HHS Public Access

Author manuscript

Curr Behav Neurosci Rep. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Curr Behav Neurosci Rep. 2015 December ; 2(4): 198–208. doi:10.1007/s40473-015-0050-5.

Novel Glutamatergic Treatments for Severe Mood Disorders

Minkyung Park, MD, **Mark J. Niciu, MD, PhD**, and **Carlos A. Zarate Jr., MD**

Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD U.S.A., 20892

Abstract

All currently approved antidepressant medications for major depressive disorder (MDD) and bipolar disorder act primarily on the monoaminergic system and have varying affinities for serotonergic, norepinephrine-ergic, and/or dopaminergic receptors. Unfortunately, these drugs are only effective in approximately two-thirds of patients. Glutamate is the major excitatory neurotransmitter in the central nervous system, and the glutamatergic system has been implicated in the pathophysiology of MDD. Here, we review the putative involvement of the glutamate receptor subtypes—N-methyl-D-aspartate (NMDA), α-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid (AMPA), kainate, and the group I, II, and III metabotropic glutamate receptors (mGluRs)—in the development of novel and more effective treatments for MDD as well as preclinical and clinical trials of drugs targeting these receptors. The rapid and robust antidepressant effects of ketamine—an NMDA receptor antagonist—have been consistently replicated in multiple trials. Other glutamatergic drugs have been investigated with varying success. Here, we highlight some of the most interesting results, including: 1) repeated oral, intramuscular, and sublingual ketamine appears to be less robustly effective than intravenous ketamine, but also causes fewer significant adverse effects; 2) the glycine partial agonist GLYX-13 appears to be effective both as monotherapy and adjunctive treatment in the treatment of MDD. An oral analogue, NRX-1074, is currently under investigation; and 3) mGluR modulators targeting mGluR5 have demonstrated convincing preclinical results.

Keywords

mood disorders; glutamate; N-methyl-D-aspartate (NMDA); antagonist; metabotropic positive allosteric modulator; negative allosteric modulator

Correspondence: Dr. Carlos A. Zarate, Jr., 10 Center Drive, CRC, Unit 7 Southeast, Room 7-5342, Bethesda, Maryland, 20892, Tel. (301) 451-0861, FAX (301) 480-8792, zaratec@mail.nih.gov.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

Conflict of Interest

Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIA-MH002857-10), by a NARSAD Independent Investigator Award to Carlos A. Zarate, and by a Brain and Behavior Mood Disorders Research Award to Carlos A. Zarate. A patent for the use of ketamine in depression has been awarded that lists Carlos A. Zarate among the inventors; he has assigned his rights on the patent to the U.S. government, but will share a percentage of any royalties that may be received by the government. Minkyung Park and Mark J. Niciu have no conflict of interest to disclose, financial or otherwise.

Introduction

Major depressive disorder (MDD) is the most common psychiatric disorder in developed countries, with an estimated prevalence of nearly 17% [1, 2]. In 2004, the World Health Organization (WHO) ranked it third among the leading causes of global disease burden [3]. Currently available conventional antidepressants, which target monoamines (dopamine, norepinephrine, and/or serotonin), unfortunately have low rates of treatment response. While one-third of MDD patients respond to these agents, approximately two-thirds will respond only after trying several classes of antidepressants. Such patients display treatment-resistant depression (TRD); its definition has evolved to encompass failure to respond to at least two antidepressants from different pharmacological classes and of adequate dose and duration [4].

In the early 1990s, a seminal rodent behavioral despair model study of depression first demonstrated that the N-methyl-D-aspartate (NMDA) receptor complex played a major role in antidepressant action [5]. Nearly a decade later, the first report of rapid antidepressant effects associated with the NMDA receptor antagonist ketamine in patients with MDD (n=7) was published [6]. Since 2006, when ketamine began to be systematically studied [7]—particularly in TRD—the number of studies investigating ketamine as well as other glutamatergic modulators in MDD has multiplied exponentially. Here, we review the classification and characteristics of central glutamate receptors and current hypotheses regarding how NMDA receptor antagonism results in rapid and robust antidepressant response. This paper also briefly reviews novel developments with regard to ketamine for the treatment of mood disorders, and describes recent preclinical and clinical studies of various glutamate receptor modulators in the treatment of TRD.

Classification and Characteristics of Glutamate Receptors

Glutamate is the most abundant excitatory amino acid neurotransmitter in the central nervous system. Glutamate receptors have historically been divided into two classes—ionotropic and metabotropic—based on their biochemical properties and functions (see Figure 1) [8]. Ionotropic receptors include NMDA, α-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid (AMPA), and kainate receptors. Metabotropic receptors (mGluRs) are categorized into three groups (group I, group II, and group III). All ionotropic glutamate receptors are located postsynaptically, so agonist binding at these receptors results in local excitation and the generation of action potential. The NMDA receptor primarily fluxes Ca^{2+} when activated by the binding of the obligatory co-agonists glutamate and glycine. On the other hand, AMPA and kainate receptors are primarily Na^{+} flux channels activated by the binding of glutamate only. mGluRs differ from ionotropic receptors in that they are also located presynaptically. The group I mGluRs are mostly postsynaptic, while groups II and III have predominantly presynaptic localization. Group I mGluRs include mGluR1 and mGluR5, group II mGluRs include mGluR2 and mGluR3, and group III mGluRs include mGluR4, 6, 7, and 8. All are G-protein coupled receptors that produce intracellular action through downstream signal transduction/secondary messenger cascades and, hence, often result in slower and longer lasting modulatory tone.

In contrast to ionotropic receptors, the net effect of mGluR activation can be either excitatory or inhibitory. Group I receptor stimulation generally enhances glutamatergic neurotransmission while group II and II receptors dampen excitatory tone. In theory, glutamatergic signaling can be modulated by regulating postsynaptic signaling, presynaptic glutamate release, or synaptic glutamate concentrations [9]. These actions can be accomplished by designing drugs that 1) directly activate the receptors; 2) change the available synaptic concentrations of natural ligands such as glutamate, glycine (or D-serine), or other ions; or 3) change the affinity and efficacy of the receptors to their natural ligands. Drugs that elicit these actions include NMDA receptor antagonists, NMDA receptor subunit (especially NR2B) antagonists, NMDA receptor glycine-site partial agonists, group I and II mGluR antagonists, and negative allosteric modulators (NAMs); all have been studied in clinical trials for MDD.

Two main hypotheses—largely drawn from the preclinical literature—are thought to explain why NMDA receptor antagonism has rapid and robust antidepressant effects. The first hypothesis proposes that the primary event is NMDA receptor blockade on cortical gamma aminobutyric acid (GABA)ergic interneurons that normally provide tonic inhibitory tone on cortical excitatory pyramidal output neurons. The antagonism at these receptors, therefore, would decrease inhibitory tone [10] with the net result of increased excitatory glutamate release, AMPA receptor activation, and downstream synaptogenesis and dendritic remodeling [11]. These changes have been associated with antidepressant effects in pre-clinical behavioral models [12, 13]. The second hypothesis suggests that the downstream action of direct NMDA antagonism is the inactivation of eukaryotic elongation factor (eEF2) kinase. eEF2 kinase is required to activate eEF2, which then stimulates local protein translation and release in dendrites, including brain-derived neurotrophic factor (BDNF). This increase in BDNF is then associated with synaptogenesis and neurogenesis [10, 14–16] (see Figure 2).

Drugs Targeting Ionotropic Glutamate Receptors

NMDA receptor non-competitive antagonists

Ketamine—Ketamine has been used safely for decades as a dissociative anesthetic. Since 2000, several clinical trials have demonstrated ketamine's rapid and robust antidepressant effects in MDD. One study found that a single subanesthetic ketamine infusion (0.5mg/kg) for 40 minutes resulted in a 14-point decrease in Hamilton Depression Rating Scale (HAM-D) score 72 hours post-infusion [6]. Another study noted that the same dose of ketamine was associated with a 71% response rate and a 29% remission rate within 24 hours [7]. The initial pioneering studies were associated with several concerns, including the integrity of a saline solution placebo, the abuse potential of ketamine, and difficulties in translation to real world use. However, subsequent trials addressed some of these concerns (see below).

Murrough and colleagues addressed the issue of integrity of the blind by substituting the inert saline with a psychoactive placebo [17]. Midazolam was used because of its rapid sedative and anxiolytic effects. It should be noted, however, that the blinding was not perfect because midazolam does not induce the same dissociative, psychotomimetic, and hemodynamic effects as ketamine. Patients had a greater antidepressant response to

ketamine than midazolam (64% vs. 28%, respectively) 24 hours post-infusion. The time response curve over the course of the week was nearly identical to that observed with earlier ketamine studies [17].

Initial studies noted that antidepressant response to a single ketamine infusion—though robust—was transient, lasting approximately up to one week in responders. Furthermore, the neurotoxic effects of chronic exposure to ketamine and other NMDA antagonists (e.g. phencyclidine (PCP)), raised concerns regarding the safety of repeated ketamine infusions and/or its long-term use. One study investigated 24 unmedicated patients with TRD who received six repeated ketamine infusions (0.5mg/kg over 40 minutes) over 12 days. At the end of two weeks, the response rate among patients was 70.8 % [18], and only mild and transient side effects were associated with the repeated infusions. Mean time to relapse after the last infusion was 18 days but, in about 30% of responders, antidepressant response lasted until the end of the naturalistic observation phase (83 days after the last infusion). Another open-label study of 13 MDD patients receiving six ketamine infusions noted similar results [19]. Eleven subjects (92%) responded to ketamine and 60% remitted. Of the responders, six subjects relapsed, on average 16 days after the last infusion (range seven to 28 days). Four weeks after the last infusion, five patients had still not relapsed. In addition, visual and working memory performance was also improved [19]. When the same amount of total ketamine was infused at a lower concentration for a longer period of time (0.3mg/kg over 100 minutes), the side effect profile did not worsen significantly (although there was no side-by-side comparison with the typical ketamine dose to confirm this) [20]. Another study looked at weekly vs. biweekly ketamine infusions (0.5mg/kg × 40 minutes) over six weeks (six infusions vs. three infusions, total) [21]. In 28 medicated patients with MDD and bipolar (BD) depression, remission rates of 29% and 14%, respectively, were observed with no added cognitive difficulties [21]. During the six-month naturalistic follow-up, a broad range in time-to-relapse was observed (approximately 70 days). Finally, in a dose-finding, placebo-controlled, pilot study of four TRD subjects, two patients experienced an antidepressant response to 0.1mg/kg of ketamine infused over two to five minutes; both relapsed within one week [22]. The higher ketamine dose was associated with greater antidepressant response, and infusion over two minutes was associated with elevated psychotomimetic side effects compared to the longer infusion.

In terms of clinical practice, ketamine infusions are labor- and resource-intensive, which may render them impractical in many clinical psychiatric settings, particularly office-based private practice. Less intensive modes of administration are therefore an attractive alternative. Intranasal [23], intramuscular [24], sublingual [25], and oral [26–29] alternatives have all been explored. In a randomized, double-blind, crossover study of intranasal ketamine (50mg) versus saline, 20 MDD patients showed a seven-point reduction in mean Montgomery Åsberg Depression Rating Scale (MADRS) score at 24 hours post-inhalation [23]. Intranasal ketamine produced only minor hemodynamic, dissociative, and psychotomimetic effects. However, no antidepressant effects were noted compared to placebo 72 hours post-administration.

Intramuscular ketamine has 93% bioavailability compared to intravenous ketamine, and a small study of two female patients found that it had dose-dependent antidepressant effects

[30]. In another case series, two patients with BD-II depression achieved symptom reduction for four to six months after intravenous ketamine followed by repeated intramuscular injections (from 32–100mg/kg every three to four days over several months) [24]. Side effects included irritability, headaches, nightmares, and dissociation. Complications associated with chronic ketamine abuse (e.g. increased intracranial pressure, muscle rigidity, or cystitis) were not observed [24].

Sublingual ketamine has 30% bioavailability compared to intravenous ketamine. In 27 depressed MDD and BD outpatients, variable administration (every two to seven days) of add-on, escalating dose sublingual ketamine had antidepressant effects in 20 patients (77%) [25]. Sublingual ketamine was well tolerated, with no reported psychotomimetic effects; the most common side effect was transient lightheadedness.

Only two small cases studies of oral ketamine—whose bioavailability is approximately 20% of intravenous ketamine's—have been conducted [27]. Eight depressed hospice patients received oral ketamine (0.5mg/kg) for 28 days and reported significant antidepressant and anxiolytic effects [28]. A major limitation of the aforementioned studies with alternative modes of administration is that ketamine levels, as well as levels of bioactive metabolites such as hydroxynorketamine, were not measured and/or reported. Such indicators are critical for contrasting the results with those from intravenous infusions.

Esketamine—Esketamine (S-enantiomer of ketamine) has two- to three-fold higher potency than racemic (R- and S-) ketamine [31]. At the 2014 International College of Neuropharmacology meeting, Janssen presented results from a double-blind, randomized, placebo-controlled trial of intravenous esketamine (0.2mg/kg vs 0.4mg/kg vs placebo) in 30 TRD patients. Both doses of esketamine had similar antidepressant effects (0.2mg/kg: −16.8 MADRS points over two days vs 0.4mg/kg: −16.9 MADRS points) in contrast to a mean 3.8 point reduction on the MADRS for individuals receiving placebo. Although not compared head-to-head, the results with esketamine were equivalent to those obtained with the racemic mixture. Common side effects included headache, nausea, and dissociation. The prevalence and severity of these side effects were not reported. As with the racemic mixture, oral esketamine's clinical utility may be hampered by its poor oral bioavailability. Intranasal esketamine is undergoing current clinical trials for safety and efficacy in TRD (clinicaltrials.gov identifier: NCT01998958).

Nitrous oxide—Nitrous oxide (N_2O) is an inhaled general anesthetic commonly used in dentistry and obstetrics due to its ability to non-competitively inhibit NMDA receptors. In a double-blind, placebo-controlled, crossover study, 20 patients with TRD received a one-hour inhalation of 50% N_2O or 50% nitrogen as placebo [32]. Compared to placebo, N_2O at both two hours (−4.8 points, $p=0.002$) and 24 hours (− 5.5 points, $p<0.001$) post-inhalation significantly improved outcome as assessed by the primary depression measure, the 21-item HAM-D. Adverse effects included nausea/vomiting, headache, and anxiety. Although no standardized scale was administered to evaluate psychotomimetic effects, none of the participants subjectively reported these symptoms. It should be noted, however, that as with the ketamine studies, 50% nitrogen gas may be an inadequate placebo, given that N_2O causes acute euphoria and has a sweet smell and taste not found in nitrogen gas. N_2O's

antidepressant efficacy was not as robust as that of intravenous ketamine; specifically, N_2O was associated with a 20% response rate and a 15% remission rate 24 hours post-inhalation, compared with response and remission rates of 71% and 29%, respectively, for ketamine [7]. Nevertheless, this trial adds credence to the idea that NMDA receptor antagonism is a major mechanism of action in rapid antidepressant response. In addition, N_2O has a broad mechanism of action similar to that of ketamine. As an example, N_2O induces corticotropin-releasing hormone, which activates opioidergic neurons, and indirectly inhibits GABAergic interneurons [33].

Dextromethorphan—Like ketamine and N_2O, dextromethorphan is a non-competitive NMDA receptor antagonist. One 12-week randomized, double-blinded, placebo-controlled trial of dextromethorphan as adjunctive therapy studied 309 subjects with BD taking valproic acid and 123 healthy subjects. No significant group differences were seen between groups as assessed by mean Young Mania Rating Scale (YMRS) score and HAM-D score [34]. Interestingly, blood concentrations for the group receiving 60 mg/day of dextromethorphan were 65.2±15.1 ng/mL, which is equivalent to 0.24 μM; however, studies have reported that 4 μM peripheral dextromethorphan is required to occupy 50% of central NMDA receptors [35], suggesting that the negative result may have been attributable to insufficient blood concentration. Another retrospective chart review of 22 patients with either BD-II or BD not otherwise specified (BD-NOS) found that the addition of 20 mg dextromethorphan and 10 mg quinidine (a cytochrome 2D6 inhibitor) once or twice daily to the current medication regimen significantly improved Clinical Global Impression (CGI) score by 1.66 (1=slightly improved, 2=much improved) [36]. This dextromethorphan-quinidine combination, Nuedexta, which is approved for the treatment of pseudobulbar affect, is now being studied for TRD (ClinicalTrials.gov identifier: NCT01882829). No published studies have explored dextromethorphan as depression monotherapy.

Memantine—Memantine is an FDA-approved treatment for moderate-to-severe Alzheimer's-like dementia. Clinical and preclinical studies of memantine for the treatment of depression, however, have shown mixed results. One eight-week, double-blind, placebo-controlled study of MDD patients found that memantine (5–20 mg/day) did not separate from placebo on the primary antidepressant measure [37]. In another eight-week, randomized, placebo-controlled trial of 31 MDD outpatients, adjunctive memantine (5–20mg/day) did not separate from placebo on the primary outcome measure, the MADRS [38]. In contrast, a three-year, naturalistic, mirror-image assessment of 30 BD patients found that adjunctive memantine (20–30mg/day) significantly decreased total time spent manic or depressed, decreased global severity of symptoms, shortened duration of illness, and reduced number of episodes per year [39]. Finally, an *in vitro* electrophysiological study found that memantine, unlike ketamine, did not phosphorylate eEF2 kinase or augment BDNF production. As noted previously, both are hypothesized to be major mechanisms of antidepressant action in NMDA receptor antagonists [40].

Lanicemine (AZD6765)—The proprietary low-trapping NMDA receptor antagonist lanicemine has been and continues to be studied in TRD. A randomized, placebo-controlled, crossover study found that a single infusion of lanicemine 150mg resulted in a 32% response

rate (7/22) as compared to 15% (3/22) for placebo [41]. Lanicemine was not associated with increased psychosis or dissociation, but its antidepressant effect was transient; it separated from placebo only at 80 minutes and 110 minutes post-infusion. In a three-week, placebo-controlled trial, six repeated infusions of lanicemine (100mg or 150mg) adjunctive to current treatment had significant antidepressant effects without ketamine-like side effects [42]. However, in a six-week phase IIb study, repeated-dose (50mg and 150mg) lanicemine failed to separate from placebo (39% placebo response rate at trial end) [43].

Subunit-Selective (NR2B) NMDA Receptor Antagonists

The NMDA receptor complex is a tetramer composed of two GluN1 (NR1) subunits and two GluN2 (NR2) subunits. The pharmacological and biophysical properties of the NMDA receptor are largely controlled by the NR2 subunit [44]. Glutamate binds to NR2 while glycine or D-serine binds to the NR1 and NR3 subunits [45, 46]. In an *in vivo* study of GluN2B knockout in cortical principal neurons, mice showed depression-like behaviors in the tail suspension and open field tests. These knockout mice also did not respond to ketamine; mammalian target of rapamycin (mTOR) signaling and synaptic protein synthesis were also blocked in the knockout mice [47]. Interestingly, a statistically significant difference in the rs1805502 polymorphism was noted within *GRIN2B*, the gene encoding GluN2B (NR2B), in a study looking at 178 subjects with TRD, 612 subjects with non-TRD, and 779 healthy controls [48]. Several NR2B subunit selective antagonists (reviewed below) have been explored in the treatment of MDD.

Ro 25-6981—In rodents exposed to unpredictable foot shock for 21 days, Ro 25-6981 injection reversed despair-like behaviors, as assessed via the sucrose preference test and novelty suppressed feeding test, which are thought to mirror symptoms of anhedonia and anxiety [13]. To date, no published clinical trials of Ro 25-6981 in MDD have been conducted.

Traxoprodil (CP101-606)—In a randomized, double-blind, placebo-controlled study, the intravenous NR2B selective antagonist CP-101606 had significant antidepressant effects (60% response rate compared to 20% in the placebo group), and 78% of treatment responders maintained this antidepressant effect for at least one week [49]. Unfortunately, further development of the drug was stopped due to potential cardiovascular toxicity (specifically, QTc prolongation). CP-101606 has also demonstrated PCP-like reinforcing effects in preclinical models of drug discrimination and self-administration and, hence, abuse potential [50].

MK-0657—The oral NR2B antagonist MK-0657 (4–8 mg/day) was tested for antidepressant efficacy in a randomized, double-blind, placebo-controlled, cross-over pilot study. Only five of 21 planned subjects completed the study because the drug manufacturer discontinued its production. MK-0657 monotherapy had antidepressant effects only on the secondary outcome measures, and no psychotomimetic side effects were reported [51]. Cerecor continues to develop this compound under the name CERC-301. Recently, a randomized, double-blind, placebo-controlled sequential parallel study of adjunctive

CERC-301 was completed in patients with severe depression and recent active suicidal ideation (ClinicalTrials.gov identifier: NCT01941043); these results are not yet available.

NMDA receptor glycine site modulators

As mentioned above, the NMDA receptor requires co-agonist binding of glutamate and glycine for its activation. Glycine and D-serine bind to NR1 and NR3 while glutamate binds to NR2.

D-cycloserine (DCS)—DCS, a broad-spectrum antibiotic, is a partial agonist at the NMDA receptor's glycine site and a functional NMDA receptor antagonist at doses ≥100mg/day [52]. In an initial six-week, placebo-controlled, cross-over trial of 250mg/day as adjunctive treatment in TRD, DCS failed to separate from placebo ($p=0.51$) [53]. The same group recruited more patients ($n=26$) into their study to assess the efficacy of escalating-dose DCS (up to 1000mg/day) [54]. Indeed, high-dose DCS had significant antidepressant effects as measured by the HAM-D ($p=0.005$) and self-reported Beck Depression Inventory (BDI) ($p=0.046$). It was well tolerated and caused no psychotomimetic effects. An eight-week, open-label trial of DCS in patients with schizophrenia or BD, followed by a six-week, double-blind, placebo-controlled study is ongoing (ClinicalTrials.gov identifier: NCT02304432). This study is specifically looking at subjects who have four copies of the glycine decarboxylase gene mutation that results in unusually low baseline glycine levels [55]. The study will explore both the clinical effectiveness of DCS as well as the effects of this mutation on glycine metabolism in the brain.

GLYX-13—GLYX-13 is a glycine site partial agonist with a short half-life (seven minutes) that readily crosses the blood-brain barrier. In preclinical studies, both peripheral administration and direct infusion of GLYX-13 into the medial prefrontal cortex had antidepressant-like effects without psychotomimetic effects. During a placebo-controlled safety and efficacy trial of GLYX-13, 33 unmedicated TRD inpatients were randomized. Subjects who received 5mg/kg or 10mg/kg of GLYX-13 displayed a significant antidepressant response while those who received either 1mg/kg or 30mg/kg did not separate from the placebo group [56]. The manufacturers of GLYX-1, Naurex Inc., will be conducting an open-label extension study for 36 weeks to examine the potential long-term side effects of repeated GLYX-13 infusion in individuals with MDD (ClinicalTrials.gov identifier: NCT02192099).

NRX-1074—This compound is an analogue of GLYX-13 that is reportedly several thousand-fold more potent at the NR1 glycine partial agonist site with potentially minimal CNS side effects [57]. A randomized, double-blind, placebo-controlled efficacy and safety study of single dose of intravenous NRX-1074 is currently ongoing (Clinicaltrials.gov identifier: NCT02067793), and there are plans to develop this compound for oral administration.

AMPA receptor agonists

As discussed above, ketamine's antidepressant efficacy is hypothesized to occur via glutamate-induced AMPA receptor stimulation with downstream effects on signal

transduction/second messenger cascades and transcription/translation of synaptic and neurogenic proteins [58]. Pretreating rodents with the AMPA receptor antagonist NBQX mitigated the antidepressant-like effects of ketamine, MK-801 (another noncompetitive NMDA receptor antagonist), and Ro 25-6981 (an NR2B subunit-selective antagonist) [59–63]. One of the potential benefits of AMPA receptor modulators is that they likely lack the psychotomimetic and dissociative side effects observed with direct NMDA receptor antagonists. Despite the substantial amount of evidence from preclinical studies that AMPA receptor activation is implicated in ketamine's rapid antidepressant response, few positive clinical findings exist. This may be because: 1) AMPA receptors are heterogeneous, due to the combination of various subunits (GluR1-4); 2) they are further diversified by splice variants; and 3) posttranslational modifications and the presence of accessory proteins make it difficult to create in vitro models in the laboratory [64].

ORG-26576—ORG-26576 is an AMPA receptor positive allosteric modulator (PAM) that demonstrated a dose-dependent antidepressant response in a small (n=30), randomized, placebo-controlled trial [65]. Although the medication groups (100mg bid or 400mg bid) showed greater change from MADRS baseline relative to placebo, the results were highly variable and there was no consistent pattern of response in drug vs. placebo groups throughout the 28-day period. Nevertheless, the higher ORG-26576 dose was associated with improved information processing speed and executive functioning.

Drugs Targeting Metabotropic Glutamate Receptors

The available drugs that modulate mGluRs are often allosteric modulators that change the affinity of natural ligands. As these modulators typically "fine-tune" receptor activity, one would theoretically expect fewer side effects than those associated with full agonist or antagonist binding [66].

Group I mGluR NAMs

mGluR5 is extrasynaptically/perisynaptically localized at postsynaptic densities, and its activation potentially limits excitotoxic glutamate synaptic spillover. In mood disorders research, mGluR5 has been preferentially targeted over mGluR1 receptors because mGluR5 concentrations are positively correlated with NMDA receptor levels and because these two receptor groups are linked by a variety of intracellular mechanisms, thus allowing for indirect modulation of the NMDA receptor by mGluR5 manipulation [9, 67, 68]. One study found that MDD patients had less mGluR5 binding in vivo as well as fewer mGluR5 proteins in postmortem brain than healthy subjects [69]. mGluR5 also regulates AMPA receptor internalization [70]. A 14-day administration of 10mg/kg 2-methyl-6-(phenylethynyl)-pyridine (MPEP) [71, 72] increased BDNF mRNA levels in the hippocampus but not in the cortex of Wistar adult male rats, thus suggesting that mGluR5 antagonism may be linked to BDNF production [73]. 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) also exhibited anxiolytic and antidepressant-like activity in preclinical rodent models of despair [74–76].

AZD2066—A three-arm (placebo, duloxetine 30–60mg/day, and the oral mGluR5 antagonist AZD2066 12–18 mg/day) randomized trial recruited 131 depressed patients, but

the study was terminated prematurely. The preliminary findings revealed no beneficial results on the primary outcome (MADRS), depression response, or depression remission (ClinicalTrials.gov identifier: NCT01145755).

Ro4917523 (Basimglurant, RG7090)—In the first completed phase II trial (NCT00809562), Ro4917523 monotherapy (at five different doses to assess safety and tolerability) was compared to oral placebo in a 10-day inpatient TRD protocol. To our knowledge, the results of this initial study have not been reported. A completed phase IIb study compared modified-release basimglurant (0.5 and 1.5 mg/day) to placebo as an adjunctive medication over nine weeks in individuals with TRD (six weeks double-blind treatment, three weeks post-treatment follow-up) [77]. Subjects (N=333) were randomized to three treatment arms (n=108 adjunctive placebo, n=112 adjunctive basimglurant 0.5mg/day, n=111 adjunctive basimglurant 1.5mg/day). Two were excluded from the study due to the emergence of mania. No statistically significant differences were observed on the primary endpoint (mean MADRS change from baseline to six weeks). However, the placebo response rate was 47%, which is well above the 40% reported in other adjunctive MDD trials as a threshold that impedes separation [78]. Keeping this high placebo response rate in mind, higher dose basimglurant positively affected several secondary endpoints, including patient self-reported depression scores and CGI scale scores. The most common adverse events were dizziness (23%) and two self-resolving cases of mania at the 1.5mg/day dose.

Group II mGluR NAM/antagonists

Glutamate has the strongest affinity for group II mGluRs [9]. These receptors are mainly presynaptic with perisynaptic localization [79]. Thus, they are only activated in the presence of excessive synaptic glutamate/spillover from neighboring synapses. Both mGluR2/3 antagonists and NAMs have been studied for the treatment of MDD in preclinical models [80, 81].

The mGluR2/3 NAM Ro4491533 [82] was found to have antidepressant-like efficacy in preclinical models of depression. In a mouse model of despair, the mGluR2/3 NAM Ro4432717 reversed some of the prototypical cognitive impairments that may also be observed in MDD (eg, short-term memory deficits and cognitive inflexibility) [83]. An initial clinical trial assessing the safety and tolerability of mGluR2/3 modulators (BCI-838, BCI-632) was completed in healthy volunteers, but results are not yet available (ClinicalTrials.gov identifiers: NCT01546051, NCT01548703).

Group III mGluR PAMs

Group III mGluRs include mGluR 4,6,7, and 8 and are predominantly located presynaptically. mGluR7 is the most abundant mGluR in the central nervous system [84]. mGluR7 null mice exhibited a resilient phenotype in standard preclinical depression and anxiety-provocation paradigms [85]. mGluR7 mRNA expression in the suprapyramidal portion of the dentate gyrus was significantly higher in stress-sensitive Wistar Kyoto rats compared to control (Sprague-Dawley) rats [86].

AMN082—AMN082, an mGluR7 PAM, showed dose-dependent antidepressant activity in the tail-suspension test in C57BL6 male mice. Furthermore, this particular study showed that AMN082 exerted its antidepressant effects by modulating AMPA and NMDA receptor phosphorylation in the hippocampus [87]. AMN082 also increased synaptic protein levels (synapsin I and GluR1, which is an AMPA receptor subunit) and mTOR phosphorylation in the prefrontal cortex of male Sprague Dawley rats, suggesting synaptogenesis as a major antidepressant mechanism of action [88]. AMN082 had no antidepressant effect in mGluR7 knockout mice, further supporting the importance of glutamatergic neurotransmission in its antidepressant properties. Two studies, however, suggest that the mechanism of action of AMN082 involves serotonin rather than glutamate; specifically, *N*-benzhydrylethane-1,2-diamine (Met-1) is a major metabolite of AMN082 that has monoaminergic affinity [89, 90]. To date, no compounds with a primary action at mGluR7 have been investigated in clinical trials for neuropsychiatric disorders.

Conclusion

Preclinical and clinical data support the use of NMDA receptor antagonists, NR2B subunit-selective antagonists, NMDA receptor glycine site partial agonists, AMPA receptor agonists, and mGluR NAMs/PAMs as possible novel therapeutics for mood disorders. It is interesting to note that, despite almost 25 years of preclinical and 15 years of clinical efficacy data, ketamine is not often considered in treatment algorithms for refractory depression. In part this is due to the lack of large, multi-site, randomized, and psychoactive placebo-controlled trials assessing ketamine's safety, efficacy, and tolerability. In light of the proven clinical success of ketamine, alternative routes of ketamine administration and safety and tolerability studies with repeated dosing are absolutely critical to its continued development.

It is also important to emphasize that high-quality clinical efficacy data are currently available only for ketamine. Studies of other NMDA receptor antagonists and non-NMDA receptor modulators are either just entering clinical studies, are supported by very small datasets, or have been marked by negative results. One hypothesis for this preferential success is that ketamine's antidepressant efficacy requires increased synaptic glutamate release and the activation of AMPA receptors. As a result, glutamate modulators that do not increase synaptic glutamate release and/or activate non-NMDA receptors would likely not have antidepressant activity in clinical trials. In addition, ketamine has been found to activate second messenger/signal transduction cascades that other glutamatergic modulators do not, and this may also be responsible for its differential antidepressant efficacy. As noted above, one example of this is the preclinical report of ketamine's ability to phosphorylate eEF2 and increase local BDNF production; in contrast, the glutamatergic modulator memantine did not have these cellular and molecular effects [40].

It should also be noted that some leading investigators have questioned the importance of glutamate in ketamine's antidepressant mechanism of action and have hypothesized that non-glutamatergic—for instance, monoaminergic, cholinergic, or opioidergic—mechanisms may contribute significantly to ketamine's antidepressant efficacy in clinical studies [91]. Other more selective glutamate modulating drugs may not have these off-target effects. Nevertheless, without results from head-to-head clinical studies comparing ketamine and

other glutamatergic modulators, no compelling conclusions can be drawn for any of the above hypotheses.

Moving forward, one must keep in mind that depression is a heterogeneous illness and, therefore, that well-characterized patient populations or subtypes of patient populations should be studied when testing the effectiveness of any novel drug. Nevertheless, as this article has underscored, recent developments in the search for new, rapid-acting antidepressant agents hold considerable promise for developing new treatments for mood disorders. In addition to being urgently needed, these novel findings have revolutionized the field, challenged old paradigms and current limitations, and brought hope to those who must live with these devastating disorders.

Acknowledgments

Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIA-MH002857-10), by a NARSAD Independent Investigator Award to CAZ, and by a Brain and Behavior Mood Disorders Research Award to CAZ. The authors thank the 7SE research unit and staff for their support, Ioline Henter for outstanding editorial assistance, and Matthew H. Sieber, PhD for help with the figures.

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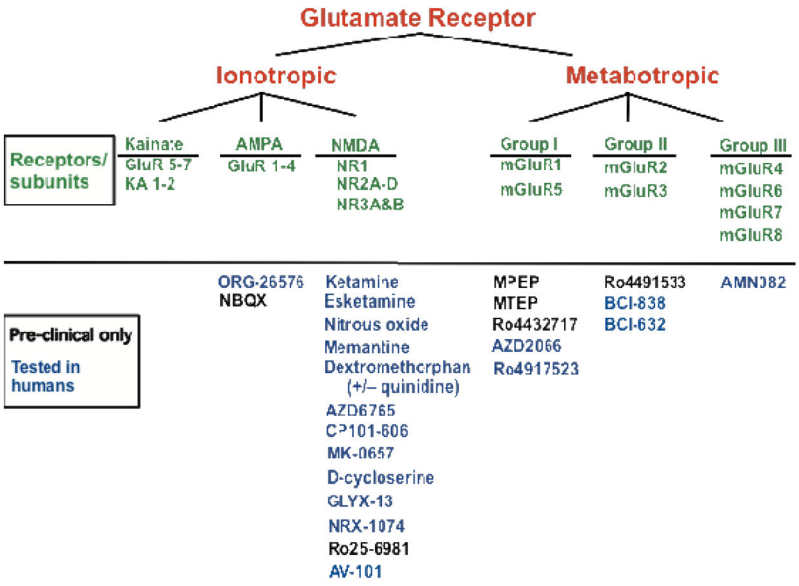

Figure 1.
Glutamate Receptor Subtypes and Novel Drugs

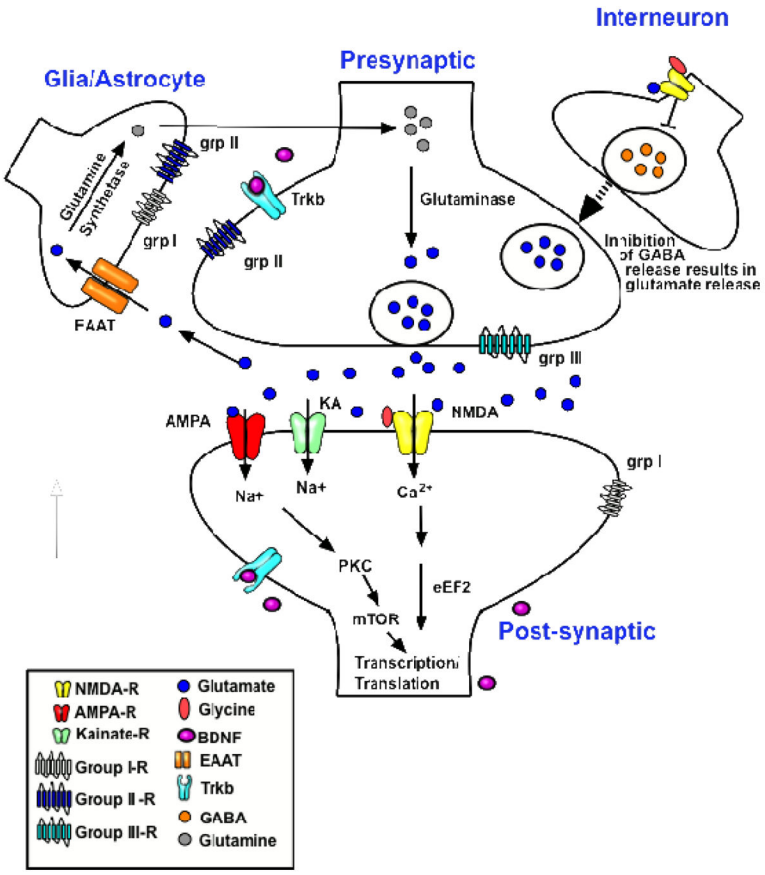

Figure 2.

Hypothesized Mechanisms of Action of Glutamate in Treatment-Resistant Depression (TRD)