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REVIEW ARTICLE

Ketamine and Beyond: Investigations into the Potential of Glutamatergic Agents to Treat Depression

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Abstract Clinical and preclinical studies suggest that dysfunction of the glutamatergic system is implicated in mood disorders such as major depressive disorder and bipolar depression. In clinical studies of individuals with major depressive disorder and bipolar depression, rapid reductions in depressive symptoms have been observed in response to subanesthetic-dose ketamine, an agent whose mechanism of action involves the modulation of glutamatergic signaling. The findings from these studies have prompted the repurposing and/or development of other glutamatergic modulators for antidepressant efficacy, both as monotherapy or as an adjunct to conventional monoaminergic antidepressants. This review highlights the evidence supporting the antidepressant effects of subanesthetic-dose ketamine as well as other glutamatergic modulators, such as D-cycloserine, riluzole, CP-101,606, CERC-301 (previously known as MK-0657), basimglurant, JNJ-40411813, dextromethorphan, nitrous oxide, GLYX-13, and esketamine.

Key Points

This review highlights evidence supporting the antidepressant effects of subanesthetic-dose ketamine as a prototypical glutamatergic-modulating agent from which other glutamatergic agents have been investigated.

Evidence suggests that ketamine may have broad biological effects on the glutamatergic system and may exert its clinical efficacy by altering other symptom domains related to depression, such as anxiety and suicidality.

This review also highlights important safety concerns regarding ketamine and selected glutamatergic agents to promote the continued development of novel, effective, and safe antidepressant drug treatments.

1 Introduction

Recent preclinical and clinical evidence implicates glutamatergic system impairments in mood disorders such as major depressive disorder (MDD) and bipolar depression. In particular, results from clinical studies have consistently found that subanesthetic intravenous (IV) doses of the glutamatergic modulator ketamine [1] exert rapid antidepressant effects [2–4]. In contrast to conventional monoaminergic antidepressants, which are associated with a 40–47% response rate and a lag time of weeks to months before onset of clinical effects [5], ketamine has been associated with a 65–70% response rate and a significant

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antidepressant response that occurs within 24 h and lasts for up to 1 week of single [2, 3, 6] and repeated [7–9] infusions. These findings have shifted our conceptualization of the pathophysiology of depression, extended the focus of research towards the glutamatergic system for identifying potential novel biomarkers for depression [10, 11], and urged new treatment paradigms in depression [6, 12–14]. Indeed, over the last decade, there has been a significant per annum increase in the rate of published clinical trials investigating the effectiveness of glutamatergic agents as rapid antidepressants, leading to a reawakening of a psychopharmacologic dormancy in this research area. Here, we provide a summary and update of published clinical studies examining the safety and antidepressant efficacy of glutamatergic agents, highlighting studies of subanesthetic-dose ketamine as a model for glutamatergic modulation and offering new directions based on emerging evidence from these studies.

2 Ketamine as a Prototypic Glutamatergic Antidepressant Agent

A glutamatergic hypothesis of depression has been posited, in large part owing to the growing clinical evidence that a single subanesthetic dose (0.5 mg/kg) of IV ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist and synaptic glutamatergic modulator, exerts antidepressant effects as rapidly as 24 h after administration; these effects have been found to last up to 7 days [15, 16].

2.1 Preclinical Studies of Stress, Depression, and Glutamate

In preclinical ketamine studies, alterations in rodent cortical glutamate levels have been associated with pharmacologic- and stress-induced depressive-like behaviors [17–19]. Animal models of stress-induced depression have shown that changes in the pattern of neuronal functioning affect both prefrontal cortical and hippocampal areas [20–25]. While acute stress appears to enhance glutamate transmission in the prefrontal cortex [26–28], chronic stress has been shown to induce dysfunction in glutamatergic neurotransmission coupled with changes in synaptic activity in the prefrontal cortex [25, 29] and hippocampus [24]. These changes have been associated with increased long-term depression as well as deficits in the ability to induce or maintain long-term potentiation [22, 29]. In association with long-term administration of traditional monoaminergic antidepressants, many of these stress-induced alterations, including glutamatergic neurotransmission [30] and pyramidal neuronal morphology and function [25], have been reversed. As a result, reversal of stress-induced changes has been linked to an antidepressant-like response to monoaminergic modulation, as well as to electroconvulsive therapy (ECT) [31, 32].

Interestingly, preclinical studies have demonstrated that behavioral changes seen in response to the rapid-acting antidepressant effects associated with ketamine may be more directly linked to direct modulation of glutamate in affected brain regions [20, 21, 23, 27, 33]. These functional changes in glutamatergic neurotransmission have been associated with neuronal morphological remodeling, dendritic retraction, and synaptic reorganization, particularly within cortical areas [33, 34]. Although data drawn from clinical studies are more controversial, alterations in glutamatergic transmission and neuronal morphology have also been reported in patients experiencing mood disorders [35–37].

Notably, a recent series of preclinical bio-behavioral and pharmacologic studies found that the antidepressant actions of ketamine may be the result of the metabolites of ketamine rather than from the *R,S*-ketamine molecule alone [38]. In this preclinical study series, the metabolism of (*R,S*)-ketamine to (*2S,6S;2R,6R*)-hydroxynorketamine (HNK) was found to be necessary for the antidepressant effects of ketamine; furthermore, the (*2R,6R*)-HNK enantiomer was found to exert antidepressant effects via early and sustained activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors independent of NMDA receptor inhibition. These findings shift the conceptualization of the potential mechanism of action of ketamine as an antidepressant agent and also open opportunities towards a more direct means of reducing depressive symptoms via glutamatergic modulation.

2.2 Discovery of the Antidepressant Effect of Ketamine

For nearly half a century, ketamine has been safely and effectively used to induce anesthesia [39] and, more recently, for procedural sedation in children in emergency medical settings [40, 41]. The earliest clinical evidence of the potential antidepressant properties of ketamine was demonstrated over a decade ago in a small double-blind study of eight depressed patients (seven with MDD, one with bipolar depression) randomized to receive either a subanesthetic (0.5 mg/kg) dose of IV ketamine or saline placebo. Four out of eight patients ($n = 7$ completers) experienced an antidepressant response to ketamine, as defined by a reduction of 50% or greater on the Hamilton Depression Rating Scale (HAM-D) [2]. Subsequent to this study, our group and others replicated this ketamine-associated antidepressant response in clinical trials with single and repeated administrations under open-label, double-blind, placebo-controlled, and double-blind active

comparator conditions via parallel-arm or crossover treatment paradigms, but notably in treatment-resistant depression [15] (see also Table 1). In the sections that follow, we highlight ketamine as the model glutamatergic agent, particularly because it is the best studied and, to date, the most efficacious of the glutamatergic agents [15, 42]. Unfortunately, other glutamatergic-modulating agents that have been developed and investigated in small clinical trials [15, 16] have not yielded such promising results. However, recent studies examining the properties of ketamine [43] and its metabolites [38] have begun to reveal the molecular mechanisms underlying the antidepressant effects of ketamine.

2.3 Characteristics of the Antidepressant Effect of Ketamine in MDD and Bipolar Depression

Since the initial clinical study by Berman and colleagues [2], our group and others have consistently demonstrated that a single IV infusion of 0.5 mg/kg of ketamine produces an antidepressant response in individuals with treatment-resistant MDD [3, 7, 44, 45]. Depressive symptoms and severity in these studies have traditionally been measured with either the HAM-D [46] (at least 17-item versions) or the Montgomery–Åsberg Depression Rating Scale (MADRS) [47], with antidepressant response defined as a $\geq$50% reduction in total score. Furthermore, in most of these studies, antidepressant response was observed in subjects who had previously not responded to at least two antidepressant medications [i.e., subjects with treatment-resistant depression (TRD)] [3, 7, 48], suggesting that ketamine may be equally effective in treating patients with a more severe type of depression. The time course of antidepressant response to ketamine is characterized by an initial reduction in depressive symptoms within 2 h, a maximal reduction in depressive symptoms within 24 h, and a sustained response for up to 1 week after administration [3, 15]. Independent single- and multi-site collaborations [3, 7] have noted that 1 day after administration, response rates ranged between 66 and 77%, and remission rates (defined as a MADRS score of $\leq$7 or 9) hovered at around 31% (reviewed in [49]).

It is important to note that, within 4 h to 1 day, a single infusion of ketamine in TRD patients achieved response rates comparable to that seen following 8 weeks of treatment with monoaminergic-based antidepressants in non-TRD patients. The fact that ketamine is capable of inducing remission in approximately one-third of TRD patients within a single day is in stark contrast to the effectiveness of monoaminergic-based approaches, which usually require 10–14 weeks of long-term use to produce similar remission rates [5]. These results introduced a new paradigm for the research and development of antidepressants with a rapid onset of action.

The potential antidepressant effects of ketamine have also been evaluated in patients with bipolar depression [2, 48, 50, 51]; please note that clinical studies examining whether ketamine affects the response to ECT are discussed in greater detail in Sect. 3 below ([52, 53], see also Table 1). Our group tested ketamine in a double-blind, add-on [to lithium or valproate (VPA)], placebo-controlled, crossover study of subjects with treatment-resistant bipolar depression [50]. Similar to patients with MDD, depressive symptoms significantly improved in subjects with bipolar depression receiving ketamine compared with those who received placebo. This antidepressant effect was seen most robustly within the first hour after administration (at 40 min) and remained significant through day 3. Seventy-one percent of patients responded to ketamine and 6% responded to placebo at some point during the trial. This finding was replicated in an independent cohort of patients with treatment-resistant bipolar depression [48]. In the replication study, 79% of subjects responded to ketamine and none responded to placebo at some point during the trial.

Notably, a recent meta-analysis of seven clinical trials examining antidepressant response to ketamine found that the odds ratio for an antidepressant response was 8.42 [95% confidence interval (CI) 3.47–20.39; $p < 0.001$] in MDD, and 24.05 (95% CI 2.96–195.56; $p = 0.003$) in bipolar depression. In the bipolar depression studies included in the meta-analysis, a statistically significant rate of symptom remission was found on day 1 (odds ratio 14.01, 95% CI 1.73–111.70, $p = 0.013$) but not on day 7 (odds ratio 1.51, 95% CI 0.22–10.49, $p = 0.674$); it should be noted that all of the bipolar depression studies used ketamine to augment therapy with a conventional mood stabilizer [15]. In contrast, another meta-analysis of five randomized control trials (two of which were conducted in patients with bipolar depression) examined the utility of ketamine administration as an adjunct to ECT and found significantly smaller standardized mean differences in response in MDD patients vs. those with bipolar depression [54]. These two meta-analyses were based on only a few existing published studies of ketamine administration in patients with bipolar depression; thus, it remains unclear whether response and remission rates differ between patients with MDD and those with bipolar depression. In addition, it is important to note that despite the hypothetically increased risk of developing mania or psychosis in response to an NMDA receptor antagonist, the risk of developing mania in response to a single ketamine infusion does not appear to be greater in patients with bipolar depression who are concurrently taking lithium or VPA [55].

Table 1 Clinical studies of ketamine in depression in chronological order

Authors, year, reference	Sample (*n*)	Diagnostic groups	Dosing and treatment groups	Clinical trial design	Primary outcome measure	Significance and findings
Berman et al. 2000 [2]	8	MDD, BD	Single-dose ketamine IV (0.5 mg/kg) vs. placebo	Randomized, double-blind, crossover	HAM-D25, BDI	Improvement in depressive symptoms within 72 h after ketamine compared with placebo; HAM-D scores decreased by 14 ± 10 vs. 0 ± 12
Zarate et al. 2006 [3]	17	MDD (TRD)	Two doses (1 week apart) of ketamine IV (0.5 mg/kg) vs. placebo	Randomized, double-blind, crossover	HAM-D21	Improvement in depressive symptoms greater in ketamine than in placebo group within 110 min; effect remained significant throughout following week. Effect size for drug difference, $d = 1.46$ (95% CI 0.91–2.01) after 24 h and $d = 0.68$ (95% CI 0.13–1.23) after 1 week. 71% of subjects met response and 29% met remission criteria the day following ketamine infusion. 35% of subjects maintained response for at least 1 week
Price et al. 2009 [56]	26	MDD (TRD)	Single- and repeated-dose ($n = 9$) ketamine IV (0.5 mg/kg)	Open-label	MADRS, IAT	Improvement in suicidality on average by 2.08 points on a 0–6 scale ($p < 0.001$; $d = 1.37$), and 81% of patients received a rating of 0 or 1 post-infusion on the MADRS suicide item. Implicit suicidal associations reduced following ketamine ($p < 0.003$; $d = 1.36$), with reductions correlated across implicit and explicit measures. Reductions in suicidality were sustained for 12 days by repeated-dose ketamine ($p < 0.001$; $d = 2.42$)
Diazgranados et al. 2010 [50]	16	BD (receiving lithium or VPA)	Single-dose ketamine IV (0.5 mg/kg) vs. placebo	Randomized, double-blind, crossover	MADRS	Improvement in depressive symptoms at 40 min in ketamine group compared with placebo ($d = 0.52$, 95% CI 0.28–0.76), remaining significant through day 3. Drug difference effect size was largest at day 2 ($d = 0.80$, 95% CI, 0.55–1.04). 71% of subjects responded to ketamine and 6% responded to placebo at some point during the trial. One subject receiving ketamine and one receiving placebo developed manic symptoms
Diazgranados et al. 2010 [57]	33	MDD (TRD)	Single-dose ketamine IV (0.5 mg/kg)	Open-label	MADRS, HAM-D, BDI, SSI	Suicidal ideation scores decreased significantly on the SSI within 40 min, remaining significant through the first 4 h post-infusion ($p < 0.001$). Ten subjects (30%) had an SSI score ≥ 4 at baseline; all these scores dropped below 4 (nine dropped by 40 min and one by 80 min). Depression, anxiety, and hopelessness improved at all timepoints ($p < 0.001$)
Aan het Rot et al. 2010 [49]	10	MDD (TRD)	Repeated-dose (six in 12 days) ketamine IV (0.5 mg/kg)	Open-label	MADRS	Improvement in depressive symptoms with an 85% (12%) mean SD reduction in MADRS scores after the sixth infusion. Eight of nine patients relapsed, on average, 19 days after the sixth infusion (range 6–45 days). One patient remained antidepressant free with minimal depressive symptoms for more than 3 months
Ibrahim et al. 2011 [100]	17 23	MDD (TRD, with and without history of ECT)	Single-dose ketamine IV (0.5 mg/kg)	Open-label	MADRS	Improvement in depressive symptoms in the ECT-resistant group at 230 min with a moderate effect size ($p < 0.001$, $d = 0.50$, 95% CI 0.21–0.80). At 230 min, the non-ECT exposed group showed significant improvement with a large effect size ($p < 0.001$, $d = 1.00$, 95% CI 0.71–1.29)

Table 1 continued

Authors, year, reference	Sample (*n*)	Diagnostic groups	Dosing and treatment groups	Clinical trial design	Primary outcome measure	Significance and findings
Larkin and Beautrais 2011 [58]	14	Suicidal ideation in emergency department	Single-dose ketamine IV (0.2 mg/kg) bolus	Open-label	MADRS	Improvement in depressive symptom scores at 240 min. Improvement in suicidality scores from 3.9 (SEM = 0.4) at baseline to 0.6 (SEM = 0.2) after 40 min post-administration with sustained improvements over 10 days
Zarate et al. 2012 [48]	14	BD (taking lithium or VPA)	Two doses (2 weeks apart) ketamine IV (0.5 mg/kg) vs. placebo	Randomized, double-blind, crossover	MADRS	Improvement in depressive symptoms and suicidal ideation within 40 min in ketamine vs. placebo groups ($d = 0.89$, 95% CI 0.61–1.16 and 0.98, 95% CI 0.64–1.33, respectively), which remained significant through day 3. 79% of subjects responded to ketamine and 0% responded to placebo at some point during the trial. The most common side effects were dissociative symptoms, which occurred only at 40 min
Abdallah et al. 2012 [52]	16	MDD, BD	Single-dose pre-ECT ketamine IV (0.5 mg/kg) plus thiopental vs. thiopental only	Randomized, double-blind, parallel	HAM-D25	ECT improved depressive symptoms in both groups ($F(2,24) = 14.35$, $p < 0.001$). No significant group effect or group-by-time interaction on HAM-D scores. Post-hoc analyses of the time effect on HAM-D showed no significant HAM-D reduction after the first ECT session for either group
Loo et al. 2012 [53]	46	MDD, BD	Single-dose pre-ECT ketamine IV (0.5 mg/kg) plus thiopental vs. thiopental only	Randomized, double-blind, parallel	HAM-D25	The ECT-ketamine group had a slightly greater improvement in depressive symptoms over the first week of treatment and at 1 week. No difference in efficacy at the end of the ECT course. No psychotomimetic effects
Wang et al. 2012 [88]	48	MDD (pre-ECT, ECT)	Single-dose pre-ECT ketamine IV 0.5 mg/kg plus propofol vs. ketamine only and propofol only	Randomized, double-blind, parallel	HAM-D17	Improvement in depressive symptoms found in all groups from 1 to 7 days after ECT. Greatest decrease in depression in ketamine and propofol plus ketamine groups ($p < 0.01$) compared with the propofol group 1, 2, and 3 days after ECT
Jarventausta et al. 2013 [87]	32	MDD (psychotic and non-psychotic)	Single-dose pre-ECT ketamine IV (0.4 mg/kg bolus) plus propofol vs. ketamine only vs. propofol only	Randomized, double-blind, parallel	MADRS	Improvement in depressive symptoms found in both study groups during ECT. There was no difference in the magnitude or speed of response between the groups
Murrough et al. 2013 [7]	72	MDD (TRD)	Single-dose ketamine IV (0.5 mg/kg) vs. midazolam	Randomized, double-blind, parallel	MADRS	Improvement in depressive symptoms greater in the ketamine group than in the midazolam group 24 h post-treatment. After adjustment for baseline scores and site, the MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% CI 3.20–12.71). Likelihood of response at 24 h was greater with ketamine than with midazolam (odds ratio 2.18, 95% CI 1.21–4.14), with response rates of 64% and 28%, respectively
Sos et al. 2013 [45]	27	MDD	Single-dose ketamine IV (0.54 mg/kg) vs. placebo	Randomized, double-blind, crossover	MADRS	Improvement in depressive symptoms greater in the ketamine group than in the placebo group at all visits (days 1, 4, and 7) with effect size (Cohen's d) of 0.62, 0.57, and 0.44, respectively. Higher intensity of psychotomimetic symptoms during ketamine administration correlated with alleviation in mood ratings

Table 1 continued

Authors, year, reference	Sample (*n*)	Diagnostic groups	Dosing and treatment groups	Clinical trial design	Primary outcome measure	Significance and findings
Lapidus et al. 2014 [85]	18	MDD	Single-dose ketamine intranasal (0.5 mg/kg) vs. placebo	Randomized, double-blind, crossover	MADRS	Improvement in depressive symptoms at 24 h after ketamine compared with placebo ($t = 4.39$, $p < 0.001$). Intranasal ketamine well tolerated. Minimal psychotomimetic or dissociative effects. No clinically significant changes in hemodynamic parameters
Lai et al. 2014 [76]	4	MDD, Comorbid Axis I or II disorders	Single-dose ketamine IV (0.1, 0.2, 0.3, or 0.4 mg/kg)	Randomized, double-blind, crossover	MADRS	Three subjects achieved antidepressant response ($\geq$ 50% decrease in MADRS scores), two subjects at the minimum 0.1-mg/kg dose, though all relapsed within a week. For two subjects, the greatest improvement occurred at 0.4 mg/kg
Yoosefi et al. 2014 [89]	29	MDD	Three doses pre-ECT 1, 2, and 6 ketamine IV (0.5 mg/kg) vs. thiopental	Randomized, double-blind, parallel	HAM-D	Improvement in depressive symptoms found in both groups. A significant difference in depressive symptom improvement noted only before the second ECT plus ketamine compared with the thiopental group
Ionescu et al. 2014 [61]	26	MDD (TRD, subgrouped into anxious and non-anxious)	Single-dose ketamine IV (0.5 mg/kg) vs. placebo	Randomized, double-blind	MADRS, HAM-D	Improvement in depressive symptoms seen in both groups with a significant group main effect ($p = 0.03$) and group-by-time interaction ($p = 0.01$). Patients with anxious depression relapsed significantly later than those with non-anxious depression (median $\pm$ SE = 19.0 $\pm$ 17.9 vs. 1.0 $\pm$ 0.0 days to relapse, respectively; $\chi^2 = 9.30$; $p = 0.002$)
Ballard et al. 2014 [60]	133	MDD and BD (both TRD)	Single-dose ketamine IV (0.5 mg/kg)	Mixed: open-label, double-blind	SSI, HAM-D, BDI, HAM-A	Improvement in suicidal ideation was associated with ketamine administration compared with placebo. At 230 min post-infusion, changes in suicidal ideation correlated with changes in depression and anxiety
Price et al. 2014 [62]	57	MDD (TRD)	Single-dose ketamine IV (0.5 mg/kg) vs. midazolam IV (0.045 mg/kg)	Randomized, double-blind, parallel	SSI, MADRS, QIDS, IAT	On all three explicit suicide measures, 53% of ketamine-treated patients scored zero at 24 h, compared with 24% of the midazolam group ($\chi^2 = 4.6$; $p = 0.03$)
Kantrowitz et al. 2015 [51]	12	BD (on olanzapine plus fluoxetine, lurasidone, or quetiapine)	Single-dose ketamine IV (0.5 mg/kg), then DCS (titrated to 1000 mg/day from the starting dose of 250 mg over 3 weeks)	Open-label	MADRS	Improvement in depressive symptoms from baseline to all rating points except at 2 weeks, with a large effect size seen at day 1 (Cohen $d = 2.0$ SD) and at 8 weeks (Cohen $d = 1.1$ SD)
Shams Alizadeh et al. 2015 [90]	42	MDD	Single-dose pre-ECT ketamine IV (0.3 mg/kg) plus propofol vs ketamine only and propofol only	Randomized, double-blind, parallel	HAM-D	Similar levels of improvement in depression severity found in both groups, with no difference between the groups in the recovery process ($p = 0.92$). Cognitive performance recovery time was lower in the ketamine group than in the control group ($p = 0.042$)
Murrough et al. 2015 [63]	24	Mood and anxiety spectrum	Single-dose ketamine IV (0.5 mg/kg) vs. midazolam IV 0.045 mg/kg	Randomized, double-blind, parallel	SSI, MADRS	Improvement in suicidality greater in the ketamine group than the midazolam group at 48 h ($p = 0.047$) but not at 24 h ($p = 0.32$). The MADRS suicidal ideation score was lower in the ketamine group compared with theo midazolam group at 24 h ($p = 0.05$). Treatment effect no longer reached significance at day 7

Table 1 continued

Authors, year, reference	Sample (*n*)	Diagnostic groups	Dosing and treatment groups	Clinical trial design	Primary outcome measure	Significance and findings
Kuscu et al. 2015 [97]	58	MDD	Eight sessions of pre-ECT ketamine IV (1 mg/kg) vs. thiopental IV (4 mg/kg) vs. both	Randomized, double-blind, parallel	HAM-D25 HAM-A	No statistical significant difference in HAM-D score between the groups. HAM-A scores were higher in both groups receiving thiopental
Salehi et al. 2015 [95]	160	MDD	Single-dose ketamine IV (0.8 mg/kg) vs. sodium thiopental IV (1.5 mg/kg)	Randomized, double-blind, parallel	HAM-D17	Both groups showed significant improvement in depressive symptoms. Improvement in depressive symptoms was mildly greater in the ketamine group than the thiopental group ($p = 0.049$)
Hu et al. 2016 [91]	30	MDD	Single-dose ketamine IV (0.5 mg/kg) with and without escitalopram 10 mg	Randomized, double-blind, parallel	MADRS, QIDS-SR	Improvement in depressive symptoms and remission greater in escitalopram plus ketamine group than the escitalopram plus placebo group (92.3% vs. 57.1%, $p = 0.04$) and (76.9% vs. 14.3%, $p = 0.001$), with significantly shorter time to response (HR 0.04, 95% CI 0.01–0.22, $p < 0.001$) and remission (HR 0.11, 95% CI 0.02–0.63, $p = 0.01$). Lower MADRS scores found in the ketamine group from 2 h to 2 weeks (peak = 3 days to 2 weeks; effect size = 1.08–1.18), QIDS-SR scores from 2 h to 2 weeks (maximum effect size = 1.27), and QIDS-SR suicidality at 2–72 h (maximum effect size = 2.24)
Zhong et al. 2016 [98]	90	MDD	Eight sessions of pre-ECT ketamine IV (1 mg/kg) vs. ketamine IV (0.5 mg/kg) plus propofol IV (0.5 mg/kg) vs. propofol IV (0.8 mg/kg)	Randomized, double-blind, parallel	HAM-D17	The ketamine group had an earlier reduction in depressive symptoms, most pronounced after the completion of the second treatment and lasting through the last treatment compared with the ketamine plus propofol and propofol groups
Rybakowski et al. 2016 [96]	45	MDD	Pre-ECT ketamine IV (1–1.5 mg/kg at ECT sessions 2 and 3 vs. ketamine IV (1–1.5 mg/kg at ECT sessions 2, 4, 6, 8, and 10) vs. thiopental IV (2–3 mg/kg) for all ECT sessions	Randomized, double-blind, parallel	HAM-D17	Depressive symptom severity was reduced after the last ECT session in the group receiving ketamine prior to the five ECT sessions compared with the group receiving thiopental only for all ECT sessions
Singh et al. 2016 [9]	30	MDD (TRD)	Single-dose esketamine IV (0.4, 0.2 mg/kg, or placebo). Those who received placebo received an additional infusion of esketamine 0.2 or 0.4 mg/kg	Randomized, double-blind, parallel	MADRS	Improvement in depressive symptoms greater in the esketamine group at both doses compared with the placebo group. The least-squares mean changes from baseline to day 2 in MADRS total score for the esketamine 20- and 40-mg/kg dose groups were −16.8 (3.00) and −16.9 (2.61), respectively, and showed significant improvement (one-sided $p = 0.001$ for both groups) compared with placebo [−3.8 (2.97)]

BD bipolar disorder, *BDI* Beck Depression Inventory, *DCS* D-cycloserine, *ECT* electroconvulsive therapy, *HAM-A* Hamilton Anxiety Rating Scale, *HAM-D* Hamilton Depression Rating Scale, *HR* hazard ratio, *IAT* implicit association task, *MADRS* Montgomery-Åsberg Depression Rating Scale, *MDD* major depressive disorder, *QIDS-SR* Quick Inventory of Depressive Symptomatology-Self-Reported, *SD* standard deviation, *SE* standard error, *SEM* standard error of the mean, *SSI* Scale for Suicide Ideation, *VPA* valproate

2.4 Potential Anti-Suicidal and Anxiolytic Effects of Ketamine

In an open-label clinical ketamine trial, Price and colleagues found that suicidality measures were reduced on average by 2.08 points on a 0- to 6-point scale ($p < 0.001$; $d = 1.37$), with 81% of patients receiving a rating of 0 or 1 24 h post-infusion on the suicidality item of the MADRS (MADRS-SI) [56]. Given that the primary outcome measure took place at the 24-h timepoint, it is uncertain how long the anti-suicidal effect was maintained. This finding was later replicated by our group in an open-label study of 33 TRD patients that found decreased Scale for Suicide Ideation (SSI) scores within 40 min of ketamine infusion (0.5 mg/kg); this measure remained significantly reduced throughout the 4-h post-infusion period [57]. In an emergency department setting, Larkin and Beautrais found that suicidal ideation resolved in 14 actively suicidal patients following an IV bolus of ketamine (0.2 mg/kg) administered over 1–2 min. In that study, antidepressant effects were seen at 40 min post-administration, and sustained improvements in suicidality scores lasted for over 10 days [58].

A meta-analysis of seven clinical trials providing unpublished data on the suicide item component of either the HAM-D or the MADRS noted a significant reduction in suicidality severity score for the ketamine group at days 1 and 3 [59]. Interestingly, the reduction in suicidality associated with ketamine administration may occur independently of its antidepressant effects [7]. This underscores the challenges of characterizing the clinical relationship between depression and suicidality as well as identifying the unique biological signatures linking depression and suicidality, to the extent that this can be achieved by examining the effects of ketamine. In a post-hoc analysis of 133 patients with treatment-resistant MDD and bipolar depression using the HAM-D, SSI, Beck Depression Inventory (BDI), and Hamilton Anxiety Rating Scale (HAM-A), improvement in suicidal ideation was observed 230 min after a single dose of ketamine (0.5 mg/kg). These improvements correlated with change in depressive symptoms (range 0.23–0.44, $p < 0.05$) as well as with anxiety (range 0.23–0.40, $p < 0.05$), each accounting for up to 19% of the variance in change in suicidal ideation [60]. This suggests that ketamine may have variable effects on anxiety and depression that act through different mechanisms, and that anxiety and depression may have a modulating, but not causative effect, on suicidality. This line of thinking, however, does not take into account the impact of anxiety on depression. For example, in a randomized, double-blind, placebo-controlled study, our group found that in association with ketamine administration, patients with anxious and non-anxious depression experienced a reduction in depressive symptoms; however, those with anxious depression relapsed significantly later than those with non-anxious depression (median ± standard error = 19.0 ± 17.9 vs. 1.0 ± 0.0 days to relapse, respectively; $\chi^2 = 9.30$; $p = 0.002$) [61].

In the first double-blind, randomized, placebo-controlled study to investigate an association between sub-anesthetic-dose ketamine and suicide, 15 patients with bipolar depression were maintained on therapeutic levels of lithium or valproate and administered a single IV ketamine infusion (0.5 mg/kg) or placebo on two test days 2 weeks apart. Compared with placebo, those who received ketamine experienced a significant reduction in suicidal ideation (as measured by the suicide item of the MADRS, HAM-D, and BDI) at 40 min that persisted 3 days post-administration [48]. The limitation in this study was that suicidality was not specifically selected for within the patient group. In two subsequent clinical studies of the association between IV ketamine administration and suicidality [56, 62], aspects of suicidality were measured via the Implicit Association Test, a scale that categorizes suicidal ideation into discrete cognitive categories. In the first study, open-label IV ketamine administration was associated with rapid reductions in explicit and implicit suicidal cognition within the first 24 h. This effect persisted for patients who received up to five additional infusions over 2 weeks [62]. In a randomized, double-blind, controlled active comparator study of 57 MDD patients who were randomized to receive either a single infusion of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg), 53% of ketamine-treated patients had no explicit suicidal ideation at 24 h post-infusion compared with 24% of the midazolam group ($\chi^2 = 4.6$; $p = 0.03$) [62]. Although this was the first randomized clinical study to examine the association between ketamine administration and suicidality using an anesthetic control condition [62], the patients were not selected based on the presence or absence of suicidality. In a follow-up study from the same group, patients with clinically significant suicidal ideation were randomized to receive either ketamine or midazolam with a 7-day assessment of suicidality via the SSI [63]. Forty-eight hours post-infusion, patients who had received ketamine had significantly lower SSI scores than those who had received midazolam, but this difference was not seen at 24 h or at any other timepoint throughout the 7-day assessment period. Although promising, this follow-up study was small ($n = 24$). Thus, additional and larger randomized clinical trials are needed to confirm the validity of both anti-suicidal and anxiolytic effects for ketamine.

2.5 Safety Profile of Subanesthetic Ketamine in Depression

Across ketamine studies, the most common side effects have been perceptual disturbances, confusion, elevations in systolic blood pressure, euphoria, dizziness, and increased libido [15, 16]. Although concerns of cognitive decline, neuronal injury, and physical dependence associated with the use of ketamine, or other NMDA antagonists, have been raised by some researchers [64–66], it is important to note that many of these concerns center around studies conducted only in animals [67, 68] or in human substance abuse populations, where ketamine use was uncontrolled and higher doses were used over a longer period of time [69–71]. In a controlled study of a single administration of IV ketamine (0.5 mg/kg) to 19 healthy subjects [72], immediate psychotomimetic symptoms and delayed recall effects returned to baseline within 2 h of initiation of infusion. Perseverative errors (as noted by the Wisconsin Card Sorting Test) were observed at the time of infusion, but there was no indication that these effects persisted and there was no significant change on the Mini-Mental Status Examination. Another study used a battery of cognitive tests (MATRICS), including processing speed, attention/vigilance, working memory (nonverbal and verbal), verbal learning, visual learning, reasoning, problem solving, and social cognition, to assess function in individuals with MDD and found that ketamine was associated with selective impairments in memory recall [73]. Another two-site, double-blind clinical trial by the same group randomized subjects 2:1 to receive ketamine or midazolam; the study found that post-treatment neurocognitive performance (as measured by MATRICS) improved following treatment regardless of treatment condition. Interestingly, although there was no differential effect of treatment on neurocognitive performance and no association with antidepressant response, lower processing speed at baseline predicted greater improvement in depression at 24 h following ketamine [74].

As noted above, in both single- [3, 7, 48, 50] and repeated-dose administration (6–12 doses) [9, 75], no severe or long-term side effects have yet been noted with subanesthetic-dose ketamine. However, it remains unclear whether cognitive changes, alterations to brain tissue, or increased risk of substance abuse can develop in association with repeated doses in humans. Furthermore, the aforementioned studies used cognitive assessment measures that were relatively insensitive, of short duration, and not specifically designed to detect cognitive changes in association with drug intervention. Towards this end, large controlled clinical studies with long-term follow-up using neurocognitive and neuroimaging assessments are warranted to address these issues. The results from such studies could help support or reject the safe administration of subanesthetic-dose ketamine as an antidepressant in clinical settings.

2.6 Dosing Optimization and Dose Frequency of Subanesthetic Ketamine for Depression

Intravenous ketamine has been used safely for procedural sedation in adults in doses as high as 2 mg/kg. In the only dose-finding study to date of IV ketamine, four subjects with TRD each received up to four IV doses of ketamine at 0.1, 0.2, 0.3, or 0.4 mg/kg (given over 2–5 min, 1 week apart); a placebo treatment was randomly inserted in a double-blind, placebo-controlled, crossover fashion. Among the three subjects achieving antidepressant response (≥50% decrease in MADRS score), two subjects responded at the 0.1-mg/kg dose; a clear dose-response relationship was demonstrated in only one subject, with the highest improvement occurring at 0.4 mg/kg [76]. In a randomized, crossover, double-blind study, 15 subjects with TRD were randomized to receive ketamine or midazolam in an ascending dose design with random insertion of a placebo comparator treatment. Patients received ketamine via one of three routes: IV ($n = 4$), intramuscular injection ($n = 5$), or subcutaneous injection ($n = 6$), starting at 0.1 mg/kg and increasing by 0.1 mg/kg until a maximum final dose of 0.5 mg/kg was reached. Ketamine doses were administered >1 week apart, with one placebo control treatment randomly inserted. Twelve patients who received ketamine achieved response and met remission criteria at doses as low as 0.1 mg/kg regardless of the route of administration. Indeed, all three routes of ketamine administration resulted in comparable antidepressant effects in a dose-related fashion, with the fewest adverse effects seen via the subcutaneous route [77]. Larger sample dose optimization studies are actively being conducted (NCT01558063).

With regard to dosing frequency, it should be noted that although antidepressant response rates to a single ketamine infusion (0.5 mg/kg) have been reported to be 50–71% in individuals with MDD [2, 3], depressive symptoms typically return within 7 days after cessation of drug administration if subsequent treatments are not administered [15]; this is consistent with single administrations of other antidepressant interventions (e.g., ECT or sleep deprivation). Thus, repeated-dose administration of IV ketamine to prolong its antidepressant and potential anti-suicidal effects has been studied in limited situations. In small open-label studies of repeated ketamine infusions administered over a 2-week interval, relapse rates have been reported to range between 55% and 89% in the month following treatment [49, 78, 79].

In an open-label study, Murrough and colleagues found that the use of up to six IV infusions of ketamine

administered over a 12-day period resulted in rapid antidepressant effects in patients with TRD [75]. They noted that the overall response rate at the end of the trial was 71%, and that, among responders, median time to relapse after the last ketamine infusion was 18 days; 80% of subjects relapsed within 28 days, but 20% maintained response to 78 days, though all subjects did eventually relapse. However, the treatments were well tolerated; no serious adverse events were noted, and no sustained increase in psychotomimetic/dissociative side effects was observed.

In a randomized, placebo-controlled, parallel-design study that investigated the use of IV ketamine (0.5 mg/kg infused over 40 min either two or three times per week), subjects who received eight or 12 IV ketamine administrations over the course of the study demonstrated a statistically significant reduction in MADRS scores from days 1 to 15 compared with those receiving placebo [9]. In another double-blind randomized study, 18 patients with MDD received either three IV ketamine infusions (0.5 mg/kg) or ECT on 3 test days (2 days apart). Within 24 h, depressive symptoms improved in subjects receiving the first dose of ketamine compared with the ECT group and this improvement remained significant throughout the study [80]. In addition, Price and colleagues found that reductions in suicidality observed after a single dose of ketamine were sustained for 12 days by repeated doses (0.5 mg/kg, three times weekly; $p < 0.001$; $d = 2.42$) [56].

As noted above, repeated ketamine infusions have been shown to be well tolerated with no associated severe adverse events. During IV ketamine administration at 0.5 mg/kg, the occurrence of perceptual symptoms (as measured by the Brief Psychiatric Rating Scale and Clinician-Administered Dissociative States Scale) resolves within 3 h of initiation of the infusion. The most common physical symptoms include dizziness, headache, hypoesthesia, paresthesia, and nausea.

With regard to physical dependence, to date, no evidence suggests that subanesthetic-dose ketamine causes physical dependence in humans [81]. Relatedly, a recent study found no evidence that repeated but limited exposure to ketamine increased the risk of more severe or more protracted psychosis, perceptual changes resembling dissociation, severe emotional distress, or euphoria in healthy subjects [82]. Although the existing data do not indicate prolonged cognitive or dissociative side effects, the evidence is drawn from only a few studies, and these specific issues have not yet been systematically examined. Furthermore, given that ketamine is considered an illicit substance in USA, a higher level of scrutiny must be considered, and large long-term follow-up studies are needed to definitively assess possible associations between ketamine use and issues of abuse and/or dependence [83, 84].

2.7 Route of Administration for Subanesthetic Ketamine for Depression

Investigators are also exploring alternative, and perhaps more convenient, routes of ketamine administration, including intranasal and sublingual. One randomized, double-blind, crossover, placebo-controlled study found that 50 mg of intranasal ketamine improved depressive symptoms within 24 h compared with placebo in 20 patients with MDD ($t = 4.39$, $p < 0.001$) [85]. Although there may be considerable variability associated with intranasal ketamine administration in terms of bioavailability, this means of administration was well tolerated with minimal psychotomimetic or dissociative effects and no significant hemodynamic changes. In addition, Lara and colleagues evaluated the tolerability and efficacy of a sublingual formulation of racemic ketamine (10 mg from a 100-mg/mL solution for 5 min, then swallowed), whose estimated bioavailability is greater than orally administered ketamine [86]. In this case series, 20 of 26 (77%) patients with bipolar depression or MDD who received sublingual racemic ketamine every 2–3 days or weekly reported improved and stable mood, cognition, and sleep with only mild and transient light-headedness as a common side effect (no euphoria, psychotic, or dissociative symptoms). In a small, placebo-controlled, crossover trial, subcutaneous and intramuscular injections of subanesthetic-dose ketamine were found to be associated with antidepressant response in a similar fashion to IV ketamine administrations; in that study, subcutaneous injection was associated with the fewest adverse effects [77]. Clearly, replication of both findings through larger randomized clinical trials is warranted.

3 Glutamatergic Synergism and the Maintenance of the Antidepressant Effects of Ketamine

Several studies (see Table 1) have examined the possibility of augmenting the rapid antidepressant effects of ketamine using other well-studied antidepressant strategies, including mood-stabilizing medications [48, 50], ECT [52, 53, 87–90], monoaminergic antidepressants [91], and agents with glutamatergic-modulating effects [6, 51, 92]; the latter are discussed in Sect. 4, below.

Our laboratory conducted two studies in which patients with bipolar depression received ketamine after being stabilized on VPA or lithium. A single ketamine infusion (0.5 mg/kg) had rapid antidepressant effects that lasted for 3 days [48, 50]. Although concomitant use of a mood-stabilizing medication does not appear to maintain antidepressant effects in patients with bipolar depression, these findings have roused interest in examining possible

lithium augmentation of ketamine in MDD patients. Interestingly, animal models suggest that both ketamine and lithium may inhibit glycogen synthase kinase-3 in a synergistic manner, leading to both antidepressant and antimanic effects [93, 94]

Ketamine has also been investigated in conjunction with ECT. In double-blind studies in which depressed patients were randomized to receive an infusion of subanesthetic-dose ketamine in addition to or separate from infusion with another anesthetic agent (thiopental or propofol), both groups saw similar levels of improvement in their depressive symptoms [52, 53, 87]. Another study found that individuals who received ketamine anesthesia prior to a single ECT administration experienced a slightly greater improvement in depressive symptoms a few days later [88]. Another randomized, double-blind, single-infusion, pre-ECT study comparing ketamine and thiopental found that both groups showed significant improvement in depressive symptoms; however, improvement in depressive symptoms was mildly greater in the ketamine group than the thiopental group ($p = 0.049$) [95]. Given that the antidepressant effects of ECT occur after a series of treatments, it is worth noting that depressive symptoms in this study as well as that of Wang and colleagues [88] were assessed after only a single administration of ketamine given prior to ECT.

Another study investigated a series of ketamine administrations pre-ECT and found a significant difference in the improvement of depressive symptoms only before the second ECT plus ketamine administration compared with the thiopental group [89]. It is worth noting that although significant reductions in depressive symptoms were associated with pre-ECT infusions of ketamine, these improvements were minimal. In addition, a randomized controlled trial of MDD patients who received pre-ECT ketamine (1–1.5 mg/kg at ECT sessions 2 and 3 or 1–1.5 mg/kg at ECT sessions 2, 4, 6, 8, and 10) or thiopental (2–3 mg/kg for all ECT sessions) found that depressive symptom severity was lower after the last ECT session in the group that received ketamine prior to the five ECT sessions than in the group that received only thiopental for all ECT sessions [96], suggesting that a greater frequency of paired ketamine and ECT may offer more clinical benefit than a single pre-ECT ketamine infusion.

In contrast, another study series compared pre-ECT infusions of ketamine (1 mg/kg), thiopental (4 mg/kg), or both agents; the investigators found that depression symptom scores improved for all groups (as assessed by the HAM-D) and no statistically significant differences were observed between groups [97]. In another study of 90 patients with TRD randomly assigned to receive either ketamine (0.8 mg/kg), subanesthetic ketamine (0.5 mg/kg) plus propofol (0.5 mg/kg), or propofol (0.8 mg/kg) prior to eight ECT sessions, those in the ketamine group had an earlier reduction in depressive symptoms; compared with the other two groups, this effect was most pronounced after completion of the second treatment and lasted until the last treatment [98].

Finally, a recent meta-analysis of 14 double-blind, randomized controlled trials examining the efficacy and tolerability of six anesthetic agents prior to ECT for depressive disorders found that ketamine and methohexital were more beneficial than propofol or thiopental [99]. The findings suggest that co-administration of ketamine and ECT may offer some additional benefit for alleviating depressive symptoms in patients. Interestingly, ketamine has also been shown to benefit patients who had not previously responded to an adequate trial of ECT [100]. A clinical trial aimed at determining the efficacy of ketamine for preventing relapse after ECT is underway [101], underscoring the need to identify subgroups of depressed patients who may respond to specific antidepressant treatments.

Ketamine has also been used in conjunction with selective serotonin reuptake inhibitors. In a double-blind study, 30 MDD patients were randomized to receive either a single administration of ketamine or placebo concomitant to daily treatment with escitalopram (10 mg) [91]. Improvement in depressive symptoms was greater, and remission rates were higher, in those that received escitalopram plus ketamine vs. those that received escitalopram plus placebo for up to 2 weeks (92.3 vs. 57.1%, $p = 0.04$ and 76.9 vs. 14.3%, $p = 0.001$, respectively), with a significantly shorter time to response (hazard ratio 0.04, 95% CI 0.01–0.22, $p < 0.001$) and remission (hazard ratio 0.11, 95% CI 0.02–0.63, $p = 0.01$). This suggests that ketamine administration may be used to offer more immediate antidepressant relief during the lag time to monoaminergic antidepressant response.

Interestingly, a small open-label study of patients with obsessive compulsive disorder, found that when a single ketamine infusion (0.5 mg/kg) was added to exposure-based cognitive behavioral therapy, an initial reduction in obsessive compulsive disorder symptoms was observed; this was accompanied by sustained response over 2 weeks [102]. Although this was an open-label study of patients with obsessive compulsive disorder, it suggests that emotion dysregulation may be rapidly and effectively targeted using synergistic approaches.

4 Non-Ketamine Glutamate Modulators for Depression

A variety of agents with direct and indirect effects on the glutamate system (see Fig. 1) have been evaluated in small clinical trials [15, 16]. In lieu of an exhaustive review of all

Glutamatergic Modulating Agent:	Molecular Target*:
R,S-Ketamine and Metabolites	A, B
Esketamine	A
D-cycloserine (DCS)	A
Riluzole	E, F
CP-101,106	A,G(?)
CERC-301	A
Basimglurant (RG7090)	C
JNJ-40411813 (ADX-71149)	D
Dextromethorphan	A, G
AVP-786	A, G
AVP-923	A, G
Nitrous Oxide	A
Rapstinel (GLYX-13)	A

*Targets are approximate and for illustrative purposes

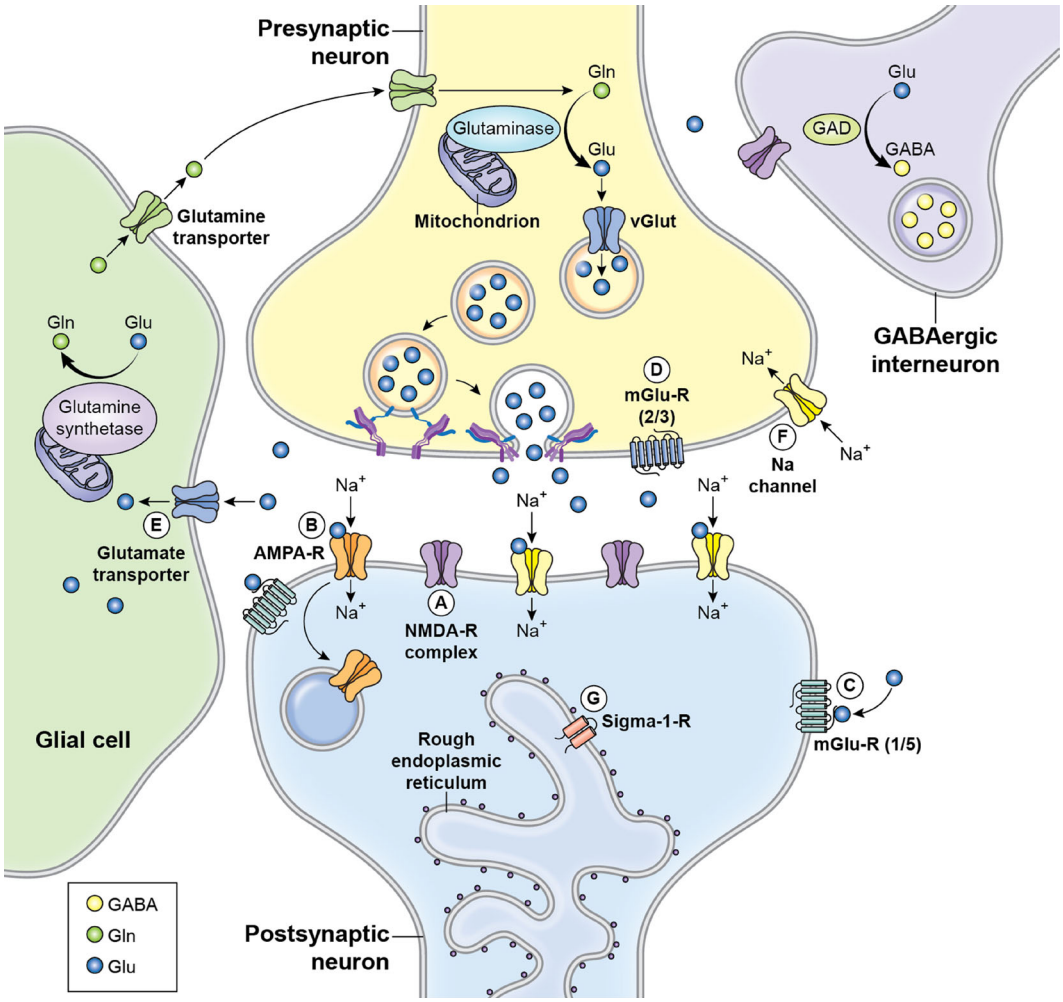

Fig. 1 Glutamatergic synapse and major mechanisms of action of potential glutamatergic antidepressant agents. *AMPA-R* alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *GABA* gamma-aminobutyric acid, *GABAergic interneuron* GABA-containing interneuron, *GAD* glutamic acid decarboxylase, *Gln* glutamine, *Glu* glutamate, *mGlu-R* metabotropic glutamate receptor, *Na channel* voltage-gated sodium channel, *NMDA-R* N-methyl-D-aspartate receptor, *Sigma-1-R* Sigma-1-receptor, *vGluT* vesicular glutamate transporter

glutamatergic-modulating agents that have been investigated in phase II clinical trials for the treatment of depression, here we highlight those agents that have shown preliminary evidence of an antidepressant effect and that may be particularly fruitful for developing novel glutamatergic-modulating agents for the treatment of depression (see Table 2).

4.1 D-Cycloserine

D-Cycloserine (DCS) is an orally administered antibiotic medication that is US Food and Drug Administration approved for the treatment of tuberculosis [51]. It has been the most promising glutamatergic-modulating agent, after ketamine, to show an acute antidepressant response. Through its effects on glycine-binding sites, the mechanism of action of DCS at higher doses prevents the opening of the NMDA receptor channel, thereby acting as a functional NMDA receptor antagonist.

In 22 subjects with TRD, a 6-week, crossover, placebo-controlled trial of adjunctive DCS (250 mg/day) reduced depressive symptoms but did not separate from placebo owing to the high placebo response rate [103]. A slightly larger study ($n = 26$) of individuals with TRD over the same 6-week period by the same group assessed the efficacy of escalating dose (up to 1000 mg/day) adjunctive DCS [104] and found that higher-dose DCS had significant antidepressant effects as measured by the clinician-administered HAM-D and self-reported BDI; more than half of the patients randomized to high-dose DCS had a >50% reduction in HAM-D scores by the end of the study.

With regard to DCS as an adjunctive therapy in bipolar depression, one open-label study investigated 12 patients ($n = 7$ completers) with bipolar depression who were stabilized on lurasidone, quetiapine, or a fluoxetine and olanzapine combination and who received ketamine (0.5 mg/kg) prior to titration with DCS [51]. In this study, improvement in depressive symptoms was seen from baseline to all rating points (except at 2 weeks) throughout the 3-week trial, with a large effect size seen at day 1 (Cohen $d = 2.0$). Four of the seven patients with bipolar depression remained in remission after 8 weeks, and clinical improvement at that timepoint correlated with the magnitude of improvement 24 h post-ketamine. It should be noted that this study did not have a control group, which may limit interpretation of its efficacy. In addition, a recent meta-analysis [15] found that among the agents that act directly on the NMDA receptor, DCS has been associated with an acute antidepressant response at high doses (1000 mg) but not at low doses (250 mg); data were drawn from the studies cited above.

4.2 Riluzole

Riluzole, which is US Food and Drug Administration approved for the treatment of amyotrophic lateral sclerosis, has been repurposed and investigated as a potential glutamatergic antidepressant agent. An animal model of depression found that chronic unpredictable stress led to glial pathology that was reversed after riluzole administration [105]; this finding led to a small collection of open-label studies examining antidepressant response to riluzole monotherapy in patients with MDD or bipolar depression. In the first open-label study of 19 TRD patients, depressive symptoms improved within 3–6 weeks (the study endpoint) of riluzole administration [106]. Consistent with a case report of antidepressant response to riluzole as an augmentation strategy in patients concurrently treated with traditional antidepressants [107], a second open-label study of ten patients with MDD showed a reduction in both depressive and anxiety symptoms after the first week and throughout the 12 weeks of the study when riluzole was added to their antidepressant regimen [108]. Another open-label study of riluzole added to ongoing treatment with lithium in 14 patients with bipolar depression similarly observed a reduction in depressive symptoms during weeks 5 through 8 of the 12-week study [109].

Riluzole was also tested in two randomized, double-blind, placebo-controlled trials in individuals with MDD as a possible augmentation strategy to maintain the antidepressant effects of ketamine. To examine the efficacy of riluzole in preventing depressive relapse after experiencing an antidepressant response to ketamine, a randomized, double-blind, placebo-controlled, flexible-dose continuation trial of riluzole (100–200 mg/day) was performed over the course of a 32-day study period [6]. In this study, 14 (out of 26) patients with TRD who received open-label ketamine met response criteria; however, an interim analysis found no significant differences in time to relapse between the riluzole and placebo groups. In another randomized, double-blind, placebo-controlled, add-on study, 42 patients with TRD received a single IV ketamine infusion (0.5 mg/kg) and were then randomized, 4–6 h post-infusion, to receive either riluzole (100–200 mg/day; $n = 21$) or placebo ($n = 21$) for 4 weeks [92]. Although a significant improvement in depressive symptoms (as measured by the MADRS) remained throughout the entirety of the 28-day trial, the difference between the riluzole and placebo treatment groups was not significant, suggesting that riluzole did not impact the antidepressant response to ketamine. Moreover, when the subgroup of ketamine non-responders was examined, an antidepressant response was still not observed in association with riluzole [110]. Taken together, the current data do not yet

Table 2 Select glutamatergic-modulating agents with potential antidepressant effects

Glutamatergic modulator	Target	Major mechanism(s) of action	Potential indication(s)	Evidence of efficacy
Ketamine (+ metabolites?)	NMDA receptor, AMPA receptor (?)	NMDA receptor antagonist, AMPA receptor agonist	MDD, BD, suicidality, anxiety, PTSD, OCD	Moderate-to-strong evidence of efficacy (see Table 1); most clinical trials in MDD patients
Esketamine (intranasal ketamine)	NMDA receptor	NMDA receptor antagonist, AMPA receptor agonist	MDD, suicidality, PTSD	Moderate evidence of efficacy (see Table 1); most clinical trials in MDD patients
D-Cycloserine	NMDA receptor	Partial agonist at glycine site; functional NMDA receptor antagonist	MDD, BD	Moderate evidence for antidepressant effect as adjunct to mood stabilizer in BD [15, 51, 103, 104]
Riluzole	Voltage-gated sodium channels	Increased synaptic glutamate reuptake, blockade of voltage-gated sodium channels	MDD, BD, OCD	Weak evidence of efficacy for MDD [6, 92, 106–110]
CP 101,606	NMDA-NR2B subunit	NMDA-NR2B non-selective antagonist	MDD	Clinical trials ceased because of an association with cardiac conduction abnormalities [111, 112]
CERC-301	NMDA-NR2B subunit	NMDA-NR2B selective antagonist	MDD	Weak evidence of efficacy for MDD [113]
Basimglurant (RG7090)	mGluR5	mGluR5 NAM	MDD	Weak evidence for antidepressant effects as adjunct to monoamine antidepressants; weak evidence for monotherapy as an antidepressant [118]
JNJ-40411813 (ADX71149)	mGluR2	mGluR2 PAM	MDD	Weak evidence as adjunct to monoamine antidepressants for anxiety [119]
Dextromethorphan	NMDA receptor, Sigma-1 receptor, SERT, NET	NMDA receptor antagonist, Sigma-1 receptor antagonist, SERT and NET inhibitor	BD	Weak evidence for antidepressant effects as adjunct to mood stabilizers in BD [120, 121]
AVP-786	NMDA receptor, Sigma-1 receptor, SERT, NET	NMDA receptor antagonist, Sigma-1 receptor antagonist, SERT and NET inhibitor	MDD	Ongoing phase II clinical trial in MDD (NCT02153502) as adjunct to monoamine antidepressants
AVP-923 (Nuedexta®)	NMDA receptor, Sigma-1 receptor, SERT, NET	NMDA receptor antagonist, Sigma-1 receptor antagonist, SERT and NET inhibitor	MDD	Ongoing phase II clinical trial in MDD (NCT01882829)
Nitrous oxide	NMDA receptor	NMDA receptor antagonist	MDD	Preliminary evidence of efficacy for MDD [122]
Rapastinel (GLYX-13)	NMDA receptor	NMDA receptor glycine site NAM	MDD	Moderate evidence of efficacy for MDD [123–125]

AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *BD* bipolar disorder, *MDD* major depressive disorder, *mGluR* metabotropic glutamate receptor, *NAM* negative allosteric modulator, *NET* norepinephrine transporter, *NMDA* *N*-methyl-D-aspartate, *OCD* obsessive compulsive disorder, *PAM* positive allosteric modulator, *PTSD* post-traumatic stress disorder, *SERT* serotonin transporter

support the use of riluzole as an antidepressant agent in patients with TRD.

4.3 CP-101,606 and CERC-301 (MK-0657)

Two investigative agents that act on the NR2B subunit of the NMDA receptor as antagonists, CP-101,606, and CERC-301 (previously known as MK-0657), have been studied in small clinical trials of depressed patients. A rapid antidepressant effect was shown in association with a single IV infusion of CP-101,606 as monotherapy in a randomized, double-blind, placebo-controlled study of 30 patients with TRD. In the first treatment period, participants received a 6-week open-label trial of paroxetine as well as a single-blind IV placebo infusion of CP-101,606. Those who did not respond then received a randomized double-blind single infusion of CP-101,606 or placebo plus continued treatment with paroxetine for up to an additional 4 weeks. Although CP-101,606 reduced depressive symptoms more effectively than placebo, and 78% of CP-101,606-treated responders maintained response status for at least 1-week post-infusion, development of this agent

was stopped because of its resulting effect on cardiac conduction (i.e., corrected QT prolongation) [111]; thus, replication has not been performed. Furthermore, this compound may have off-site effects at sigma receptors [112], suggesting that any signal of efficacy may not be directly attributable to NR2B antagonism.

CERC-301 (previously known as MK-0657) is an orally administered NR2B-selective antagonist. A small, randomized, double-blind, placebo-controlled, crossover clinical trial that examined depressive symptoms after daily administration of CERC-301 as monotherapy over 12 days in 21 patients with TRD obtained mixed results [113]. Although a reduction in depression scores was not observed when assessed by the MADRS, the primary outcome measure, reductions in depression scale scores were observed via the clinician-administered HAM-D and the self-reported BDI [113]. In contrast to CP-101,106, no serious or dissociative adverse effects were observed with this orally administered agent. Most recently, a phase II placebo-controlled trial (NCT02459236) using higher doses of CERC-301 (12 and 20 mg) did not meet the primary endpoint of mean improvement on subset scores of the HAM-D17, despite significant improvement in depressive symptoms at day 2 with the 20-mg dose (http://ir.cerecor.com/press-releases/detail/30/cerecor-reports-top-line-data-from-cerc-301-phase-2-study).

4.4 Negative and Positive Allosteric Modulators: Basimglurant and JNJ-40411813/ADX71149

Agents that act as a negative or positive allosteric modulator (NAM or PAM) on the metabotropic glutamate receptor (mGluR)5 have shown preliminary modest evidence as antidepressant agents. Found in the postsynaptic density [114–116] and in glial cells [117], mGluRs are expressed widely throughout the brain and are an additional glutamate signaling pathway outside of the NMDA receptor and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor pathways. Basimglurant (RO4917523, RG7090), an mGluR5 NAM, is currently in clinical development for depression (NCT00809562, NCT01437657). In a multicenter 9-week, double-blind, placebo-controlled study of 333 patients with MDD, basimglurant was administrated orally at two dose levels (0.5 or 1.5 mg daily) adjunctive to ongoing treatment with selective serotonin reuptake inhibitors or serotonin-noradrenaline reuptake inhibitors [118]. No difference was observed on the clinician-rated MADRS, the primary outcome measure, compared with placebo from baseline to endpoint. However, at a dose of 1.5 mg daily (but not at 0.5 mg), an antidepressant effect was observed at multiple timepoints as assessed by patient-rated scales (MADRS and the Quick Inventory of Depressive Symptomatology-Self Reported).

The efficacy, safety, and tolerability of PAMs have also been evaluated in individuals with MDD. In a phase IIa, randomized, multicenter, double-blind, proof-of-concept study, JNJ-40411813/ADX71149, a novel mGluR2 PAM, was administered adjunctively to MDD patients with significant anxiety (as measured by the HAM-D and HAM-A) who were already taking an selective serotonin reuptake inhibitors or serotonin-noradrenaline reuptake inhibitors. The first study period, lasting 4 weeks, comprised randomization to either flexibly dosed JNJ-40411813 or placebo, followed by a re-randomization and another 4-week study period for those who received placebo and continued to meet entry severity criteria. Among the 100 patients who completed the study, no differences were observed in depression or anxiety rating scale scores via primary outcome measures, although some reductions in anxiety symptoms, as assessed by secondary measures, were noted [119]. Taken together, the evidence suggests that neither mGluR NAMs nor PAMs have yet demonstrated a strong antidepressant effect.

4.5 Dextromethorphan

Dextromethorphan is the active agent in over-the-counter antitussive medications. Although it acts on opioid receptors, at higher doses dextromethorphan acts as a sigma-1 receptor agonist and inhibitor of the serotonin and norepinephrine transporters, as well as a non-competitive NMDA receptor antagonist. To date, no randomized clinical trials have explored dextromethorphan as monotherapy in mood disorders. A 12-week placebo-controlled study of 250 patients with bipolar depression added dextromethorphan to treatment with VPA and found that this combination reduced depressive symptoms; however, this difference in treatment groups did not reach statistical significance, potentially owing to metabolism-related reductions in drug concentrations [120]. A retrospective chart review of 22 subjects with bipolar disorder (BD)-II or BD not otherwise specified found that adding 20 mg dextromethorphan and 10 mg quinidine (a cytochrome 2D6 inhibitor) once or twice daily to a current medication regimen over a 90-day treatment period significantly improved Clinical Global Impression scale scores [121]. This dextromethorphan-quinidine combination, Nuedexta® (Avanir Pharmaceuticals, Inc, Aliso Viejo, CA, USA) (AVP-923), which is US Food and Drug Administration approved for the treatment of pseudobulbar affect, is currently under investigation as a potential antidepressant agent in patients with MDD (NCT01882829). In addition, AVP 786, a combination of deuterated (d6)-dextromethorphan and an ultra-low dose of quinidine, received fast-track designation for agitation in Alzheimer's disease; it is currently under investigation for use in depression (NCT02153502).

4.6 Indirect Glutamatergic Modulators: Nitrous Oxide and GLYX-13

Indirect glutamatergic modulation as a potential mechanism of antidepressant effects has been investigated in clinical trials using nitrous oxide (N_2O) [122] and the glycine partial agonist GLYX-13 (rapastinel) [123, 124]. Nitrous oxide, a non-competitive NMDA receptor inhibitor, has been used as an inhaled general anesthetic in medical and dental settings. In a placebo-controlled, double-blind, crossover study examining 20 patients with TRD who received an inhalation of 50% N_2O or 50% nitrogen (placebo), both over 1 h, those who received N_2O experienced a reduction in depressive symptoms (as measured by the HAM-D) at both 2 and 24 h post-inhalation compared with placebo [122]. Adverse effects included anxiety, headache, and nausea/vomiting, but there were no psychotomimetic effects associated with N_2O inhalation.

In a clinical trial of GLYX-13 (rapastinel), an NMDA receptor glycine-site functional partial agonist, as monotherapy, 116 non-medicated patients with TRD were randomized to receive a single IV GLYX-13 dose of 1, 5, 10, or 30 mg/kg, or placebo over 3–15 min and then followed for 7 days. At 1-week post-infusion, those who received 5 and 10 mg/kg of GLYX-13 had experienced a significant antidepressant response compared with placebo [124]. The same investigators subsequently performed a randomized, double-blind, clinical trial of adjunctive GLYX-13 in 116 patients with TRD (concurrently maintained on a psychotropic medication regimen). Subjects were randomized to receive weekly infusions of IV GLYX-13 (at doses of 1, 5, or 10 mg/kg) or placebo, with follow-up on days 3, 7, and 14. After an interim safety and efficacy analysis was performed, an additional cohort was added and randomized to receive IV GLYX-13 (30 mg/kg) or placebo, with follow-up at days 3, 7, 14, 21, and 28. Those who received IV GLYX-13 at doses of 5 or 10 mg/kg showed a reduction in HAM-D scores on days 1 through 7, but no antidepressant effects were observed thereafter [123]. The authors suggested that the U-shaped dose-response curve observed for GLYX-13 may be the result of the unique molecular interactions of GLYX-13 as a partial agonist on the glycine site of the NMDA receptor. GLYX-13 infusion at any dose was not associated with psychotomimetic properties, and no serious adverse events were reported in either study.

Interestingly, in a recently published series of preclinical studies, a single infusion of GLYX-13 led to increased dendritic arborization within the medial prefrontal cortex, presumably in part via the mTORC1 pathway, as well as increased synaptic responses to hypocretin in thalamocortical synapses [125]. Thus, it appears that GLYX-13 may induce specific intracellular molecular pathways that can lead to plastic changes within specific brain regions, providing a possible link between a drug action, brain function, and antidepressant response.

5 Mechanism of Action of Ketamine Revisited

Despite the preponderance of the evidence supporting the antidepressant effects of ketamine, the active molecule(s) as well as the molecular and intracellular pathways responsible for the mechanism of action has not yet been fully elucidated. In this context, it is interesting to note that there are currently six ongoing, phase III clinical trials studying the efficacy of esketamine (the *S*-enantiomer of ketamine) in TRD. A recent proof-of-concept clinical trial examining the antidepressant efficacy and safety of 0.20 and 0.40 mg/kg IV esketamine compared with IV placebo in 30 patients with TRD found that subjects who received either dose demonstrated an improvement in depressive symptoms as measured by the MADRS [43]. Another double-blind, placebo-controlled, multi-center study (SYNAPSE) evaluated the antidepressant efficacy and dose response of intranasal esketamine in 67 individuals with TRD [126]. Over a 1-week period, a change in MADRS total scores on day 8 in all three esketamine treatment groups (28, 56, or 84 mg) was statistically superior to placebo. Dissociative symptoms appeared to diminish with repeated dosing. Finally, a 12-week, randomized, placebo-controlled, double-blind, multi-center study investigated the efficacy of intranasal esketamine (84 mg) in 68 adults with MDD and active suicidal ideation. Intranasal esketamine significantly reduced depressive symptoms (measured by the MADRS) and thoughts of suicide (measured by the SSI) [127]. Taken together, these results suggested that the 'S' enantiomer of ketamine may contribute to its antidepressant effect.

In contrast, and as mentioned earlier in this review, a recent study series that sought to identify which, if any, of the major ketamine metabolites were responsible for the antidepressant effects of ketamine found that metabolism of (*R,S*)-ketamine to (2*S*,6*S; 2R,6R)*-HNK is essential to the antidepressant effects of ketamine. Furthermore, the (2*R*,6*R*)-HNK enantiomer, which is one of the direct metabolites of (*R,S*)-ketamine, is the primary agent involved in exerting the antidepressant effects of ketamine [38]. In addition, mice treated with a single dose of (2*R*,6*R*)-HNK showed behavioral, cellular, and electrophysiological improvements in their depression-related symptoms that lasted up to 3 days. The significant antidepressant effects of (2*R*,6*R*)-HNK were not associated with any dissociative effects, suggesting that the antidepressant actions exerted by this metabolite occurred independently of NMDA receptor inhibition. Notably, these specific ketamine metabolites induced early and sustained

activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, contrary to prior suggestions that the antidepressant effect of ketamine is exerted primarily through the NMDA receptor.

6 Conclusions

As the evidence reviewed above has underscored, a number of clinical avenues are currently being investigated in the quest to develop an equally effective, more convenient alternative to ketamine that is not associated with psychotomimetic and dissociative side effects. Although some have suggested that the antidepressant effects of ketamine may be related to mechanisms other than glutamate [64], suggesting, for instance, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid throughput as a potential venue, mechanistic confirmatory studies are lacking at this stage. Similar to subanesthetic-dose ketamine, pre-clinical studies of GLYX-13 (rapastinel) [125] have emphasized the importance of further investigating mechanisms of action that can allow for continued work towards developing more effective and safe treatments for mood disorders.

Given that our current armamentarium of psychotropic medications has shown to be the most effective for psychiatric disorders acting on multiple receptors and molecules (e.g., clozapine for schizophrenia), we may need to find the right combination of molecular actions and cellular effects to develop more effective medications for mood disorders. The most recent evidence suggests that, as observed in recent ketamine studies, other molecular and cellular actions in addition to primary NMDA receptor effects may need to converge to induce antidepressant action. Therefore, linking biological to clinical effects requires simultaneous preclinical and clinical investigations, with each paving the way towards the other. Finally, with regard to clinical investigations, an integrated approach using different functional brain imaging techniques, psychophysiological methods, and reconceptualization of clinical phenomenology may be essential to disentangling clinical biological heterogeneity of patients with depression [13].

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Compliance with Ethical Standards

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Conflict of interest Dr. Zarate is listed as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (*R,S*)-ketamine metabolites in the treatment of depression and neuropathic pain. Dr. Zarate is listed as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. Dr. Zarate has assigned his patent rights to the US Government but will share a percentage of any royalties received by the government. Drs. Lener and Kadriu have no conflict of interest to disclose, financial or otherwise.

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