors in bipolar disorder. *Bipolar Disord*. 2003; **5**(4): 257–264.
38. Hashimoto K, Sawa A, Iyo M. Increased levels of glutamate in brains from patients with mood disorders. *Biol Psychiatry*. 2007; **62**(11): 1310–1316.
39. Beneyto M, Meador-Woodruff JH. Lamina-specific abnormalities of AMPA receptor trafficking and signaling molecule transcripts in the prefrontal cortex in schizophrenia. *Synapse*. 2006; **60**(8): 585–598.
40. Nowak G, Ordway GA, Paul IA. Alterations in the N-methyl-D-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. *Brain Res*. 1995; **675**(1–2): 157–164.
41. Nudmamud-Thanoi S, Reynolds GP. The NR1 subunit of the glutamate/NMDA receptor in the superior temporal cortex in schizophrenia and affective disorders. *Neurosci Lett*. 2004; **372**(1–2): 173–177.
42. McCullumsmith RE, Kristiansen LV, Beneyto M, *et al*. Decreased NR1, NR2A, and SAP102 transcript expression in the hippocampus in bipolar disorder. *Brain Res*. 2007; **1127**(1): 108–118.
43. Boyce-Rustay JM, Holmes A. Genetic inactivation of the NMDA receptor NR2A subunit has anxiolytic and antidepressant-like effects in mice. *Neuropsychopharmacology*. 2006; **31**(11): 2405–2414.
44. Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov*. 2008; **7**(5): 426–437.
45. Choudary PV, Molnar M, Evans SJ, *et al*. Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. *Proc Natl Acad Sci U S A*. 2005; **102**(43): 15653–15658.
46. Valentine GW, Sanacora G. Targeting glial physiology and glutamate cycling in the treatment of depression. *Biochem Pharmacol*. 2009; **78**(5): 431–439.
47. McCullumsmith RE, Meador-Woodruff JH. Striatal excitatory amino acid transporter transcript expression in schizophrenia, bipolar disorder, and major depressive disorder. *Neuropsychopharmacology*. 2002; **26**(3): 368–375.
48. Rajkowska G, Miguel-Hidalgo JJ. Gliogenesis and glial pathology in depression. *CNS Neurol Disord Drug Targets*. 2007; **6**(3): 219–233.
49. Soriano FX, Hardingham GE. Compartmentalized NMDA receptor signalling to survival and death. *J Physiol*. 2007; **584**(2): 381–387.
50. Hardingham GE. Pro-survival signalling from the NMDA receptor. *Biochem Soc Trans*. 2006; **34**(5): 936–938.
51. Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci*. 2003; **1003**: 250–272.
52. Owen RT. Glutamatergic approaches in major depressive disorder: focus on ketamine, memantine and riluzole. *Drugs Today (Barc)*. 2012; **48**(7): 469–478.
53. Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science*. 1989; **244**(4910): 1360–1362.
54. Réus GZ, Abelaira HM, Stringari RB, *et al*. Memantine treatment reverses anhedonia, normalizes corticosterone levels and increases BDNF levels in the prefrontal cortex

induced by chronic mild stress in rats. *Metab Brain Dis*. 2012; **27**(2): 175–182.
55. Réus GZ, Stringari RB, Kirsch TR, *et al*. Neurochemical and behavioural effects of acute and chronic memantine administration in rats: further support for NMDA as a new pharmacological target for the treatment of depression? *Brain Res Bull*. 2010; **81**(6): 585–589.
56. Garcia LS, Comim CM, Valvassori SS, *et al*. Ketamine treatment reverses behavioral and physiological alterations induced by chronic mild stress in rats. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; **33**(3): 450–455.
57. Garcia LS, Comim CM, Valvassori SS, *et al*. Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; **32**(1): 140–144.
58. Réus GZ, Stringari RB, Ribeiro KF, *et al*. Ketamine plus imipramine treatment induces antidepressant-like behavior and increases CREB and BDNF protein levels and PKA and PKC phosphorylation in rat brain. *Behav Brain Res*. 2011; **221**(1): 166–171.
59. Monteggia LM, Gideons E, Kavalali ET. The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. *Biol Psychiatry*. In press. DOI: 10.1016/j.biopsych.2012.09.006.
60. Palucha A, Tatarczynska E, Branski P, *et al*. Group III mGlu receptor agonists produce anxiolytic- and antidepressant-like effects after central administration in rats. *Neuropharmacology*. 2004; **46**(2): 151–159.
61. Li X, Need AB, Baez M, Witkin JM. Metabotropic glutamate 5 receptor antagonism is associated with antidepressant-like effects in mice. *J Pharmacol Exp Ther*. 2006; **319**(1): 254–259.
62. Yoshimizu T, Shimazaki T, Ito A, Chaki S. An mGluR2/3 antagonist, MGS0039, exerts antidepressant and anxiolytic effects in behavioral models in rats. *Psychopharmacology (Berl)*. 2006; **186**(4): 587–593.
63. Yoshimizu T, Chaki S. Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039. *Biochem Biophys Res Commun*. 2004; **315**(2): 493–496.
64. Chaki S, Yoshikawa T, Hirota S, *et al*. MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity. *Neuropharmacology*. 2004; **46**(4): 457–467.
65. Koike H, Fukumoto K, Iijima M, Chaki S. Role of BDNF/TrkB signaling in antidepressant-like effects of a group II metabotropic glutamate receptor antagonist in animal models of depression. *Behav Brain Res*. 2013; **238**: 48–52.
66. Black MD. Therapeutic potential of positive AMPA modulators and their relationship to AMPA receptor subunits: a review of preclinical data. *Psychopharmacology (Berl)*. 2005; **179**(1): 154–163.
67. Bleakman D, Lodge D. Neuropharmacology of AMPA and kainate receptors. *Neuropharmacology*. 1998; **37**: 1187–1204.
68. Zarate CA, Singh JB, Manji HK. Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. *Biol Psychiatry*. 2006; **59**(11): 1006–1020.
69. Berman RM, Cappiello A, Anand A, *et al*. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000; **47**(4): 351–354.
70. Zarate CA, Singh JB, Carlson PJ, *et al*. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006; **63**(8): 856–864.
71. aan het Rot M, Collins KA, Murrough JW, *et al*. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry*. 2010; **67**(2): 139–145.
72. Diazgranados N, Ibrahim L, Brutsche NE, *et al*. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010; **67**(8): 793–802.
73. Zarate CA Jr, Brutsche NE, Ibrahim L, *et al*. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry*. 2012; **71**(11): 939–946.
74. Rybakowski JK, Permoda-Osip A, Skibinska M, Adamski R, Bartkowska-Sniatkowska A. Single ketamine infusion in bipolar depression resistant to antidepressants: are neurotrophins involved? *Hum Psychopharmacol*. In press. DOI: 10.1002/hup.2271.
75. Cusin C, Hilton GQ, Nierenberg AA, Fava M. Long-term maintenance with intramuscular ketamine for treatment-resistant bipolar II depression. *Am J Psychiatry*. 2012; **169**(8): 868–869.
76. DiazGranados N, Ibrahim LA, Brutsche NE, *et al*. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2010; **71**(12): 1605–1611.
77. Okamoto N, Nakai T, Sakamoto K, *et al*. Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression: comparing ketamine and propofol anesthesia. *J ECT*. 2010; **26**(3): 223–227.
78. Wang X, Chen Y, Zhou X, *et al*. Effects of propofol and ketamine as combined anesthesia for electroconvulsive therapy in patients with depressive disorder. *J ECT*. 2012; **28**(2): 128–132.
79. Duncan WC Jr, Selter J, Brutsche N, Sarasso S, Zarate CA Jr. Baseline delta sleep ratio predicts acute ketamine mood response in major depressive disorder. *J Affect Disord*. In press. DOI: 10.1016/j.jad.2012.05.042.
80. Zarate CA, Singh JB, Quiroz JA, *et al*. A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am J Psychiatry*. 2006; **163**(1): 153–155.
81. Zarate CA, Payne JL, Quiroz J, *et al*. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry*. 2004; **161**(1): 171–174.
82. Sanacora G, Kendell SF, Levin Y, *et al*. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biol Psychiatry*. 2007; **61**(6): 822–825.

83. Zarate CA, Payne JL, Singh J, *et al*. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry*. 2004; **56**(1): 54–60.
84. Zarate CA, Quiroz JA, Singh JB, *et al*. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry*. 2005; **57**(4): 430–432.
85. Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. *Int J Neuropsychopharmacol*. 2010; **13**(1): 71–82.
86. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. 2012; **338**(6103): 68–72.
87. Liebrenz M, Stohler R, Borgeat A. Repeated intravenous ketamine therapy in a patient with treatment-resistant major depression. *World J Biol Psychiatry*. 2009; **10**(4 pt 2): 640–643.
88. Messer M, Haller IV, Larson P, Pattison-Crisostomo J, Gessert CE. The use of a series of ketamine infusions in two patients with treatment-resistant depression. *J Neuropsychiatry Clin Neurosci*. 2010; **22**(4): 442–444.
89. Zarate CA, Charney DS, Manji HK. Searching for rational anti-N-methyl-D-asparte treatment for depression. *Arch Gen Psychiatry*. 2007; **64**(9): 1100–1101.
90. Maeng S, Zarate CA, Du J, *et al*. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry*. 2007; **63**(4): 349–352.
91. Ibrahim L, Diazgranados N, Luckenbaugh DA, *et al*. Rapid decrease in depressive symptoms with an N-methyl-d-aspartate antagonist in ECT-resistant major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; **35**(4): 1155–1159.