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REVIEW ARTICLE

Therapeutic Modulation of Glutamate Receptors in Major Depressive Disorder

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Abstract: Current pharmacotherapies for major depressive disorder (MDD) have a distinct lag of onset that can prolong distress and impairment for patients, and real-world effectiveness trials further suggest that antidepressant efficacy is limited in many patients. All currently approved antidepressant medications for MDD act primarily through monoaminergic mechanisms, *e.g.*, receptor/reuptake agonists or antagonists with varying affinities for serotonin, norepinephrine, or dopamine. Glutamate is the major excitatory neurotransmitter in the central nervous system, and glutamate and its cognate receptors are implicated in the pathophysiology of MDD, as well as in the development of novel therapeutics for this disorder. Since the rapid and robust antidepressant effects of the N-methyl-D-aspartate (NMDA) antagonist ketamine were first observed in 2000, other NMDA receptor antagonists have been studied in MDD. These have been associated with relatively modest antidepressant effects compared to ketamine, but some have shown more favorable characteristics with increased potential in clinical practice (for instance, oral administration, decreased dissociative and/or psychotomimetic effects, and reduced abuse/diversion liability). This article reviews the clinical evidence supporting the use of glutamate receptor modulators with direct affinity for cognate receptors: 1) non-competitive NMDA receptor antagonists (ketamine, memantine, dextromethorphan, AZD6765); 2) subunit (NR2B)-specific NMDA receptor antagonists (CP-101,606/traxoprodil, MK-0657); 3) NMDA receptor glycine-site partial agonists (D-cycloserine, GLYX-13); and 4) metabotropic glutamate receptor (mGluR) modulators (AZD2066, RO4917523/basimglurant). Several other theoretical glutamate receptor targets with preclinical antidepressant-like efficacy, but that have yet to be studied clinically, are also briefly discussed; these include α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) agonists, mGluR2/3 negative allosteric modulators, and mGluR7 agonists.

Keywords: α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA), antagonist, glutamate, major depressive disorder (MDD), metabotropic, N-methyl-D-aspartate (NMDA), negative allosteric modulator, positive allosteric modulator.

INTRODUCTION

Major depressive disorder (MDD) is the most common mental disorder in developed countries, with an estimated prevalence of nearly 17% [1, 2]. The discovery and dissemination of first-generation antidepressants (monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs)) ignited a pharmacological revolution in the treatment of MDD and provided valuable insights into the neuro-transmitter systems involved in this disorder: serotonin, dopamine, and norepinephrine [3]. However, our standard armamentarium of antidepressants is not effective for all MDD patients and, moreover, these agents often take weeks to months to reach maximal effectiveness. Thus, there remains a critical need to develop more effective and rapid-acting interventions for MDD. A growing body of evidence has demonstrated that the glutamatergic system contributes to the pathophysiology of MDD. Glutamate is the major excitatory neurotransmitter in the central nervous system and has two broad classes of receptors: ionotropic and metabotropic [3]. Both glutamate receptor subtypes are modulated by glutamate and other agonists, antagonists, and modulators; nevertheless, significant differences between these glutamate receptor subtypes exist based on their structure, ion selectivity, and mechanism of action of downstream effectors.

This article begins by reviewing the anatomy and function of the various glutamate receptor subclasses. We then discuss the clinical evidence supporting the use of glutamate receptor modulators with direct affinity for cognate receptors, including: 1) non-competitive NMDA receptor antagonists (ketamine, memantine, dextromethorphan, AZD6765); 2) subunit (NR2B)-specific NMDA receptor antagonists (CP-101,606/traxoprodil, MK-0657); 3) NMDA receptor glycine-site partial agonists (D-cycloserine, GLYX-

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13); and 4) metabotropic (mGluR5) glutamate receptor modulators (AZD2066, RO4917523/basimglurant). Several other theoretical glutamate receptor targets with preclinical antidepressant-like efficacy, but that have yet to be studied clinically, are also briefly discussed; these include α-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid (AMPA) agonists, mGluR2/3 negative allosteric modulators, and mGluR7 agonists. Discussion of glutamatergic modulators that act indirectly to alter glutamate release (e.g, lamotrigine, acamprosate, and riluzole) is beyond the scope of this review. The interested reader is directed to these excellent reviews on this topic [4, 5].

Ionotropic Glutamate Receptors

Ionotropic glutamate receptors form tetrameric complexes of individual/heteromeric subunits embedded in phospholipid bilayers (Fig. **1**). Ionotropic glutamate receptors are ion channels that flux cations (calcium (Ca^{2+}), sodium (Na^{+})), which allows channels to "open" in response to agonist binding. To date, three classes of ionotropic glutamate receptors have been identified based on their affinity for exogenous ligands: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid (AMPA), and kainate (KA). The natural ligand for all these receptors is glutamate, and NMDA receptors have the highest affinity for glutamate. There are three subcategories of NMDA receptor subunits: NR1, NR2A-D, and NR3A-B. AMPA and KA receptors are often grouped together due to their similar subunit composition and pharmacological properties; AMPA and KA subunits are designated GluR1-4, and KA subunits are GluR5-7 and KA1-2. NMDA receptor complexes primarily flux Ca^{2+} in response to binding of their obligatory co-agonists, glutamate and glycine, and have more delayed excitatory effects. AMPA and KA receptors primarily flux Na^{+} and are responsible for the fast excitatory component of depolarization.

Metabotropic Glutamate Receptors

Eight different classes of metabotropic glutamate receptors have been identified and subcategorized into three subtypes based on their amino acid homology, binding properties, and activation/inhibition of second messenger/signal transduction cascades [6]. Nevertheless, all metabotropic receptors are seven transmembrane G-protein coupled receptors that, depending on their respective G-protein coupling, either activate or inhibit second messengers/signal transduction pathways [3]. The Group 1 metabotropic receptors—mGluR1 and mGluR5—are generally stimulatory and activate protein kinase C (PKC)-coupled pathways. The Group 2 metabotropic receptors—mGluR2 and mGluR3—as

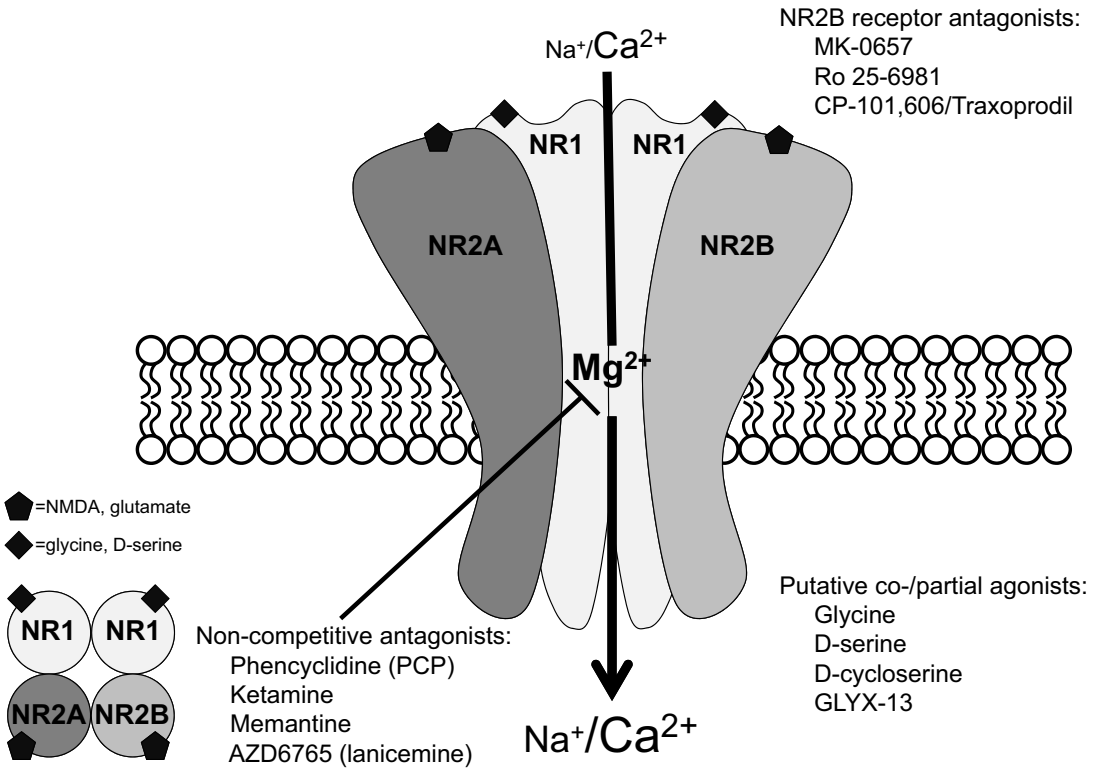

Fig. (1). Direct NMDA Receptor Modulators. As displayed in the lower left-hand corner, N-methyl-D-aspartate (NMDA) receptors are tetra/heteromeric receptor complexes whose natural ligands in the brain are glutamate and glycine. Activation of these receptors leads to the release of the magnesium (Mg^{2+}) pore block and the flux of cations (Ca^{2+} preferentially) from the synapse into the postsynaptic cytoplasm, which facilitates continuing neuronal depolarization. Non-selective, non-competitive antagonists of NMDA receptors include phencyclidine (PCP), ketamine, memantine, and AZD6765 (lanicemine). NR2B-subunit selective NMDA receptor antagonists include CP-101,606/ traxoprodil, MK-0657, and Ro 25-6981. Glycine, D-serine, D-cycloserine, and GLYX-13 are putative agonists at the glycine modulatory site.

well as the Group 3 metabotropic receptors—mGluR4-8—share major sequence homology (~70%) and generally inhibit glutamatergic neurotransmission [7].

NON-SELECTIVE/NON-COMPETITIVE NMDA RECEPTOR ANTAGONISTS

Ketamine

Table **1** and Fig. **2** summarize results from single-and multiple-dose studies exploring the efficacy of subanesthetic-dose ketamine in patients with depression (both MDD and bipolar depression).

Single-Dose Ketamine Studies

Pre-clinical studies suggested that the antidepressant-like efficacy of the non-competitive NMDA receptor antagonists AP-7 and MK-801 might make glutamate receptors a viable therapeutic target in depression [8]. Ketamine, a non-competitive NMDA receptor antagonist, was a reasonable translational candidate due to decades of safe clinical use as

Table 1. Summary of single and multiple subanesthetic dose ketamine infusion studies in depression.

Study	Diagnosis	N	# of Doses	Comorbidity	Dose/ Route	Adjunctive Medications	Response Rate at 24 Hours Post-Infusion	Response Rate at 1 Week Post-Infusion	Remission Rate at 24 Hours Post-Infusion	Remission Rate at 1 week Post-Infusion	Response Rate After Final Dose	Remission Rate After Final Dose
Single Dose												
Berman *et al.* (2000) [9]	MDD & Bipolar Depression (TRD not reported)	8	**1**	Current anxiety disorder: 13%	0.5mg/kg racemic/IV	None	25% (2/8)	N/A (final endpoint at 72 hours)	0% (0/8) (HAM-D ≤7)	N/A (final endpoint at 72 hours)	N/A	N/A
Zarate *et al.* (2006) [10]	MDD/ TRD	17	**1**	Lifetime anxiety disorder: 65%	0.5mg/kg racemic/IV	None	71% (12/17)	38% (6/16)	29% (5/17) (HAM-D ≤7)	31% (5/16) (HAM-D ≤7)	N/A	N/A
Valentine *et al.* (2011) [11]	MDD (TRD not reported)	10	**1**	Current anxiety disorder: 20%	0.5mg/kg racemic/IV	None	20% (2/10)	20% (2/10)	20% (2/10) (HAM-D ≤7)	30% (3/10) (HAM-D ≤7)	N/A	N/A
Murrough *et al.* (2013) [12]	MDD/ TRD	73	**1**	Not Reported	Ketamine: 0.5 mg/kg racemic IV; Midazolam: 0.045 mg/kg IV	None	Ketamine: 64% (30/47); Midazolam: 28% (7/25)	Ketamine: 45% (21/47); Midazolam: 16% (4/25)	Not Included	Not Included	N/A	N/A
Multiple Dose												
aan het Rot *et al.* 2010 [15]	MDD/ TRD	10	**6**	Current anxiety disorder: 70%	0.5mg/kg racemic/IV	None	90% (9/10)	N/A	10% (1/10)	N/A	100% (9/9)	80% (8/10)
Murrough *et al.* 2013 [16]†	MDD/ TRD	24	**6**	Current anxiety disorder: 25%	0.5 mg/kg racemic/IV	None	Not Included	N/A	Not Included	N/A	71% (17/24)	Not Included
Rasmussen *et al*., 2013 [17]	MDD & Bipolar Depression (TRD reported)	10	**4**	Not Reported	0.3 mg/kg x 100 min	Venlafaxine, Duloxetine, Lithium, Lamotrigine, Bupropion	30% (3/10)	N/A	10% (1/10)	N/A	80% (8/10)	50% (5/10)
Diamond *et al*., 2014 [18]	MDD & Bipolar Depression (TRD reported)	28	3 or 6	Not Reported	0.5 mg/kg racemic/IV	Patients remained on anti-depressants	Not Included	N/A	Not Included	N/A	29% (8/28)	14% (4/28)

†Includes data from the aan het Rot *et al.* 2010 study
Abbreviations: MDD: major depressive disorder; TRD: treatment-resistant depression; HAM-D: Hamilton Depression Rating Scale.

a dissociative anesthetic. In 2000, Berman and colleagues published the first randomized controlled trial of subanesthetic-dose ketamine for the treatment of MDD (n=8) and bipolar depression (n=1) [9]. This was a randomized, double-blind, placebo-controlled, cross-over study that consisted of a single subanesthetic-dose (0.5mg/kg) ketamine infusion over 40 minutes. Although the study had a small sample size (n=7 completers), a mean change of 14 points was observed on the Hamilton Depression Rating Scale (HAM-D) from baseline to 72 hours post-infusion; no mean change occurred in response to a saline (placebo) infusion. These initial promising results were then replicated in 2006 with a larger sample (n=18) of treatment-resistant MDD (TRD) inpatients [10]. Zarate and colleagues reported a 71% response rate and 29% remission rate within 24 hours of ketamine (0.5mg/kg x 40 minute) infusion. The antidepressant effect of ketamine abated over the following week; nevertheless, 35% of patients continued to meet response criteria [10]. The rapid and robust antidepressant effect of a single subanesthetic-dose ketamine infusion was replicated in another 10 TRD patients in a single-blind, non-counter-balanced design [11]. One of the major potential limitations of these three studies, however, was the possible inadequacy of an inert (saline) placebo, which may have hampered the integrity of the blind. To address this, Murrough and colleagues used a psychoactive placebo (the short-acting benzodiazepine midazolam) to mimic the sedative and anxiolytic effects of intravenous ketamine [12]. Their study design was a 2 ketamine:1 midazolam randomization scheme with 73 TRD outpatients. Consistent with other clinical trials in MDD, the authors found a greater antidepressant response of placebo; however, subanesthetic-dose ketamine infusion (0.5mg/kg x 40 minutes) maintained greater antidepressant efficacy 24 hours post-infusion (response rates were 64% and 28%, respectively, in subjects randomized to ketamine and midazolam). It should be noted that although midazolam is a better control than saline, blinding may still be compromised because midazolam does not mimic the dissociative, psychotomimetic, and hemodynamic effects of ketamine.

Repeated-Dose Ketamine Studies

Although the rapid antidepressant effect size is large in TRD patients [10] (standardized same- and next-day mean difference of approximately -1.0 in two recent meta-analyses [13, 14]), ketamine's antidepressant effects are also transient in most patients. Thus, repeated dosing strategies have been hypothesized to offer more sustained antidepressant benefits. aan het Rot and colleagues (2010) published preliminary data exploring the safety, tolerability, and efficacy of repeated-dose ketamine for TRD [15]. Over a 12-day period, 10 unmedicated TRD patients were given six open-label subanesthetic dose (0.5 mg/kg x 40 minutes) ketamine infusions, resulting in antidepressant efficacy and a mild, transient side effect profile. Another study of 24 medication-free TRD patients (including the initial 10 in the sample from aan het Rot and colleagues [15]) again administered six infusions over a 12-day period [16]. After 12 days, the antidepressant response rate was 70.8%. These patients were then followed naturalistically (which allowed for traditional antidepressant treatment) over the next 83 days. The mean time to relapse was 18 days, but in about 30% of responders, antidepressant response was maintained until the end of naturalistic observation.

Another repeated subanesthetic-dose ketamine study examined the effects of an open-label 0.3mg/kg infusion over 100 minutes (to approximate the total amount of 0.5mg/kg over 40 minutes without the institutional requirement of anesthesia supervision and potentially limiting side effects). Ten TRD patients received these infusions twice weekly for two weeks until the subject either received four total infusions or their symptoms remitted [17]. At 14 days, six subjects had received the maximum number of doses (four). Of the 10 total subjects, five remitted, three were responders, and two were non-responders. The patients were then monitored for four weeks after the test phase; 50% of the responders achieved remission while another two patients retained their initial symptom remission. Although no firm conclusions can be drawn (as they were not compared head-to-head), this low-dose slow ketamine infusion protocol did not appear to reduce side effect burden.

Finally, in the first published ketamine study outside the United States (Oxford, UK), Diamond and colleagues reported results from 28 medicated TRD and treatment-resistant bipolar depression patients who received either weekly or biweekly (0.5mg/kg x 40 minutes) ketamine infusions over the course of three weeks for a total of either three or six infusions [18]. These participants were then followed for 21 days to monitor for cognitive deficits often seen in ketamine abusers; if found, these may severely limit the utility of repeated-dose ketamine infusions as a treatment option for depression [19-22]. Eight participants responded, of whom four achieved full remission (29% and 14% of the study sample, respectively) without any detected cognitive difficulties. In addition, a six month naturalistic follow-up found a broad range in time to relapse (approximately 70 days) [18].

Despite these promising findings, no randomized, placebo-controlled, multiple-dose ketamine studies have assessed long-term efficacy, safety, and tolerability. As such, insufficient data exist to recommend the long-term, off-label use of ketamine for the treatment of MDD.

Alternative Modes of Ketamine Administration

In addition to studies examining the effects of intravenous single- or repeated-dose ketamine infusions, researchers are also turning to alternative (and more convenient) means of administration. These include: intranasal [23], intramuscular [24], oral [25-28], and sublingual [29].

Intranasal

Intranasal administration of ketamine has been most commonly associated with dental procedures in children requiring anesthesia, with bioavailability ranging from 25-50% [30]. In a randomized, double-blind, cross-over, placebo-controlled trial, 20 MDD patients were randomized to receive either intranasal ketamine (50mg) or a saline intranasal solution [23]. The primary outcome was change in depressive symptoms from baseline to 24 hours post-administration, as assessed by change in Montgomery

Åsberg Depression Rating Scale (MADRS) scores. Within 24 hours, intranasal ketamine had a significant antidepressant effect (mean change in MADRS score = 7.6 ± 3.7, 95% confidence interval: 3.9-11.3). Only minor hemodynamic, dissociative, and psychotomimetic effects were seen. However, there were several limitations, including use of saline as a control, the permitted use of concomitant psychotropic medications, and the lack of antidepressant efficacy over placebo at 72 hours post-administration. The results suggest that intranasal ketamine may be a useful adjunct, but the heterogeneity of psychotropic medication regimens may limit interpretation, especially given that 10 of 20 patients were concomitantly receiving benzodiazepines in the study by Lapidus and colleagues [31, 32]. It should also be noted that despite the reduced dissociative properties associated with intranasal ketamine, one preliminary study found a positive correlation between dissociation and ketamine's antidepressant efficacy [33]; therefore, a side-by-side comparison study is needed to determine the effectiveness, safety, and tolerability of the varying methods of administration.

Intramuscular

Intramuscular ketamine has similar bioavailability (93%) to intravenous ketamine. This method of administration also has a higher peak exposure than an equal dose of intravenous ketamine as well as the additional benefit of not requiring specialized equipment for office-based administration, *e.g.* an infusion pump. It can also be administered to patients with poor intravenous access, *e.g.* depressed patients receiving hemodialysis [34]. In one case series, two treatment-refractory depressed females were given open-label ketamine intramuscularly at ascending doses (0.5, 0.7, 1.0 mg/kg), and a dose-dependent antidepressant response was observed [34]. At the highest studied dose, remission was achieved in one patient 24 hours post-injection. A second case series investigated repeated-dose intramuscular ketamine for patients with treatment-resistant bipolar II depression [24]. Two patients received non-intramuscular preparations of ketamine before receiving repeated intramuscular injections (from 32-100mg every three to four days). Both patients achieved symptom reduction for four to six months; side effects included irritability, headaches, nightmares, and dissociation. Yet, despite months of injections, none of the adverse medical sequelae often seen in ketamine abusers (*e.g.*, neurological deficits or (urinary) cystitis) were noted. Finally, in a small (n=9 per group), randomized, open-label trial, an Indian group reported antidepressant non-inferiority (for up to three days) with 0.25mg/kg and 0.5 mg/kg intramuscular ketamine compared to a 0.5mg/kg intravenous infusion [35].

Oral

Due to ease of administration, oral ketamine is an appealing alternative method. However, oral administration has much lower bioavailability (20%) than non-parenteral preparations. Two case studies that examined the effectiveness of oral ketamine obtained positive results, although these must be considered preliminary due to their limited sample sizes [25, 26]. In the first larger study [27], oral ketamine (0.5mg/kg) had significant antidepressant and anxiolytic effects in eight depressed hospice patients who received oral ketamine daily for 28 days. A second follow-up study administered escalating doses of oral ketamine (0.5mg/kg up to 3mg/kg with boosters) to two treatment-resistant MDD patients with suicidal ideation, and found that ketamine demonstrated sustained antidepressant and antisuicidal effects [28]. Again, ketamine and metabolite blood levels were not measured, though such measures are critical for antidepressant correlation and interpretation.

Sublingual

Due to its slightly improved theoretical bioavailability (~30%) compared to oral ketamine, investigators are also pursuing sublingual ketamine administration. In 27 currently depressed MDD and bipolar outpatients, variable administration (every two to seven days) of add-on, escalating (but still subanesthetic) dose sublingual ketamine had antidepressant effects in 20 patients (77%) [29]. Sublingual ketamine was also well-tolerated—the most common side effect was transient lightheadedness; furthermore, unlike intravenous or intramuscular preparations, there were no reported dissociative or psychotomimetic side effects. Ketamine and ketamine metabolite (hydroxynorketamine) levels were not obtained in this study, so blood levels by sublingual administration cannot yet be compared and correlated with other forms of administration and antidepressant efficacy.

Anti-Suicidal Ideation Effects

Studies have also found that, in addition to its anti-depressant and anxiolytic effects, ketamine has rapid-onset anti-suicidal ideation properties. In one study, 33 TRD patients received a single open-label infusion of ketamine (0.5mg/kg) and completed the Scale for Suicidal Ideation (SSI) to measure levels of suicidal thinking. Suicidal ideation decreased within 40 minutes of infusion, and this effect was maintained for up to four hours post-infusion [36]. Other studies of TRD patients found that ketamine infusion reduced both explicit suicidal thinking and implicit suicidal ideation, as assessed via the Implicit Association Test (IAT), which measures suicidal cognition and potential predictors of future suicidal behavior [37, 38]. Another study from our laboratory examined 108 patients with treatment-resistant MDD or bipolar depression who received a single subanesthetic dose ketamine infusion to assess the relationship between improvements in depression/anxiety and suicidality. We found that improvements in suicidal thinking were related to, but not fully explained by, improvements in depression and anxiety symptoms [39]. In this study, ketamine's antidepressant and anxiolytic efficacy explained only up to 20% of the improvement in suicidal ideation. A secondary analysis performed on the same sample noted that lacking a lifetime history of suicide attempt(s) also predicted improved antidepressant response to ketamine at one week post-infusion [40]. However, it must be noted that these studies excluded patients who were actively suicidal with an intention of self-harm or with a recent suicide attempt. Only one such study can be found in the extant literature. That study, which evaluated 14 acutely suicidal patients at Yale's psychiatric emergency room, found that open-label, intravenous ketamine (0.2mg/kg intravenous ketamine, administered over the span of one to two minutes) had rapid

anti-suicidal and antidepressant efficacy [41]. The above data suggest that future investigations into the specific neuro-biological and/or psychological effects of ketamine on suicidal thinking are warranted.

Safety & Tolerability

Ketamine has a long history of safe clinical use and was approved by the United States Food and Drug Administration (FDA) as a dissociative anesthetic in the 1960s [42]. In addition to studies investigating ketamine's utility for treating mood disorders, the supervised use of ketamine has expanded into other areas of neuropsychiatric research, most notably the transient induction of schizophrenia-like symptoms in healthy volunteers [43, 44]. In an initial evaluation of ketamine's safety and tolerability in neuropsychiatric research, Perry and colleagues described 450 subjects who received a total of 833 ketamine infusions. Only 10 adverse mental status changes (for instance, excessive sedation and acute dysphoria) were noted in their analysis, and these symptoms resolved in all but one patient by the end of the testing day. Of the patients who agreed to a week-long follow-up, only three reported adverse effects in the post-infusion period (nausea, fatigue, headache, lightheadedness, or nightmares/vivid dreams). No post-infusion neuropsychiatric sequelae were reported, *e.g.* increased anxiety or ketamine cravings. After this initial report, a secondary follow-up analysis reported two cases of next-day dysphoria, anxiety, and suicidal ideation in two subjects with obsessive-compulsive disorder (OCD), MDD, and personality vulnerabilities who received open-label subanesthetic-dose ketamine (0.5mg/kg x 40 minutes) [45].

Mt. Sinai and Baylor combined their datasets to perform a systematic safety and tolerability analysis from their psychoactive placebo (midazolam) and multiple infusion ketamine trials [46]. Data were pooled from 97 MDD patients who received a total of 205 intravenous ketamine infusions over a six-year span. Four of the 205 infusions were discontinued due to adverse events—two due to increased blood pressure, one to transient hypotension and bradycardia during venipuncture, and one because of anxiety. The attrition rate was 3.1%. Among the dropouts, the most commonly reported adverse effects were sedation, dizziness, incoordination, lightheadedness, blurry vision, and derealization/depersonalization. Subanesthetic dose ketamine also resulted in increased but transient feelings of dissociation and hemodynamic vital sign changes. Despite these short-term adverse effects, no patients reported any long-term problems as a result of their research participation.

Other Non-Selective/Non-Competitive NMDA Receptor Antagonists

Some of the major clinical concerns with the use of ketamine as an antidepressant are its typical non-parenteral administration, its side effects (particularly its acute dissociative and psychotomimetic properties), and the potential abuse liability and neurotoxicity associated with its chronic use. As a result, other NMDA receptor antagonists with high oral bioavailability and/or more benign side effect profiles have been studied for the treatment of MDD.

Memantine, another non-competitive NMDA receptor antagonist, is FDA-approved for the treatment of moderate-to-severe Alzheimer's-like dementia. Two studies found that memantine had preliminary antidepressant-like efficacy in rodent models of despair [47, 48]. In the first clinical trial of memantine in MDD—an eight-week, double-blind, placebo-controlled study—daily memantine (5-20 mg/day) did not separate from placebo on the primary antidepressant measure [49]. In 2008, a case study reported antidepressant efficacy with repeated-dose ketamine followed by memantine; it should be noted that the patient was eventually placed on seven psychotropic medications, but remained in remission for 13 weeks [50]. Recently, Gideons and colleagues investigated potential antidepressant mechanistic differences between memantine and ketamine in rodents [51]. They found that memantine had no antidepressant-like effects as assessed by the forced swim test and novelty-suppressed feeding paradigm. In addition, at physiological doses of magnesium (Mg^{2+}), ketamine, but not memantine, inhibited the phosphorylation of eukaryotic elongation factor-2 (eEF2) and increased brain-derived neurotrophic factor (BDNF) expression.

Like ketamine, the antitussive dextromethorphan is a non-selective, non-competitive NMDA receptor antagonist with abuse liability [52] as well as theoretical potential as a rapid-acting antidepressant [53, 54]. To date, no randomized controlled trials have explored dextromethorphan as monotherapy for the treatment of depressive disorders, although it has been studied in a randomized, placebo-controlled trial as add-on to valproic acid in bipolar disorder [55]. One case report found that dextromethorphan-quinidine, which has been approved for the treatment of pseudobulbar affect under the trade name Nuedexta®, had antidepressant effects in a single depressed patient with emotional lability [56]. Finally, a randomized controlled trial of Nuedexta is currently being conducted in TRD (ClinicalTrials.gov identifier: NCT01882829).

AZD6765 is another non-selective, non-competitive NMDA receptor antagonist with a Ki (inhibitory constant) similar to ketamine (AZD6765=0.56-1.48 μM; ketamine=0.76 μM) [57], but lower trapping, *i.e.* greater on-off NMDA receptor pharmacodynamics. Because ketamine has greater receptor affinity, AZD6765 may have reduced psychotomimetic or dissociative adverse effects while retaining antidepressant efficacy. A single 150mg infusion of AZD6765 in unmedicated TRD patients had antidepressant efficacy over placebo without increased psychosis or dissociation; however, the antidepressant response was not as robust or sustained as ketamine's—AZD6765 had lower response rates, lower remission rates, and a shorter duration of effect [58]. In a subsequent three-week, placebo-controlled trial, TRD patients received repeated adjunctive AZD6765 (now renamed lanicemine) infusions at two doses (100mg and 150mg); as hypothesized, lanicemine had antidepressant effects without ketamine-like side effects [59]. However, in a six-week phase IIb study, adjunctive repeated-dose (50mg and 150mg) lanicemine failed to separate from placebo, potentially due to the large placebo effect (39% placebo response rate at trial end) [60, 61].

Subunit-Selective (NR2B) NMDA Receptor Antagonists

Like the non-trapping antagonists discussed above, subtype-specific NMDA receptor antagonists may have fewer undesirable adverse effects while retaining antidepressant activity. One preclinical study using the unpredictable foot shock paradigm found that the NR2B antagonist Ro 25-6981 had antidepressant-like behavioral effects and also increased the expression of postsynaptic and second messenger intermediaries (including mechanistic target of rapamycin (mTOR)) as rapidly as ketamine [62]. A randomized, double-blind, placebo-controlled study of the intravenous NR2B-selective receptor antagonist CP-101,606 in TRD (n=30) found a 60% response rate compared to 20% in the placebo group; 78% of treatment responders maintained this antidepressant effect for at least one week [63]. However, the continued development of this compound was halted due to potential cardiovascular toxicity (specifically, QTc prolongation). Another small, randomized, double-blind, placebo-controlled, cross-over pilot study assessed the efficacy of an oral NR2B antagonist, MK-0657, in TRD [64]. Although antidepressant improvement was demonstrated with other depression rating scales, no improvement was observed over placebo using the primary outcome measure (MADRS). Nevertheless, MK-0657 is now being developed by Cerecor and has been renamed CERC-301.

NMDA RECEPTOR PARTIAL AGONISTS

D-cycloserine (DCS)

D-cycloserine (DCS) is a broad-spectrum antibiotic previously used for treatment-resistant tuberculosis; it is also a partial agonist at the NMDA receptor's glycine site and, at doses ≥ 100mg/day, is a functional NMDA receptor antagonist [65]. In an initial six-week, placebo-controlled, cross-over trial of 250mg/day as adjunctive treatment in TRD, DCS reduced depressive symptoms but did not separate from placebo (p=0.51) due to a high placebo response rate [66]. A larger trial of 26 TRD patients (by the same research group and with the same trial design) assessed the efficacy of escalating-dose (up to 1000mg/day) adjunctive DCS [67]. In this trial, higher-dose DCS had improved antidepressant effects as measured by the clinician-administered HAM-D (p=0.005) and self-reported Beck Depression Inventory (BDI) (p=0.046). Interestingly, 54% of the patients randomized to high-dose DCS had a ≥50% reduction in HAM-D scores by the end of the trial.

GLYX-13

GLYX-13 is an amidated tetrapeptide glycine-site modulator at NR2B-containing NMDA receptors that is hypothesized to be a partial agonist [68-70]. GLYX-13 has a seven-minute plasma half-life and appears to readily cross the blood-brain barrier. Among its other effects in preclinical paradigms, it increases long-term potentiation and reduces long-term depression to enhance learning and memory. Both peripheral administration and direct infusion into the medial prefrontal cortex of GYLX-13 in rodent models of despair (Porsolt, novelty-induced hypophagia, learned helplessness) had antidepressant-like effects and no psychotomimetic effects.

Based on these preclinical observations, GLYX-13 has been in clinical development by Naurex, Inc. The results of a Phase IIb safety and efficacy trial were reported in 2014 [71]. In this study, unmedicated TRD inpatients were randomized to receive a single saline placebo (n=33) or GLYX-13 intravenous infusion (1m/kg (n=25), 5mg/kg (n=20), 10 mg/kg (n=17), or 30 mg/kg (n=21) over three to 15 minutes (prespecified based on dose and weight). Subjects randomized to the 5 and 10 mg/kg arms had a significant antidepressant response compared to placebo one week after administration. The 1 and 30 mg/kg arms did not statistically separate from placebo, suggesting an "inverted U" antidepressant response that has been observed with other NMDA receptor modulators. Unlike NMDA receptor antagonists, GLYX-13 infusion at any dose was not associated with psychotomimetic properties. No serious adverse events were reported in this study, and the most prevalent side effect was dizziness (10%).

The Naurex group also recently published the results of a randomized, double-blind, clinical trial of adjunctive GLYX-13 in TRD [72, 73]. All currently depressed TRD participants were maintained on their current psychotropic medication regimen and randomized to 5mg/kg or 10 mg/kg intravenous GLYX-13 weekly for six weeks. If a subject achieved antidepressant response (as defined by a ≥50% improvement from baseline HAM-D score), the subject was then switched to placebo infusion until relapse occurred. At the end of this initial six-week phase, subjects were then randomized to either weekly or biweekly dosing (based on time-to-relapse) of either adjunctive GLYX-13 or placebo infusion for the following six weeks. In the final phase of the study, all subjects received weekly placebo infusions for four weeks and were then monitored for relapse. At the end of the initial phase, 53% (195/368) achieved antidepressant response, and 67% relapsed within two weeks. The remaining 33% who relapsed more slowly were randomized to the biweekly phase. Of these patients, 65% achieved response and 45% achieved remission; no statistically significant differences were observed between the 5 and 10 mg/kg groups. After the six-week randomized withdrawal period, GLYX-13 was not associated with depression relapse for up to 10 weeks. However, no statistically significant difference in relapse was observed between GLYX-13 and placebo during this discontinuation phase.

Naurex, Inc. has also developed NRX-1074, an orally-bioavailable analogue of GLYX-13, which is purportedly several thousand-fold more potent than GLYX-13 at the glycine partial agonist site [unpublished data available at www.naurex.com/pipeline/nrx-1074]. Although these glycine partial agonists are exciting and promising lead compounds for the treatment of depression, these preliminary results await replication and peer-reviewed confirmation in larger cohorts.

AMPA AGONISTS ("AMPA POTENTIATORS, AMPAKINES")

Because ketamine's antidepressant efficacy is hypothesized to depend on AMPA receptor activation in response to increased synaptic glutamate [74-76], there is theoretical interest in developing AMPA receptor agonists

("AMPA potentiators" or AMPAkines) for the treatment of MDD. Preclinical studies found that these agents exhibit antidepressant-like efficacy [77, 78], and several lead AMPA agonists are being developed to treat MDD, including the AMPA agonist farmampator (CX-691/ORG 2448). ORG-26576, an AMPA receptor positive allosteric modulator, is the most developed of these compounds in the drug development pipeline. An initial dose selection study with both healthy volunteers and MDD subjects found that MDD patients (n=54) tolerated twice the maximum tolerated dose as healthy volunteers (n=36) [79]; in response, a phase Ib safety and efficacy trial was performed that confirmed the maximum tolerated dose (450mg po bid) and demonstrated preliminary antidepressant efficacy in a small cohort (n=30) [80]. Although subjects randomized to 400mg po bid had numerically greater improvement relative to 100mg po bid and placebo, none of the arms statistically separated over the 28-day testing period. Nevertheless, the higher dose was associated with improved speed of information processing, improved executive functioning, increased growth hormone, and decreased cortisol; no effect was seen on prolactin or BDNF levels. Finally, quantitative electroencephalogram Antidepressant Treatment Response index (i.e. reductions in frontal cordance/activity [81]) at one week predicted symptomatic improvement in social acuity by trial end. As is true for other glutamate modulators, replication in larger cohorts will be critical to assess the overall safety, tolerability, and antidepressant efficacy of AMPA receptor modulators.

METABOTROPIC GLUTAMATE RECEPTOR MODULATORS

Type I – mGluR2/3 Negative Allosteric Modulators

mGluR2/3s are located presynaptically at glutamatergic synapses; their activation decreases neurotransmitter release and, therefore, limits excitotoxicity from excessive synaptic glutamate levels and NMDA receptor over-activation. Both mGluR2/3 antagonists and negative allosteric modulators have been studied for the treatment of MDD. Several mGluR2/3 antagonists [82, 83] as well as the negative allosteric modulator RO4995819 [84] were found to have antidepressant-like efficacy in rodent models of depression. In a mouse model of despair, the mGluR2/3 negative allosteric modulator RO4432727 reversed some of the prototypical cognitive impairments observed in MDD—for instance, short-term memory deficits, cognitive rigidity, and compulsive decision-making [85]. In addition, the safety and tolerability of mGluR2/3 modulators have been investigated in healthy volunteers (ClinicalTrials.gov identifiers NCT01547703 and NCT01546051) but, to date, these mGluR2/3 modulators have not been studied clinically for the treatment of MDD.

Type II – mGluR5 Negative Allosteric Modulators

mGluR5s are extrasynaptically localized at postsynaptic densities, and their activation potentially limits the excitotoxic synaptic spillover of glutamate. mGluR5 activation stimulates downstream G-protein coupled pathways linked to phospholipase C. mGluR5 activation also plays a critical role in local mRNA translation at dendritic spines [86]. Inhibition of this local translation is one of the proposed mechanisms of efficacy for mGluR5 antagonists in Fragile X Syndrome [87]. Several mGluR5 antagonists have demonstrated anxiolytic and antidepressant-like activity in preclinical rodent models, including 2-methyl-6-(phenylethynyl)-pyridine (MPEP) [88, 89] and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) [90-92].

Several mGluR5 antagonists have been studied in TRD. AZD2066 12-18 mg/day was studied in a three-arm (vs oral placebo and the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine 30-60mg/day), six-week randomized controlled trial (NCT01145755). None of the arms statistically separated based on either total score change from baseline on the primary outcome measure (MADRS), depression response, or depression remission. Due diligence was done in a dose-finding PET receptor occupancy study in healthy volunteers, which found a diffuse dose-dependent occupancy of radioligand at mGluR5 [93]. No open studies with AZD2066 are currently listed on ClinicalTrials.gov.

In addition, an F. Hoffman-La Roche compound, RO4917523 (basimglurant, RG7090), has been studied in TRD [93]. 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 yet to be reported on ClinicalTrials.gov or in a peer-reviewed journal. A completed phase IIb (MARIGOLD) study compared adjunctive (to concomitant selective serotonin reuptake inhibitor (SSRI) or SNRI) modified-release basimglurant (0.5 and 1.5mg) to adjunctive placebo over nine weeks in individuals with TRD (six weeks double-blind treatment, three weeks post-treatment follow-up) [94]. Patients (n=333) were randomized to the three treatment conditions (n=108 adjunctive placebo, n=112 adjunctive basimglurant 0.5mg, and n=111 adjunctive basimglurant 1.5mg). No statistically significant difference was observed on the primary endpoint (mean MADRS change from baseline to six weeks) in the context of a 47% placebo response rate, but promising results were observed on several exploratory secondary endpoints, including patient self-reported depression scores at 1.5mg vs. placebo. The most common adverse events were dizziness (23%) and two self-resolving cases of mania at the 1.5mg dose.

Type III – mGluR7 Positive Allosteric Modulators

Type III mGluRs (4-8) are mainly expressed presynaptically to modulate glutamate release and response, *i.e.* coupling to inhibitory G-proteins and subsequently inhibiting the adenylyl cyclase/protein kinase A intracellular second messenger/signal transduction cascade. To date, no compounds with known primary activity at type III mGluRs have been investigated in clinical studies for the treatment of MDD. However, the preclinical literature has identified several potential type III mGluR targets. mGluR7 null mice have a resilient phenotype in standard depression and

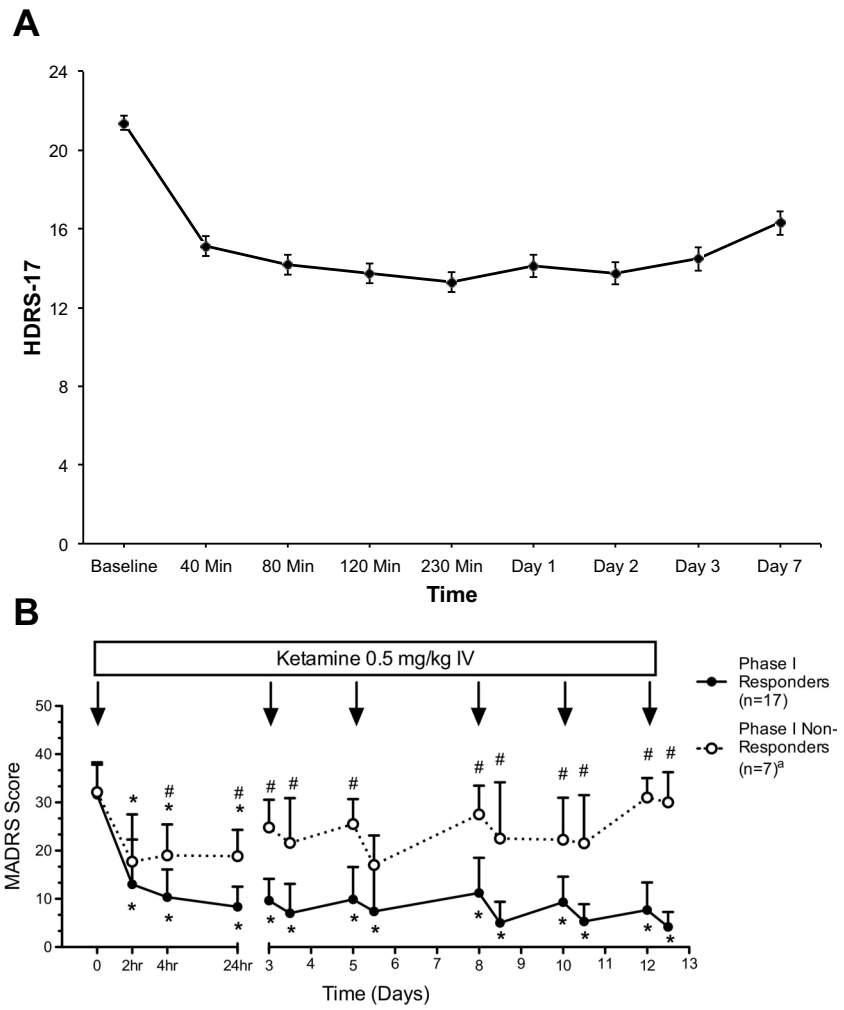

Fig. (2). Single and Multiple Subanesthetic Dose Ketamine Infusion Studies in Major Depression. A. Change in severity of depressive symptoms after a single subanesthetic dose ketamine infusion (0.5mg/kg x 40 minutes) in treatment-resistant major depressive disorder (MDD) and bipolar I/II depression (n=136) as measured by the 17-item Hamilton Depression Rating Scale (HAM-D17) score (mean ± SE) over one week post-infusion. The 136 subjects were obtained from four separate protocols: 1) unmedicated subjects with treatment-resistant MDD (TRD) (n=21) [10]; 2) subjects with treatment-resistant bipolar depression maintained on either lithium or valproate (n=34) [102, 103]; 3) unmedicated TRD subjects who received an open-label ketamine infusion followed by double-blind randomization to either placebo (n=31) or riluzole (n=24) [104]; and 4) an unpublished cohort of combined TRD and treatment-resistant bipolar depression subjects who underwent neuroimaging (n=26). **B.** Change in severity of depressive symptoms after repeated ketamine infusions in TRD. The figure depicts change in depression severity as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) (mean ± SD) over a 12-day period during which ketamine (0.5 mg/kg) was administered intravenously on a Monday-Wednesday-Friday schedule, corresponding to study days 0, 3, 5, 8, 10, and 12. Trajectories of depressive symptom severity are plotted for Phase I responder and nonresponder subgroups, defined using final observed MADRS score. Depression severity was initially measured at baseline before the first ketamine infusion and then at 2, 4, and 24 hours while participants were inpatients. Subsequent infusions occurred on an outpatient basis, and depression severity was measured in the morning before each infusion and then at four hours post-infusion. *MADRS score significantly decreased at given time point compared with baseline, $p < 0.05$. #MADRS score significantly different at given time point between responder and nonresponder subgroups. [a]Three participants in the nonresponder group did not receive all six ketamine infusions. Fig. **2B** and its corresponding legend are reproduced with permission from [16].

anxiety-provocation paradigms [95], and mGluR7 mRNA expression is increased in the stress-sensitive Wistar Kyoto rat [96]. Based on these initial findings, the mGluR7 positive allosteric modulator AMN082 was unexpectedly found to have antidepressant-like properties in rodent models of despair [97, 98], potentially due to its ability to modulate the phosphorylation of other glutamate receptors (NMDA, AMPA) in the hippocampus [99]. AMN082 also increased synaptic protein levels (synapsin I, GluR1) and mTOR phosphorylation in the prefrontal cortex [100], which overlaps with ketamine's known antidepressant mechanisms of action [101].

Table 2. Glutamate receptor targets for the treatment of major depressive disorder (MDD).

Mechanism of Action	Examples
Non-selective NMDA Receptor Antagonists	Ketamine, Memantine, Dextromethorphan, AZD6765/lanicemine
NR2B-Selective Receptor Antagonists	CP-101,606/Traxoprodil, MK-0657/CERC-301
NMDA Receptor Glycine-Site Partial Agonists	D-cycloserine, GLYX-13, NRX-1074
AMPA Agonists/Positive Allosteric Modulators	ORG-26576
mGluR2/3 Negative Allosteric Modulators	none studied in MDD to date
mGluR5 Negative Allosteric Modulators	AZD2066, RO4917523/Basimglurant
mGluR7 Positive Allosteric Modulators	none studied in MDD to date

Abbreviations: NMDA: N-methyl-D-aspartate; AMPA: α-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid; mGluR: metabotropic glutamate receptor.

CONCLUSION

Table **2** reviews a number of potential compounds that bind to and modulate ionotropic and mGluR response and antidepressant activity in clinical trials for MDD. It is, however, beyond the scope of this paper to review the many other medications demonstrating indirect glutamatergic effects and antidepressant efficacy in mood dysregulation, including lamotrigine, topiramate, and riluzole. Among these compounds that bind directly to a glutamate receptor, subanesthetic doses of the non-competitive NMDA receptor antagonist ketamine have emerged as the most promising antidepressant treatment. Despite the preponderance of the evidence, some investigators question whether ketamine has additional non-glutamatergic mechanism(s)—for instance, monoaminergic or opioidergic—that contribute to its antidepressant efficacy [60]. It should be noted that glutamate is the major excitatory neurotransmitter in the central nervous system (CNS); it is estimated that up to 50% of CNS neurons use glutamate as their primary neurotransmitter in contrast to only 10-20% of monoaminergic neurons. In addition, both clinical and preclinical studies support the notion that glutamatergic dysfunction plays a key role in the pathophysiology of MDD, suggesting that a subsidiary role for glutamate in ketamine's antidepressant response is unlikely. Despite their promise, ketamine and related glutamatergic medications cannot presently be routinely recommended outside of a research milieu due to the lack of multi-site, randomized, placebo-(and active placebo) controlled trials with much larger samples (n>100) to better assess efficacy, safety, and tolerability. However, some experts now consider ketamine as a late option in the treatment algorithm for (temporary) symptom relief, and/or a bridge to alternative therapies in specialized TRD clinics.

Future research should focus on modulating *specific* glutamatergic circuitry thought to be involved in antidepressant response to ketamine and other glutamate receptor modulators (for instance, GABAergic cortical interneurons to glutamatergic cortical outflow (pyramidal) neurons). Manipulation of this circuitry may occur either pharmacologically—for instance, via more selective glutamatergic medications—or technologically—for instance, via transcranial magnetic or deep brain stimulation—to redress circuitry-level deficits in TRD.

CONFLICT OF INTEREST

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