Glutamatergic Modulators in Depression

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Abstract: Both preclinical and clinical studies have implicated glutamatergic system dysfunction in the pathophysiology of mood disorders such as bipolar depression and major depressive disorder. In particular, rapid reductions in depressive symptoms have been noted in response to subanesthetic doses of the glutamatergic modulator ketamine in subjects with major depressive disorder or bipolar depression. These results have prompted the repurposing or development of other glutamatergic modulators, both as monotherapy or adjunctive to other therapies. Here, we highlight the evidence supporting the antidepressant effects of various glutamatergic modulators, including (1) broad glutamatergic modulators (ketamine, esketamine, dextromethorphan, dextromethorphan-quinidine [Nuedexta], AVP-786, nitrous oxide [N$_2$O], AZD6765), (2) subunit (NR2B)-specific N-methyl-D-aspartate (NMDA) receptor antagonists (CP-101,606/traxoprodil, MK-0657 [CERC-301]), (3) glycine-site partial agonists (D-cycloserine, GLYX-13, sarcosine, AV-101), and (4) metabotropic glutamate receptor modulators (AZD2066, RO4917523/basimglurant, JNJ40411813/ADX71149, R04995819 [RG1578]).

Keywords: AMPA receptor, bipolar disorder, major depressive disorder, NMDA receptor, treatment

M ajor depressive disorder (MDD) and bipolar disorder (BD) are highly prevalent worldwide and leading causes of disability. Unfortunately, therapeutic options for MDD patients are associated with variable treatment response that is difficult to predict. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that only about one-third of MDD patients achieved remission after an adequate trial with a traditional antidepressant,[1] underscoring the notion that currently available antidepressants are not effective for most MDD patients. The situation is similar for the treatment of bipolar depression. A number of treatments are available for the manic phase of the illness, particularly antiepileptic agents, but few effective treatments exist for bipolar depression.[2] A large, 26-week study found that antidepressant use did not benefit patients with BD-I or BD-II depression;[3] furthermore, many patients with bipolar depression also experience partial remission, where depressive symptoms persist despite the use of medications.[4] For both MDD and BD, currently available therapeutics are often poorly tolerated or associated with a delayed onset of action of several weeks. This significant latency period increases the risk of suicide and is an important public health issue.[5]

The glutamatergic system is an important target for developing new treatments in mood disorders. Glutamate receptor subtypes include the ionotropic receptors, which are ligand-gated ion channels that open when an agonist binds to them (N-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], and kainite receptors), and the eight G-protein–coupled metabotropic receptors (mGluRs), which are attached to both presynaptic and postsynaptic neurons. In vivo evidence of glutamate dysfunction in mood disorders comes largely from proton magnetic resonance spectroscopy (^{1}H-MRS), an imaging technique for detecting neurochemicals that enables the evaluation of both brain glutamate and glutamate/glutamine (Glx) levels. Studies have noted glutamate reductions in the dorsolateral prefrontal cortex (PFC) of individuals with MDD[6] as well as in other PFC areas such as the dorsomedial and dorsoanterolateral PFC[7] and the anterior cingulate cortex (ACC)[8]. A meta-analysis of MDD patients who underwent ^{1}H-MRS found reduced Glx levels in the PFC that were associated with the number of failed antidepressant treatments, reflecting severity of illness.[9] Other studies found that glutamate levels were increased in the occipital cortex (OCC).[10]

The evidence suggesting that glutamatergic dysfunction may play a role in the pathophysiology of BD is mixed. Some studies that compared glutamate levels in individuals with BD and healthy controls found decreased glutamate levels,[11] and others found no difference;[12,13] however, two meta-analyses evaluating ^{1}H-MRS studies noted increased glutamate levels in BD.[14,15]

Notably, several glutamatergic genes have been implicated in mood disorders. Glutamatergic genes found to be particularly relevant for mood disorders include *GRIA3*, which codes a protein of the AMPA receptor; *GRIK4* and *GRIK2*, which code proteins of the kainate receptor; and *GRM7*, a gene that encodes a protein of the metabotropic receptor.[16] Although neuroimaging studies have obtained mixed results, the evidence suggests that glutamatergic genes increase the risk for BD more than for MDD (reviewed in De Sousa et al. [2017][16]). In addition, the effects of the broad glutamatergic modulator ketamine in bipolar depression have been shown to be rapid and robust,[17,18] echoing that agent's effects in MDD.

The present manuscript reviews new glutamatergic compounds with clinical antidepressant efficacy in either MDD or BD. The review was not systematic; rather, our goal was to provide a summary and update of published clinical studies examining the antidepressant efficacy of multiple glutamatergic agents. It should be noted at the outset that several other potentially intriguing glutamate receptor targets with preclinical antidepressant-like efficacy exist, including AMPA agonists (for instance, farampator [CX-691/ORG-2448] and ORG-26576) and mGluR7 agonists. Given the paucity of the clinical evidence surrounding these targets, however, they will not be discussed further in this manuscript. Much of the clinical evidence is drawn from the past decade of research with the glutamatergic modulator ketamine; numerous controlled studies have consistently described rapid, robust, and relatively sustained antidepressant response rates for a single, subanesthetic-dose ketamine infusion[19–22] (reviewed in greater detail below). These findings have fundamentally altered our underlying conceptualization of the pathophysiology of depression and refocused research interest on the glutamatergic system as a source for possible targets, compounds,[23–26] and new biomarkers for depression.[27,28] A significant annual increase in the rate of published clinical trials investigating the effectiveness of glutamatergic agents as rapid antidepressants has occurred over the last decade, commensurately reawakening interest in this research area.

Within this framework, a fundamental tenet—established by the recent clinical evidence that will be reviewed in this manuscript—is that rapid antidepressant effects are indeed achievable in humans.[29] This paradigm shift lends additional urgency to the development of novel treatments for MDD and bipolar depression, particularly for patient subgroups that do not respond to currently available therapies. Here, we review several glutamate-modulating agents that have been tested in proof-of-concept studies for mood disorders. See Table 1. These agents include the following: (1) broad glutamatergic modulators (ketamine, esketamine, dextromethorphan, dextromethorphan-quinidine/Nuedexta, AVP-786, nitrous oxide [N$_2$O], AZD6765); (2) subunit (NR2B)-specific NMDA receptor antagonists (CP-101,606/traxoprodil, MK-0657 [CERC-301]); (3) glycine-site partial agonists (D-cycloserine, GLYX-13, sarcosine, AV-101); and (4) metabotropic glutamate receptor modulators (AZD2066, RO4917523/basimglurant, JNJ40411813/ADX71149, and

R04995819 [RG1578]). See Table 1. Finally, convergent evidence from behavioral, cellular, and molecular ketamine studies supports the theory that enhanced AMPA receptor activity—with a concomitant increase in synaptic plasticity—is critical to ketamine's mechanism of action and to that of other glutamatergic modulators reviewed here that also show antidepressant properties.

BROAD GLUTAMATERGIC MODULATORS*

Ketamine
Ketamine is, by far, the best studied of the glutamatergic agents, as well as the most effective, at least to date.[22,30,31] It has a long history of safe use in humans; it has been used as an anesthetic[32] for roughly 50 years as well as for procedural sedation of children in emergency medical settings.[33,34] The first clinical study exploring ketamine's potential antidepressant properties was conducted over 15 years ago.[20] That small, double-blind study randomized eight participants (one with bipolar depression and seven with MDD) to receive either subanesthetic (0.5 mg/kg) IV ketamine or saline placebo and found that four of the seven patients who completed the study demonstrated a significant antidepressant response to ketamine, as assessed by Hamilton Depression Rating Scale (HAM-D) score reductions of 50% or more.[20] These findings were subsequently extensively replicated. Regardless of whether the clinical trials were single-dose or repeated administration or whether the studies were open-label, double-blind, placebo-controlled, or double-blind active comparator conditions via parallel arm or crossover treatment paradigms, patients with treatment-resistant MDD experienced a rapid and robust antidepressant response to ketamine.[21,30,35–37] The studies found that, broadly, antidepressant response to ketamine typically involves an initial reduction in depressive symptoms that occurs within two hours of administration, that the strongest reduction in depressive symptoms occurs within 24 hours, and that a sustained response can last for up to one week after ketamine administration.[21,30]

What is particularly notable about ketamine is the rapidity of its antidepressant effects. Within four hours to one day after a single ketamine infusion, the observed response rates were comparable to those seen after roughly eight weeks of treatment with currently available monoaminergic-based antidepressants. Indeed, ketamine's ability to induce remission in roughly a third of treatment-resistant patients within a single day differs sharply from the effectiveness of currently available monoaminergic-based antidepressants, which traditionally require 10–14 weeks of chronic administration before similar remission rates are observed.[1] No other treatment for depression to date has shown similar effects with regard to the magnitude of response to a single dose for treatment-resistant patients. In addition, ketamine rapidly and robustly

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*While here and throughout the manuscript we use the term *glutamatergic modulator*, it should be noted that ongoing research into existing mechanisms of action may uncover other unknown targets that could modify current classifications.

Table 1

Glutamatergic Drugs[a] Tested for Use in Mood Disorders

	Mechanism of action	Evidence for depression[b]	Route of administration	Dose	Acute side effects
Broad glutamatergic modulators					
Ketamine	NMDA antagonism and AMPA receptor activation	I	Intravenous (also intramuscular, intranasal, oral, sublingual)	0.5 mg/kg	Acute: transient psychotomimetic and dissociative effects, increased blood pressure and tachycardia. Chronic: possibly abuse, neurotoxicity, cystitis, and dissociative side effects
Esketamine	NMDA antagonism; three- to fourfold higher affinity for NMDA receptors than ketamine	II	Intravenous	0.20 or 0.40 mg/kg	Most common side effects were nausea, headache, and transient dissociation
Esketamine		II	Intranasal	28, 56, or 84 mg twice weekly for two weeks	Transient elevations in blood pressure and heart rate, but dissociative symptoms diminished with repeated dosing
Dextromethorphan	Nonselective, noncompetitive NMDA receptor antagonist; also acts on opioid receptors and, at higher doses, as a sigma-1 receptor agonist and inhibitor of the serotonin and norepinephrine transporters	Did not meet primary outcome measure[c]	Oral	60 mg/day	NA
Dextromethorphan-quinidine combination (Nuedexta)	Same as above; also quinidine inhibits cytochrome 2D6, increasing dextromethorphan levels	III	Oral	45 mg dextromethorphan/10 mg quinidine twice daily	Gastrointestinal complaints, dizziness, and sedation; one patient reported severe insomnia
AVP-786 (combination of [d6]-dextromethorphan and quinidine)	Same as above; also quinidine inhibits cytochrome 2D6, increasing dextromethorphan levels	NA[d]	Oral	NA	NA
Nitrous oxide (N2O)	Noncompetitive NMDA receptor inhibitor; acts on other targets	II	Inhalation	50% N2O/50% O2	Anxiety, headache, and nausea/vomiting
AZD6765 (lanicemine)	Low-trapping, nonselective NMDA receptor channel blocker	One large study was positive, and a larger study was negative	Intravenous	50, 100, or 150 mg	No psychotic or dissociative side effects

Table 1

Continued

	Mechanism of action	Evidence for depression[b]	Route of administration	Dose	Acute side effects
Subunit (NR2B)-specific N-methyl-D-aspartate (NMDA) receptor antagonists					
CP-101,606/traxoprodil[e]	NR2B subunit NMDA selective antagonist	II	Intravenous	0.75 mg/kg per hour for 1.5 hours followed by 0.15 mg/kg per hour for 6.5 hours	Potentially cardiotoxic (QTc prolongation)
MK-0657 (CERC-301)	NR2B subunit NMDA selective antagonist	Did not meet primary outcome measure	Oral	20 mg	No serious or dissociative side effects
Glycine-site partial agonists					
D-cycloserine	Glycine partial agonist	II	Oral	1000 mg/day	Frequent gastrointestinal symptoms, dizziness, sleep disturbances, peripheral neuropathy, depression, tinnitus, and visual disturbances; seizures and psychosis occur in <5% of patients
GLYX-13	Glycine$_B$-like functional partial agonist	II	Intravenous	5 or 10 mg/kg	Dizziness (10%), but no psychotomimetic properties or serious adverse events
Sarcosine	Glycine transporter–I inhibitor and potentiator for NMDA function	III	Oral	1000–1500 mg/day	Mild sleep-related complaints
AV-101	Highly selective glycine receptor antagonist	NA[f]	Oral	1080 or 1440 mg/day	NA
Metabotropic glutamate receptor modulators					
AZD2066	mGluR5 antagonist	Did not meet primary outcome measure	Oral	12–18 mg/day	One serious adverse event; mild gastrointestinal symptoms, headache, and sleep-related complaints
RO4917523/basimglurant	mGluR5 negative allosteric modulator	Did not meet primary outcome measure	Oral	0.5 or 1.5 mg/day	Dizziness (23%) and two cases of mania

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Table 1

Continued

	Mechanism of action	Evidence for depression[b]	Route of administration	Dose	Acute side effects
JNJ40411813/ADX71149	mGluR2 positive allosteric modulator	Did not meet primary outcome measure	Oral	50–150 mg	Vertigo was the most reported side effect
R04995819 (RG1578)	mGluR2/mGluR3 antagonist and negative allosteric modulator	Did not meet primary outcome measure	Oral	5, 15, or 30 mg/day	Not reported

[a] While here and throughout the manuscript we use the term *glutamatergic modulator*, it should be noted that ongoing research into existing mechanisms of action may uncover other unknown targets that could modify current classifications.
[b] Levels of evidence: I, ≥2 double-blind, randomized, controlled trials; II, at least one double-blind, randomized, controlled trial; III, prospective, uncontrolled trial with ≥10 subjects.
[c] In bipolar depression.
[d] Completed.
[e] Drug development stopped because of cardiotoxicity.
[f] Ongoing study.
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NA, not applicable; NMDA, N-methyl-D-aspartate.

improves anhedonia, fatigue, and suicidal thoughts in individuals with treatment-resistant depression.[38–41]

Building on these findings, ketamine's rapid antidepressant effects were subsequently explored in patients with treatment-resistant bipolar depression, though these placebo-controlled studies used ketamine adjunctively with lithium or valproate rather than as monotherapy. Ketamine demonstrated similarly rapid and robust antidepressant effects in these patients.[17,18,20,42–44] It should be noted that one analysis found that a single ketamine dose had very low risk (similar to placebo) of inducing mania/hypomania, suggesting that ketamine use is safe for individuals with bipolar depression.[45]

From a public health perspective, recent studies have demonstrated that ketamine has rapid-onset antisuicidal effects in clinical trials;[38,46–48] this finding was also observed in patients with bipolar depression.[49] A meta-analysis of seven clinical trials using unpublished data on the suicide-item component of either the Montgomery-Åsberg Depression Rating Scale (MADRS) or the HAM-D found that the ketamine group had significantly reduced suicidal-ideation severity scores at days 1 and 3.[50] Interestingly, it appears that ketamine's ability to reduce suicidal-ideation measures may occur independently of its antidepressant effects.[36,49] Although the biological mechanisms underlying ketamine's antisuicidal effects remain unclear, one study found that MDD patients who experienced an antisuicidal response to ketamine showed reduced nocturnal wakefulness.[51]

To better assess ketamine's antidepressant effectiveness, the American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments conducted a meta-analysis of ketamine studies (n = 147 drawn from seven trials). The analysis concluded that ketamine had rapid and transient antidepressant effects and caused brief dissociative and psychotomimetic effects. The odds ratios for response and transient remission of symptoms at 24 hours were 9.87 (4.37–22.29) and 14.47 (2.67–78.49), respectively; the odds ratio for antidepressant response in MDD was 8.42 (95% CI, 3.47–20.39; p < .001), and the odds ratio for antidepressant response in bipolar depression was 24.05 (95% CI, 2.96–195.56; p = .003).[30] With regard to the bipolar depression studies included in the meta-analysis, symptom remission rates were significant on day 1 (odds ratio = 14.01 [95% CI, 1.73–111.70; p = .013]) but not on day 7 (odds ratio = 1.51 [95% CI, 0.22–10.49; p = .674]); however, and as mentioned above, all bipolar depression studies conducted to date have used ketamine in conjunction with a conventional mood stabilizer (lithium or valproate).[30]

In response to these promising findings, investigators are increasingly exploring alternative—and largely more convenient—means of ketamine administration. These include intranasal,[52,53] intramuscular,[54] oral,[55–58] and sublingual[59] routes. Results from these studies are preliminary; larger, controlled studies are needed to fully assess the efficacy of these alternate routes. Given the strength of the evidence described above, however, ketamine use in clinical settings has seen rapid growth.[60]

Nevertheless, ketamine's off-label clinical use in the community is not standardized and remains unregulated, and concerns about possible risks associated with chronic ketamine use—including neurotoxicity, cystitis, dissociative side effects, cognitive effects, and abuse[61]—remain largely unaddressed with regard to the subanesthetic doses used to treat depression (0.5 mg/kg). It should be noted that the acute effects of ketamine administration at subanesthetic doses—typically, psychotomimetic and dissociative side effects—have been transient and mostly mild.[23] Efforts are under way to address these concerns, bring ketamine to the market, standardize its use, and determine its real-world effectiveness (see, for instance, http://www.pcori.org/research-results/2016/electroconvulsive-therapy-versus-ketamine-severe-resistant-depression).

With regard to novel developments in this area, and as an example of the rapid pace at which research in this field is progressing, a recent preclinical study has called into question whether NMDA receptor inhibition is indeed the primary mechanism of ketamine's antidepressant action.[62] While this manuscript focuses almost entirely on clinical evidence, the paradigm-shifting nature of this preliminary preclinical evidence warrants inclusion here. The researchers found that ketamine's antidepressant effects appeared to be produced by one of its metabolites—2R,6R-hydroxynorketamine (HNK)—through an NMDA receptor–independent mechanism that seems to enhance AMPA receptor activation.[62] The researchers began by investigating the two enantiomers S- and R-ketamine. S-ketamine was found to block NMDA receptors more potently than the R isomer, but did not reduce depressive-like behaviors as successfully. When the investigators studied the breakdown of S- and R-ketamine, they found that the 2S,6S;2R,6R-HNK metabolites were pharmacologically active.[62] Furthermore, 2S,6S;2R,6R-HNK reached levels that were three times higher in female than male mice, a finding that was particularly intriguing because previous studies had demonstrated that female mice respond more effectively to ketamine's antidepressant effects than male mice.[62] When formation of the metabolite was blocked, ketamine's antidepressant effects also disappeared.[62] The study found that both 2S,6S-HNK and 2R,6R-HNK improved depressive-like symptoms in rodents; however, the latter metabolite was more robust and well tolerated, and was thus selected as the lead candidate drug for further testing. Interestingly, mice treated with a single dose of 2R,6R-HNK had significant improvements in their depressive-like symptoms; these improvements lasted three days and were not associated with any dissociative effects.[62] Nevertheless, it is important to emphasize that these results were found in mice. Additional research is certainly needed to explore whether 2R,6R-HNK will have similar antidepressant effects in humans and to determine whether ketamine's mechanism of antidepressant action is due to one of its metabolites or to one of its many off-site targets (e.g., adenosine, glycogen synthase kinase [GSK], cyclic adenosine monophosphate [cAMP], or the opioid, alpha-7, or nicotinic receptors).

Esketamine

Esketamine is the S-enantiomer of ketamine and has a three- to fourfold higher affinity for NMDA receptors and greater anesthetic potency than R-ketamine.[63,64] Three phase 2 and five phase 3 clinical trials are currently under way to study the efficacy of intranasal and intravenous esketamine in treatment-resistant MDD.

A multicenter, randomized, placebo-controlled trial (NCT01640080) investigating the efficacy of intravenous esketamine was conducted in 30 patients with treatment-resistant depression who were randomized to receive an IV esketamine infusion (either 0.20 or 0.40 mg/kg) or placebo over 40 minutes.[65] Both 0.20 and 0.40 mg/kg of esketamine had a robust and rapid (within two hours) antidepressant effect (as assessed by the MADRS) compared to placebo. No dose-response association was observed, and systematic dose-finding studies are needed to determine whether there is indeed a dose-response relationship. The most common side effects were nausea, headache, and dissociation, but the last was transient and did not persist more than four hours postinfusion.

Recently, another multicenter, double-blind, placebo-controlled study (SYNAPSE, NCT01998958) assessed the antidepressant efficacy and dose response of three different doses of intranasal esketamine (28, 56, or 84 mg) versus placebo administered twice weekly for two weeks in 67 individuals with treatment-resistant depression; changes in MADRS total scores on day 8 in all three esketamine treatment groups were statistically superior to placebo.[66] On the days when patients received the drug, esketamine led to transient elevations in blood pressure and heart rate in most patients, but dissociative symptoms diminished with repeated drug administration.

Another multicenter, placebo-controlled, double-blind, randomized, 12-week study investigated the efficacy of intranasal esketamine (84 mg) in 68 adults with MDD and active suicidal ideation. Within four hours, as well as at day 1, this dose of intranasal esketamine significantly reduced both depressive symptoms (as assessed by the MADRS) and suicidal thoughts (as assessed by the Scale for Suicide Ideation).[67]

Taken together, the results suggest that the S-enantiomer of ketamine may contribute to its antidepressant effects. Based on these positive results, in August 2016 the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation for intranasal esketamine in MDD with imminent risk for suicide;[68] this FDA designation grants priority review to esketamine due to preliminary results suggesting that the therapy might be substantially superior to existing options. Esketamine subsequently entered phase 3 development as add-on therapy to oral antidepressants in treatment-resistant depression.

Dextromethorphan, Dextromethorphan-Quinidine (Nuedexta), and AVP-786

Best known as a cough suppressant, dextromethorphan is a nonselective, noncompetitive NMDA receptor antagonist with sedative and dissociative properties that also has potential as a rapid-acting antidepressant.[69,70] Dextromethorphan

acts on opioid receptors and, at higher doses, as a sigma-1 receptor agonist and inhibitor of the serotonin (SERT) and norepinephrine (NET) transporters.

A randomized, placebo-controlled trial of dextromethorphan studied this agent as an adjunct to valproate in bipolar depression. No significant group differences were observed between groups on the outcome measures of interest (mean HAM-D and Young Mania Rating Scale scores), potentially due to metabolism-related reductions in drug concentrations.[71] To date, no randomized, controlled trials have explored the use of dextromethorphan as monotherapy for the treatment of mood disorders.

A dextromethorphan-quinidine combination is now being studied for treatment-resistant depression under the trade name Nuedexta (AVP-923), which is FDA approved for the treatment of pseudobulbar affect; quinidine is a cytochrome 2D6 inhibitor. A retrospective chart review of 22 subjects with BD-II or BD not otherwise specified found that 20 mg dextromethorphan and 10 mg quinidine once or twice daily, when added to a current medication regimen over a 90-day treatment period, significantly improved Clinical Global Impression scale scores.[72] A case report also found that dextromethorphan-quinidine had antidepressant effects in a depressed patient with emotional lability.[73] Dextromethorphan-quinidine was also tested in an open-label, one-arm trial of 20 patients with treatment-resistant depression who received oral doses of dextromethorphan-quinidine (45 mg and 10 mg, respectively) every 12 hours.[74] After ten weeks, 45% of subjects responded, and 35% remitted; the results can be considered modest for an open-label trial. Mild side effects such as gastrointestinal complaints, dizziness, and sedation occurred, but one patient experienced severe insomnia.

AVP 786, a combination of deuterated (d6)-dextromethorphan and an ultra-low dose of quinidine, recently received FDA Fast Track designation for agitation in Alzheimer's disease; Fast Track designation will allow the FDA to conduct an expedited review of this agent. A ten-week, phase 2, randomized, controlled trial is currently investigating the efficacy, safety, and tolerability of AVP 786 as adjunctive therapy in patients with MDD and inadequate response to antidepressant treatment (NCT02153502). The study was recently completed, but no results have been posted.

Nitrous Oxide

Nitrous oxide (N$_2$O) has a broad mechanism of action similar to ketamine's. An inhaled general anesthetic most often used in dentistry or obstetrics, N$_2$O is a noncompetitive NMDA receptor inhibitor. A recent double-blind, placebo-controlled, crossover study administered either a one-hour inhalation of 50% N$_2$O or 50% nitrogen as placebo to 20 patients with treatment-resistant depression.[75] At two hours and also at 24 hours post-inhalation, N$_2$O significantly improved antidepressant response rates (as measured by the HAM-D) compared to placebo. No psychotomimetic effects were observed, but adverse effects included anxiety, headache, and nausea/vomiting.

AZD6765 (lanicemine)

AZD6765 (lanicemine) is a low-trapping, nonselective NMDA receptor channel blocker. In a study of 22 unmedicated subjects with treatment-resistant MDD, a single AZD6765 infusion (150 mg) was more effective than placebo; no psychotic or dissociative side effects were observed.[76] While the antidepressant effects of a single infusion of AZD6765 occurred very rapidly (within 80 minutes), response was not as robust or sustained as that observed with ketamine. The effects were short-lived—lasting less than two days—and the response rate was low (32% compared to 15% for placebo). Another three-week, placebo-controlled trial studied repeated adjunctive AZD6765 infusions in subjects with treatment-resistant MDD. AZD6765—which was given at two different doses (100 mg and 150 mg)—again demonstrated antidepressant effects without ketamine-like side effects, but these effects were not rapid-acting.[24] Finally, adjunctive, repeated-dose (50 mg and 150 mg) AZD6765 did not separate from placebo in a six-week phase 2b study, possibly due to the large placebo effect (39% at trial endpoint).[24,77] Based on the existing evidence, AstraZeneca discontinued the development of AZD6765 for the treatment of MDD.[78]

SUBUNIT NR2B-SPECIFIC NMDA RECEPTOR ANTAGONISTS

NR2B is a subunit of the NDMA receptor. Investigations into the therapeutic potential of NMDA receptor subunit antagonists stem largely from the hypothesis that—because these agents nonselectively block the NMDA receptor—they may be more specific and have fewer undesirable adverse effects than ketamine. Two such agents have been investigated: CP-101,606 (traxoprodil) and MK-0657; the latter has been renamed CERC-301 and is now in development by Cerecor.

CP-101,606 (Traxoprodil)

The antidepressant efficacy of CP-101,606 (traxoprodil) as monotherapy was investigated in a randomized, double-blind, placebo-controlled study of 30 patients with treatment-resistant MDD. The investigators found a 60% response rate to CP-101,606 compared to 20% in the placebo group, an effect that lasted for at least one week in 78% of treatment responders.[79] The antidepressant effect was noted at day 5 but not at day 2. Development of this compound was stopped, however, because of potential cardiovascular toxicity (QTc prolongation).

MK-0657 (CERC-301)

MK-0657 (CERC-301) is an oral NR2B antagonist whose antidepressant efficacy was tested in 21 patients with treatment-resistant MDD in a 12-day, double-blind, placebo-controlled, randomized, crossover pilot study.[80] CERC-301 was administered daily as monotherapy. No antidepressant improvement over placebo was observed (as assessed by the MADRS, the primary outcome measure), but some improvement was noted using the clinician-administered HAM-D and the self-reported

Beck Depression Inventory. In contrast to CP-101,606, no serious or dissociative adverse effects were observed with CERC-301.

CERC-301 received Fast Track designation for the treatment of MDD in November 2013.[81] Subsequent results from a clinical phase 2, placebo-controlled trial using higher doses of CERC-301 (12 and 20 mg) (NCT02459236) found that CERC-301 had no significant antidepressant effects compared to placebo, although significant improvements in depressive symptoms were observed at day 2 with the 20 mg dose.[82] Another phase 2, randomized, controlled trial of adjunctive CERC-301 in subjects with severe MDD and recent active suicidal ideation (NCT01941043) investigated daily use of CERC-301 (8 mg) for 28 days and found no change in primary endpoint measures (change in HAM-D-17 at day 7).[83]

NMDA RECEPTOR GLYCINE-SITE PARTIAL AGONISTS

D-Cycloserine

D-cycloserine (DCS) is a broad-spectrum antibiotic and, at doses greater than 100 mg/day, a functional NMDA glycine receptor partial agonist[84] that may act by antagonizing the NMDA receptor.[85] A six-week, crossover, placebo-controlled trial of adjunctive DCS (250 mg/day) in 22 subjects with treatment-resistant MDD found that DCS reduced depressive symptoms but that this effect did not separate from placebo.[86] A second study of 26 subjects with treatment-resistant MDD investigated escalating dose (up to 1000 mg/day) adjunctive DCS. Higher-dose DCS had significant antidepressant effects as measured by the clinician-administered HAM-D and self-reported Beck Depression Inventory, with over half the patients randomized to high-dose DCS experiencing a greater than 50% reduction in HAM-D scores by the end of the study.[87] Another large study (n = 818) found that the side effects of DCS frequently included gastrointestinal symptoms as well as dizziness, sleep disturbances, peripheral neuropathy, depression, tinnitus, and visual disturbances; seizures and psychosis occurred in 4% and 3.4% of the sample, respectively.[88]

In bipolar depression, one open-label study investigated adjunctive use of DCS as a maintenance treatment after a single ketamine infusion in 12 patients (n = 7 completers).[44] Investigators observed an improvement in depressive symptoms lasting from baseline through week 8 (except at two weeks); a large effect size was seen at day 1 (Cohen d = 2.0). Four of the seven patients with bipolar depression who completed the study remained in remission after eight weeks. Furthermore, clinical improvement at the eight-week time point correlated with the magnitude of improvement 24 hours post-ketamine. This study had no control group, however, which may limit interpretation of DCS's efficacy.

Finally, a recent meta-analysis that assessed the efficacy of agents acting directly on the NMDA receptor found that DCS has been linked to acute antidepressant response at high doses (1000 mg) but not at low doses (250 mg);[30] data were drawn from the studies cited above.

GLYX-13 (Rapastinel)

GLYX-13 (Rapastinel) is a glycine$_B$-like functional partial agonist. A large phase 2b safety and efficacy trial randomized 116 unmedicated inpatients with treatment-resistant MDD to receive either intravenous GLYX-13 (1 m/kg [n = 25], 5 mg/kg [n = 20], 10 mg/kg [n = 17], or 30 mg/kg [n = 21]) or a single saline placebo (n = 33) over 3 to 15 minutes.[89] Investigators found that, at one week post-administration, inpatients who had received either 5 or 10 mg/kg of GLYX-13 had significantly improved depressive symptom scores compared to those who had received saline placebo. In contrast to the response observed with NMDA receptor antagonists, GLYX-13 infusion at any dose caused no psychotomimetic properties, and no serious adverse events were reported. The most common side effect was dizziness (10%).

The same investigators then investigated adjunctive GLYX-13 in a randomized, double-blind, clinical trial of 116 patients with treatment-resistant depression who were concurrently maintained on a psychotropic medication regimen.[90] Subjects were randomized to receive weekly infusions of IV GLYX-13 at doses of 1 mg/kg, 5 mg/kg, or 10 mg/kg, or placebo. Follow-up occurred on days 3, 7, and 14. After an interim safety and efficacy analysis, an additional cohort was added who received IV GLYX-13 (30 mg/kg) or placebo, with follow-up at days 3, 7, 14, 21, and 28. Onset of action (assessed via the Bech-6 subscale of the HAM-D) occurred within two hours. Those who received 5 or 10 mg/kg of IV GLYX-13 had significantly reduced HAM-D scores on days 1 through 7 compared to placebo, but no antidepressant effects were observed after the day 7 time point. GLYX-13 infusion at any dose caused no psychotomimetic effects, and no serious adverse events were reported. The investigators commented that the U-shaped dose response curve observed for GLYX-13 might have been due to this agent's unique molecular interactions as a partial agonist on the glycine site of the NMDA receptor.

Based on these promising preliminary findings, Allergan announced in January 2016 that GLYX-13 had received Breakthrough Therapy designation from the FDA for adjunctive treatment of MDD.[91]

Sarcosine

Sarcosine is a glycine transporter–1 inhibitor and potentiates NMDA function. A six-week, double-blind, randomized study of 40 patients with MDD found that sarcosine had superior antidepressant effects to citalopram, which served as a control. Improvements in depressive symptoms were assessed using the HAM-D, Clinical Global Impression, and Global Assessment of Functioning rating scales.[92] Patients treated with sarcosine demonstrated remission and response rates higher than those treated with citalopram and, in addition, were less likely to drop out of the study. No significant side effects were noted. While these preliminary results are encouraging, the study had several significant limitations—particularly the absence of a placebo control group and a

high dropout rate in the comparator treatment group. Larger, placebo-controlled studies will be needed to fully assess sarcosine's therapeutic potential.

AV-101

4-Cl-KYN (AV-101) is a potent and highly selective glycine receptor antagonist.[93] In an animal study exploring potential ketamine-like antidepressant agents, AV-101 demonstrated rapid, dose-dependent, and persistent antidepressant effects following a single treatment.[94] This study also found that the antidepressant effects of AV-101 were prevented by pretreatment with glycine or the AMPA receptor antagonist NBQX, further underscoring the potential influence of AMPA receptor activation on the rapid antidepressant effects of glutamatergic modulators. A phase 2 randomized, controlled trial investigating the antidepressant efficacy of AV-101 in individuals with treatment-resistant MDD is ongoing (NCT02484456).

METABOTROPIC GLUTAMATE RECEPTORS

Metabotropic glutamate receptors (mGluRs), which are found in the postsynaptic density[95–97] and also in glial cells,[98] are expressed widely throughout the brain and are an additional glutamate-signaling pathway outside of the NMDA receptor and AMPA receptor pathways. The antidepressant efficacy of presynaptic mGluR2 agonists would hypothetically act to reduce excessive glutamate release; by contrast, GluR2/3 antagonists are thought to enhance synaptic glutamate levels, thereby boosting AMPA receptor transmission and firing rates as well as extracellular monoamine levels. A number of agents that act as positive or negative allosteric modulators have been studied in treatment-resistant MDD.

AZD2066

The antidepressant properties of the mGluR5 antagonist AZD2066 were assessed in a six-week, randomized, controlled trial (NCT01145755) comprising three treatment arms: AZD2066 (12–18 mg/day), the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine (30–60 mg/day), and oral placebo. None of the arms statistically separated on any efficacy measures (results available at https://www.clinicaltrials.gov/ct2/show/results/NCT01145755). Presently, no ongoing studies investigating the use of AZD2066 in mood disorders are listed on ClinicalTrials.gov.

RO491753/basimglurant

The antidepressant effects of the mGluR5 negative allosteric modulator RO4917523 (basimglurant, RG7090) were investigated in individuals with treatment-resistant MDD (NCT00809562, NCT01437657). A nine-week, multicenter, phase 2b study of 333 subjects with treatment-resistant MDD compared adjunctive modified-release RO491753 to adjunctive placebo; six weeks of double-blind treatment were followed by three weeks of post-treatment follow-up.[99] Subjects were randomized to receive either adjunctive placebo (n = 108) or one of two doses of adjunctive RO491753 (0.5 mg [n = 112] or

1.5 mg [n = 111]). No statistically significant difference was observed on the primary endpoint of change in MADRS score from baseline to six weeks. At the 1.5 mg dose, however, promising results were observed for several exploratory secondary endpoints, including on patient-rated scales (MADRS and the Quick Inventory of Depressive Symptomatology Self-Report). The most common adverse event was dizziness (23%) at the 1.5 mg dose. Two cases of mania were reported.

JNJ40411813/ADX71149

The safety, tolerability, and efficacy of the mGluR2 positive allosteric modulator JNJ-40411813/ADX71149 was investigated in a phase 2a, multicenter, randomized, double-blind, proof-of-concept study of MDD patients who were already taking an SSRI or SNRI and who had significant anxiety (as assessed via the HAM-D and Hamilton Anxiety Rating Scale).[100] JNJ-40411813 was administered adjunctively. In the first study period, which lasted four weeks, patients were randomized to receive flexibly dosed JNJ-40411813 or placebo; subjects who received placebo and continued to meet entry severity criteria were subsequently re-randomized in another four-week study period. No differences were observed in depression or anxiety rating-scale scores via primary outcome measures for the 100 patients who completed the study.

RO4995819

RO4995819 is an mGluR2/mGluR3 antagonist and a negative allosteric modulator.[101] A phase 2, randomized, controlled trial evaluating the antidepressant efficacy of adjunctive RO4995819 in patients with treatment-resistant MDD was completed in June 2014. This agent showed no antidepressant efficacy, and its development for treatment-resistant MDD was therefore terminated by Roche (under the code name RG1578).[102(p 79)]

Taken together, the evidence suggests that neither mGluR negative nor positive allosteric modulators have demonstrated a strong antidepressant effect. It is worth noting, however, that the lack of a finding might have been due to the lack of an adequate biomarker of target engagement.

CONCLUSION

As the evidence reviewed above has underscored, many studies to date—including placebo-controlled studies, case reports, case series, and early proof-of-concept studies—have investigated the potential antidepressant effects of glutamatergic modulators, though most of these studies have had relatively small sample sizes. Nevertheless, the bulk of the evidence suggests that the novel agents reviewed in this article may have considerable clinical utility for treating individuals with MDD and bipolar depression, particularly those whose illness is categorized as treatment-resistant.

To date, the ionotropic glutamate receptors appear to be the most promising targets for treating mood disorders. Nevertheless, ketamine and similar glutamatergic modulators

cannot yet be recommended for routine use outside of research settings; large (n > 100), multisite, randomized, placebo-controlled trials are still needed to better assess the overall safety, tolerability, and efficacy of these agents. It should be noted, however, that ketamine is now being considered by some experts as a late treatment option for individuals with treatment-resistant mood disorders, either for temporary symptom relief or as a bridge to alternative therapies.[103] In this context, research on drugs such as ketamine and esketamine is especially promising, given their clinical efficacy and broad glutamatergic action. Other promising agents with robust antidepressant effects include the glycine-site partial agonist DCS and the broad glutamatergic modulators N_2O and dextromethorphan/quinidine; the latter two drugs still require more investigation to establish the robustness of their effects. It should be noted here that despite promising preliminary theories, the metabotropic glutamate receptor modulators did not prove effective in clinical trials; the reason for these disappointing results remains unclear despite considerable effort.

In this regard, ongoing efforts to develop "better" alternatives for ketamine have proven challenging. As described above, several clinical avenues are currently being investigated in the search for equally effective but more convenient alternatives to ketamine that are not associated with psychotomimetic or dissociative side effects. A number of broad and subunit-selective NMDA antagonists that had been shelved after failing to demonstrate efficacy for other indications were reinvestigated as proof-of-concept agents for treatment-resistant mood disorders. While some of these other NMDA receptor antagonists have indeed demonstrated antidepressant properties—and a number of the agents reviewed above may conceivably yield promising results (e.g., GLYX-13)[22]—it should be noted that no agent investigated to date appears to possess all of ketamine's positive traits, which include (1) rapid onset of antidepressant effects, (2) robustness of antidepressant response, (3) sustained efficacy with a single administration, (4) efficacy in treatment-resistant mood disorders, (5) antisuicidal and anti-anhedonic properties, and (6) therapeutic potential in other disorders (e.g., posttraumatic stress disorder, obsessive-compulsive disorder, and anxiety, all of which are currently being investigated in conjunction with ketamine).

Continued investigation into this rapidly growing research area is clearly needed to better assess the utility and safety of the multiple agents reviewed herein in order both to confirm their antidepressant efficacy in larger samples and to clarify the underlying mechanisms of action responsible for their clinical effects. The results of such studies will help refine the most promising therapeutic targets and develop new, effective treatments within those targets. Because currently available antidepressants act on multiple receptors and molecules, another key issue of importance is discovering the right combination of cellular effects and molecular actions needed to develop more effective medications for MDD and bipolar depression. As reviewed above, the most recent evidence suggests that NMDA-receptor effects may need to converge with other molecular and cellular actions in order to exert antidepressant action—in particular, enhanced AMPA receptor activation. Combining these clinical and biological effects will require a global approach that simultaneously incorporates preclinical and clinical investigations, each paving the way toward the other. Finally, with regard to clinical investigations in particular, an integrated approach is needed to reconceptualize clinical phenomenology and psychophysiological methods; in addition, a variety of functional brain-imaging techniques may be needed to fully elucidate the clinical biological heterogeneity of patients with mood disorders, thus paving the way for the successful identification of novel targets and therapeutics.[104,105]

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