Published in final edited form as:

Expert Rev Clin Pharmacol. 2017 February ; 10(2): 153–166. doi:10.1080/17512433.2017.1253472.

Mood Therapeutics: Novel Pharmacological Approaches for Treating Depression

Ioline D. Henter[1], **Rafael T. de Sousa**[1], **Philip W. Gold**[1], **Andre R. Brunoni**[2], **Carlos A. Zarate Jr**[1], and **Rodrigo Machado-Vieira**[1]

[1]Experimental Therapeutics and Pathophysiology Branch, NIMH-NIH, USA

[2]Laboratory of Neuroscience, LIM- 27, Institute and Department of Psychiatry, University of São Paulo, São Paulo, Brazil

Abstract

Introduction—Real-world effectiveness trials suggest that antidepressant efficacy is limited in many patients with mood disorders, underscoring the urgent need for novel therapeutics to treat these disorders.

Areas Covered—Here, we review the clinical evidence supporting the use of novel modulators for the treatment of mood disorders, including specific glutamate modulators such as: 1) high-trapping glutamatergic modulators; 2) subunit (NR2B)-specific N-methyl-D-aspartate (NMDA) receptor antagonists; 3) NMDA receptor glycine-site partial agonists; and 4) metabotropic glutamate receptor (mGluR) modulators. We also discuss other promising, non-glutamatergic targets for potential rapid antidepressant effects in mood disorders, including the cholinergic system, the glucocorticoid system, and the inflammation pathway, as well as several additional targets of interest. Clinical evidence is emphasized, and non-pharmacological somatic treatments are not reviewed. In general, this paper only explores agents available in the United States.

Expert Commentary—Of these novel targets, the most promising—and the ones for whom the most evidence exists—appear to be the ionotropic glutamate receptors. However, moving forward will require us to fully embrace the goal of personalized medicine and will require health professionals to pre-emptively identify potential responders.

Keywords

AMPA receptor; bipolar disorder; depression; glutamate; major depressive disorder (MDD); mood; N-methyl-D-aspartate (NMDA); treatment

Correspondence: Rodrigo Machado-Vieira, Experimental Therapeutics and Pathophysiology Branch, 10 Center Dr, Room 7-5341, Bethesda, MD, 20892, Phone: 301-443-3721, Fax: 301-480-8792, machadovieirar@mail.nih.gov.

Declaration of Interest: CA 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. CA Zarate is listed as 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; he has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

1. Introduction

Mood disorders—specifically, major depressive disorder (MDD) and bipolar disorder (BD)—are highly prevalent worldwide and a leading cause of disability. Although a number of therapeutic options exist for MDD patients, treatment response is quite variable and difficult to predict. Furthermore, currently available antidepressants are not effective for all MDD patients—or even most MDD patients. For instance, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that approximately one-third of MDD patients achieved remission after an adequate trial with a traditional antidepressant agent [1]. The situation is similarly sub-optimal for the treatment of bipolar depression. While a number of treatments are available for the manic phase of the illness—antiepileptic agents in particular—few effective treatments exist for bipolar depression. For instance, a large, 26-week study found that antidepressant use was not beneficial in patients with BD-I or BD-II depression [2] and, to date, no agent has been developed specifically to treat bipolar depression. It should also be noted that for both MDD and BD, when currently available therapeutics do work, they are sometimes poorly tolerated, or associated with a delayed onset of action of several weeks. This significant latency period increases risk of suicide or self-harm and is a key public health issue [3].

Here, we review new compounds and targets that have demonstrated clinical antidepressant efficacy in mood disorders; we focus on novel drugs that have shown efficacy in human studies, particularly those affecting the glutamatergic system. CANMAT criteria [4] (modified here to encompass evidence of secondary measures in double-blind, randomized, controlled trials) were used to assess the most important studies, which are ranked in Table 1 for each therapeutic agent according to evidence of efficacy. Within this framework, it is important to underscore from the outset that recent clinical evidence—much of which will be reviewed in this paper—suggests that rapid antidepressant effects are indeed achievable in humans [5]. This paradigm of rapid antidepressant effects lends additional urgency to the development of novel treatments for mood disorders that target alternate neurobiological systems, particularly for patient subgroups that do not respond to currently available therapies. Novel targets of interest include the glutamatergic system, the cholinergic system, the glucocorticoid system, and the inflammation pathway, as well as several additional targets of interest. Specific agents reviewed include ketamine, dextromethorphan, AZD6765, CP-101,606/traxoprodil, MK-0657 (CERC-301), D-cycloserine, GLYX-13, AZD2066, RO4917523/basimglurant, scopolamine, biperiden, mifepristone (RU-486), pregnenolone, ketoconazole, metyrapone, DHEA, celecoxib, infliximab, N-acetyl cysteine (NAC), pioglitazone, erythropoietin, and silexan. While preclinical evidence exists for all these agents, this manuscript, with few exceptions, emphasizes clinical results. In general, this paper also only explores agents available in the US (for instance, evidence suggests that the melatonergic system may be a promising novel target for mood disorders, but because those agents are not available in the US, they will not be discussed further in this paper).

2. The Glutamatergic System

A number of glutamate-modulating agents have been tested in “proof-of-concept” studies in subjects with mood disorders. The clinical evidence supporting the use of glutamate receptor

modulators includes: 1) broad glutamatergic modulators (ketamine, dextromethorphan, AZD6765); 2) subunit (NR2B)-specific N-methyl-D-aspartate (NMDA) receptor antagonists (CP-101,606/traxoprodil, MK-0657 (now called CERC-301)); 3) glycine-site partial agonists (D-cycloserine, GLYX-13); and 4) metabotropic (mGluR5) glutamate receptor modulators (AZD2066, RO4917523/basimglurant). It should be noted that several other potentially intriguing glutamate receptor targets with preclinical antidepressant-like efficacy exist. These include AMPA agonists (most notably farampator (CX-691/ORG 2448) and ORG-26576), mGluR2/3 negative allosteric modulators, and mGluR7 agonists. However, given the paucity of the clinical evidence surrounding these targets, they will not be discussed further in this manuscript.

2.1 High-Trapping Glutamatergic Modulators

Below, we describe the considerable clinical evidence surrounding the antidepressant effects of the glutamatergic modulator ketamine.

2.1.1 Single-dose (IV) ketamine studies—An initial pilot study demonstrated that individuals with MDD or bipolar depression improved within 72 hours of ketamine infusion [6]. Building on this work, a subsequent placebo-controlled, double-blind, crossover study found that a single ketamine infusion (0.5 mg/kg for 40 minutes) had rapid (within two hours) antidepressant effects in subjects with treatment-resistant MDD, [7]. In that study, more than 70% of patients responded to ketamine at 24 hours post-infusion and, moreover, 35% maintained a sustained response at one week post-infusion. Other studies have since replicated these effects, including a single-blind, non-counter-balanced design study of 10 patients with treatment-resistant depression [8] and another larger study that used the short-acting benzodiazepine midazolam as an active comparator to mimic ketamine's sedative and anxiolytic effects [9]. In the latter study, the authors found that subanesthetic-dose ketamine infusion (0.5mg/kg × 40 minutes) was more effective than placebo (response rates were 64% and 28%, respectively, at 24 hours post-infusion in subjects randomized to ketamine and midazolam).

Ketamine's rapid antidepressant effects have also been explored in patients with treatment-resistant bipolar depression, though these placebo-controlled studies used ketamine adjunctively with lithium or valproate rather than as monotherapy. In one study of 18 subjects with treatment-resistant bipolar depression maintained on therapeutic levels of mood stabilizers, a rapid (within 40 minutes) and relatively sustained (up to three days) antidepressant response was observed in patients receiving a single subanesthetic dose of ketamine [10]. This result was replicated in a study using an identical design (N=15) [11]. Another single, open-label study of ketamine used adjunctively with mood stabilizers in patients with bipolar depression (N=42) confirmed these previous findings [12]. It should be noted that ketamine use appears to be safe for individuals with bipolar depression and that a single dose has very low risk (similar to placebo) of inducing hypo/mania [13].

In a meta-analysis of ketamine studies (N=147 drawn from seven trials), the APA Council of Research Task Force on Novel Biomarkers and Treatments concluded that ketamine produces rapid, but transient, antidepressant effects accompanied by brief dissociative and

psychotomimetic effects; odds ratios for response and transient remission of symptoms at 24 hours were 9.87 (4.37-22.29) and 14.47 (2.67-78.49), respectively [14].

Most recently, two promising case studies also suggested that ketamine may be useful in the treatment of mood disorders with a history of psychosis [15]. This is particularly notable because patients with a history of psychosis have often been excluded from ketamine trials because of this agent's psychotomimetic effects.

2.1.2 Repeated-dose ketamine studies—Despite the large effect sizes associated with antidepressant response to ketamine, these effects are also transient for most patients (standardized same- and next-day mean difference of approximately -1.0 in two recent meta-analyses [16,17]). Thus, investigators have explored the possibility that repeated dosing strategies may offer more sustained antidepressant benefits. One repeated-dose study investigated 28 medicated treatment-resistant patients with either MDD (N=22) or bipolar depression (N=6) who received a standard dose (0.5 mg/kg × 40 minutes) of ketamine weekly or bi-weekly over three weeks; participants received a total of three or six infusions, respectively, and were then followed for 21 days to monitor for the cognitive deficits often seen in ketamine abusers [18]. Eight patients responded to ketamine, and four achieved full remission (29% and 14%, respectively). No cognitive impairment was noted, though one BD patient experienced rapid cycling (hypomanic switches) after three infusions [18].

Another preliminary study investigated the safety, tolerability, and efficacy of repeated-dose ketamine in subjects with treatment-resistant MDD [19]. Ten unmedicated patients with treatment-resistant MDD received six open-label subanesthetic dose (0.5 mg/kg × 40 minutes) ketamine infusions over 12 days. Antidepressant effects and a mild, transient side effect profile were noted. Another study of 24 medication-free patients with treatment-resistant MDD (including the 10 subjects in the above study [19]) found an antidepressant response rate of 70.8% in patients who received six infusions over 12 days [20]. A naturalistic follow-up phase lasting 83 days (which allowed for traditional antidepressant treatment) found that mean time to relapse was 18 days. Notably, however, roughly one-third of responders maintained antidepressant response until the end of the observation period.

Another open-label study in 10 patients with treatment-resistant MDD investigated the effects of repeated subanesthetic-dose ketamine (0.3 mg/kg over 100 minutes to approximate the total amount of 0.5mg/kg over 40 minutes without the institutional requirement of anesthesia supervision). Participants received ketamine infusions twice weekly for two weeks until they had either received four infusions or their symptoms had remitted [21]. At study endpoint, six participants had received the maximum number of doses (four), and three and five patients were responders and remitters, respectively; there were two non-responders. Participants were monitored for four additional weeks, and 50% of responders achieved remission while another two patients retained their initial symptom remission. Interestingly, however, this low-dose, slow ketamine infusion protocol did not appear to reduce side effect burden.

Finally, another recent study of 67 patients with treatment-resistant MDD demonstrated that serial intravenous ketamine (0.5 mg/kg over 40 minutes twice or thrice weekly for four

weeks) was associated with a good overall response rate compared to placebo [22]. Interestingly, there were no differences in response between those who received infusions twice or thrice weekly. Ketamine was also well tolerated and safe in a study evaluating 97 patients who received 205 intravenous ketamine infusions (0.5 mg/kg) across three clinical trials at two centers [23].

Overall, a recent meta-analysis found that the mean percentage of improvement, weighted for sample size, showed a consistent efficacy for ketamine compared to placebo [24]. Specifically, percentage improvement for ketamine vs placebo was: day 1 (−41.17% vs −6.06%); day 2 (−41.24% vs −.94%); day 3–4 (−34.24% vs −7.03%); day 7; (−20.04% vs −7.18%); and day 14 (−15.38% vs −5.87%).

Despite the breadth and promise of these findings, to date no randomized, placebo-controlled, multiple-dose ketamine studies have assessed the long-term safety, tolerability, and efficacy of repeated-dose strategies. As such, insufficient data presently exist to recommend the long-term, off-label use of ketamine for the treatment of mood disorders.

2.1.3 Alternative Modes of Ketamine Administration—Investigators are increasingly exploring alternative (and more convenient) means of ketamine administration, including intranasal, intramuscular, oral, and sublingual.

2.1.3.1 Intranasal: Intranasal ketamine administration has typically been used for dental procedures in children who require anesthesia (bioavailability ranges from 25-50%) [25]. A randomized, double-blind, crossover, placebo-controlled trial, randomized 20 MDD patients to receive either intranasal ketamine (50mg) or a saline intranasal solution [26]. A significant antidepressant effect was noted within 24 hours of intranasal ketamine administration (as assessed via change from baseline in Montgomery Asberg Depression Rating Scale (MADRS) score), and only minor dissociative, psychotomimetic, and hemodynamic effects were observed. However, no antidepressant efficacy over placebo was seen at 72 hours post-ketamine administration. In addition, the study had several limitations, including use of a saline control and concomitant use of psychotropic medications (notably, 10 of 20 patients were concomitantly receiving benzodiazepines), suggesting that intranasal ketamine may be most useful as an adjunctive treatment. It is also interesting to note that despite the reduced dissociative properties associated with intranasal ketamine, one preliminary study found a positive correlation between dissociative side effects and antidepressant response to ketamine [27]; this suggests that a head-to-head comparison study is needed to determine the effectiveness, safety, and tolerability of the varying methods of ketamine administration.

2.1.3.2 Intramuscular: Intramuscular ketamine has similar bioavailability to intravenous ketamine (93%). This method of administration also has the additional benefit of not requiring specialized equipment for office-based administration (specifically, an infusion pump) and can also be administered to patients with poor intravenous access. In one case series, two female patients with treatment-resistant MDD received open-label intramuscular ketamine at ascending doses (0.5, 0.7, 1.0 mg/kg); a dose-dependent antidepressant response was observed [28] and, at the highest dose, one patient achieved remission 24 hours post-

injection; intramuscular ketamine use was found to be safe, and the reported adverse events were similar to those associated with intravenous administration. In addition, a small (N=9 per group), randomized, open-label trial found that intramuscular ketamine (0.25mg/kg or 0.5 mg/kg) was not inferior to intravenous ketamine (0.5 mg/kg) for up to three days post-ketamine administration [29].

2.1.3.3 Oral: Oral ketamine is a particularly appealing alternative method of administration due to its ease of use. However, oral administration has considerably lower bioavailability (20%). Two small, preliminary case studies that examined the effectiveness of oral ketamine obtained positive results [30,31]. Another study of eight depressed hospice patients who received oral ketamine (0.5mg/kg) daily for 28 days found that it had significant antidepressant and anxiolytic effects [32]. Another study investigated escalating doses of oral ketamine (0.5mg/kg up to 3mg/kg) in two subjects with treatment-resistant MDD and suicidal ideation and found that ketamine had sustained antidepressant and antisuicidal effects [33]. However, blood levels of ketamine and its metabolites were not measured in these studies, making it difficult to interpret its antidepressant effects.

2.1.3.4 Sublingual: Sublingual ketamine was investigated in outpatients with either MDD or bipolar depression currently experiencing a major depressive episode; variable administration (every two to seven days) of add-on, escalating (but still subanesthetic) dose sublingual ketamine was found to have antidepressant effects in 20 of 27 patients (77%) [34]. Sublingual ketamine was well-tolerated and associated with no reported dissociative or psychotomimetic side effects. As with the results for oral ketamine noted above, ketamine and ketamine metabolite blood levels were not obtained in this study, making it difficult to compare and correlate sublingual administration with other forms of ketamine administration.

2.1.4 Ketamine's anti-suicidal effects—Recent studies have shown that ketamine also has rapid-onset anti-suicidal effects. A study from our laboratory found that a single open-label ketamine infusion (0.5 mg/kg) reduced measures of suicidal ideation in 33 patients with treatment-resistant MDD, an effect that was maintained for up to four hours post-infusion [35]. In two studies of patients with treatment-resistant MDD, Price and colleagues found that ketamine infusion reduced both explicit suicidal ideation and implicit suicidal thinking [36,37]. Another study that evaluated acutely suicidal patients in a psychiatric emergency room (N=14) found that open-label ketamine (0.2mg/kg intravenous ketamine, administered over one to two minutes) had rapid anti-suicidal and antidepressant effects [38]; however, it should be noted that this method of administration has not been further pursued.

Finally, another recent study of 108 patients with either treatment-resistant MDD or bipolar depression found that a single, standard-dose infusion of ketamine (0.5 mg/kg over 40 minutes) rapidly improved measures of suicidal ideation compared to placebo [39]. Interestingly, in that study, improvements in suicidal thinking were related to, but not fully explained by, improvements in depression and anxiety symptoms [39]; specifically, ketamine's antidepressant and anxiolytic efficacy accounted for only up to 20% of the improvement in suicidal ideation. The authors performed a secondary analysis on the same

sample and found that lacking a lifetime history of suicide attempt(s) also predicted improved antidepressant response to ketamine at one week post-infusion [40]. Nevertheless, this study excluded patients who were actively suicidal or who had a recent suicide attempt, which may have affected the results.

2.1.5 Esketamine—Esketamine is the *S*(+) enantiomer of *ketamine*. There are currently six ongoing, Phase 3 clinical trials studying the efficacy of intranasal and intravenous esketamine in treatment-resistant depression.

A recent multicenter, randomized, placebo-controlled trial (NCT01640080) assessing the efficacy of intravenous esketamine was conducted in 30 patients with treatment-resistant depression [41]. Patients were randomly assigned to receive an IV infusion of .20 mg/kg or . 40 mg/kg esketamine or placebo over 40 minutes. A rapid (within two hours) and robust antidepressant effect (as assessed by the MADRS) was observed with either 0.20 mg/kg or 0.40 mg/kg of esketamine compared to placebo. The most common side effects were headache, nausea, and dissociation, but the latter was transient and did not persist beyond four hours post-infusion.

Another double-blind, placebo-controlled, multicentre study (SYNAPSE, NCT01998958) evaluated the antidepressant efficacy and dose response of intranasal esketamine in 67 individuals with treatment-resistant depression [42]. Over a one-week period, changes in MADRS total scores on Day 8 in all three esketamine treatment groups (28mg, 56mg, or 84mg) were statistically superior to placebo. Transient elevations in blood pressure and heart rate were observed in most patients receiving esketamine on dosing days. Dissociative symptoms appeared to diminish with repeated dosing.

Finally, a 12-week, randomized, placebo-controlled, double-blind, multicentre study investigated the efficacy of intranasal esketamine (84mg) in 68 adults with MDD and active suicidal ideation. Intranasal esketamine significantly reduced depressive symptoms (as assessed by the MADRS) and thoughts of suicide (as assessed by the Scale for Suicide Ideation (SSI)) [43]. Based on these positive results, the US Food and Drug Administration (FDA) recently granted Breakthrough Therapy Designation for intranasal esketamine in MDD with imminent risk for suicide in August 2016 [44].

2.1.6 New Directions in Ketamine Research—As reviewed in detail above, the antidepressant actions of the broad glutamatergic modulator ketamine have been an active topic of clinical investigation over the past decade. However, a very recent preclinical study has called into question whether NMDA receptor inhibition is indeed the primary mechanism of ketamine's antidepressant action. Although this manuscript focuses almost entirely on clinical evidence, the paradigm-shifting nature of this finding leads us to here present the preliminary preclinical evidence.

Specifically, investigators found that the antidepressant effects of ketamine appear to be produced not by ketamine itself but by one of its metabolites: (2*R*,6*R*)-hydroxynorketamine (HNK) through a mechanism that is NMDA receptor-independent and that appears to enhance AMPA activity throughput [45]; this metabolite is currently being developed as a

treatment. In this study, researchers began by investigating *(S)*- and *(R)*-ketamine; the former was found to block NMDA receptors more potently but did not reduce depressive-like behaviors as well as the *(R)* isomer. The researchers then studied the effects of the metabolites created as *(S)*- and *(R)*-ketamine were broken down and discovered that (2*S*,6*S*; 2*R*,6*R*)-HNK were pharmacologically active and reached levels that were three times higher in female than male mice. Because previous studies have shown that female mice respond more effectively to ketamine's antidepressant effects than males, the discovery suggested that differences in these HNK metabolites might explain this finding; when the researchers blocked formation of the metabolite, ketamine's antidepressant effects also disappeared. The researchers then found that mice treated with a single dose of one of these metabolites—(2*R*, 6*R*)-HNK—showed improvements in their symptoms that lasted for three days. Furthermore, (2*R*,6*R*)-HNK's significant antidepressant effects were not associated with any dissociative effects.

While additional research is certainly needed to explore whether (2*R*,6*R*)-HNK's antidepressant effects will work similarly in humans and can commensurately lead to improved therapeutics for patients, this recent study highlights the quick pace of research in the development of glutamatergic agents, and underscores the role of ketamine as a proof-of-concept agent for elucidating this new class of potentially lifesaving drugs.

2.2 Non-Selective and Other NMDA Receptor Antagonists

Major clinical concerns regarding use of ketamine as an antidepressant include its usual parenteral administration, its acute dissociative and psychotomimetic side effects, and the potential abuse liability and neurotoxicity associated with its chronic use. Thus, other glutamatergic modulators have been studied for the treatment of mood disorders.

2.2.1 Nitrous Oxide—Nitrous oxide (N_2O) is a non-competitive NMDA receptor inhibitor and an inhaled general anesthetic most often used in obstetrics or dentistry. A recent placebo-controlled, double-blind, crossover study examined 20 patients with treatment-resistant depression who received a one-hour inhalation of 50% N_2O or 50% nitrogen as placebo [46]. N_2O at both two hours and 24 hours post-inhalation significantly improved outcome (as assessed via the Hamilton Depression Rating Scale (HAM-D)) compared to placebo. Adverse effects included anxiety, headache, and nausea/vomiting; no participant reported psychotomimetic effects. N_2O has a broad mechanism of action similar to ketamine's. However, N_2O's antidepressant efficacy was not as robust as that of intravenous ketamine (see above).

2.2.2 Dextromethorphan—Dextromethorphan is a non-selective, non-competitive NMDA receptor antagonist and cough suppressant with sedative and dissociative properties as well as theoretical potential as a rapid-acting antidepressant [47,48]. To date, no randomized controlled trials have explored dextromethorphan as monotherapy for the treatment of mood disorders. It was, however, studied adjunctively with valproic acid in BD in a randomized, placebo-controlled trial, though no significant group differences were seen between groups (as assessed by mean HAM-D and Young Mania Rating Scale (YMRS) scores) [49]. In addition, a retrospective chart review of 22 subjects with BD-II or BD not

otherwise specified (BD-NOS) found that adding 20 mg dextromethorphan and 10 mg quinidine (a cytochrome 2D6 inhibitor) once or twice daily to a current medication regimen significantly improved Clinical Global Impression (CGI) scale scores [50]. This dextromethorphan-quinidine combination is now being studied (NCT01882829) for treatment-resistant depression under the name Nuedexta, which is approved for treating pseudobulbar affect. One case report found that Nuedexta had antidepressant effects in a depressed patient with emotional lability [51].

2.2.3 AZD6765—AZD6765 is a low-trapping non-selective NMDA receptor channel blocker. One study found that a single infusion of AZD6765 (150mg) in unmedicated subjects with treatment-resistant MDD was more effective than placebo, with no psychotic or dissociative side effects [52]. Nevertheless, antidepressant response was not as robust or sustained as response to ketamine; AZD6765 was associated with a shorter duration of effect as well as lower response and remission rates. A three-week, placebo-controlled trial studied repeated adjunctive AZD6765 (now renamed lanicemine) infusions received in two doses (100mg and 150mg) in subjects with treatment-resistant MDD; lanicemine again demonstrated antidepressant effects without ketamine-like side effects [53]. A subsequent six-week phase IIb study, however, found that adjunctive repeated-dose (50mg and 150mg) lanicemine did not separate from placebo, potentially due to the large placebo effect (39% at trial endpoint) [53,54].

2.3 Subunit-Specific NMDA Receptor Antagonists

2.3.1 CP-101,606 and CERC-301—Subtype-specific NMDA receptor antagonists may also have fewer undesirable adverse effects while retaining antidepressant activity. Two agents have been successfully tested in this arena: CP-101,606 and MK-0657; the latter has been renamed CERC-301 and is now in development by Cerecor.

With regard to CP-101,606, a randomized, double-blind, placebo-controlled study found a 60% response rate compared to 20% in the placebo group in a group of 30 patients with treatment-resistant MDD; interestingly, 78% of treatment responders maintained this antidepressant effect for at least one week [55]. The antidepressant effect was noted at day 5, but not at the earlier time point of day 2. Unfortunately, there was no replication study and development of this compound was stopped because of potential cardiovascular toxicity (specifically, QTc prolongation). Interestingly, off-site effects at the sigma-1 receptor have been reported with CP-101,606, suggesting that it may not be selective for NR2B [56].

Efficacy of the oral NR2B antagonist MK-0657 (CERC-301) in treatment-resistant MDD was tested in a small, randomized, double-blind, placebo-controlled, crossover pilot study [57]. While no antidepressant improvement over placebo was observed using the primary outcome measure (MADRS), some improvement was noted as assessed by other depression rating scales. However, reports from a more recent clinical trial with CERC-301 found that it failed to demonstrate significant antidepressant effects compared to placebo [58]. A trial using higher doses is underway (NCT02459236).

2.3.2 D-cycloserine (DCS)—At doses greater than 100mg/day, the broad-spectrum antibiotic D-cycloserine (DCS) is a functional NMDA glycine receptor partial agonist [59].

In participants with treatment-resistant MDD, an initial six-week, placebo-controlled, crossover trial of 250mg/day of adjunctive DCS reduced depressive symptoms but did not separate from placebo due to high placebo response rate [60]. A larger, subsequent study of 26 subjects with treatment-resistant MDD assessed the efficacy of escalating dose (up to 1000mg/day) adjunctive DCS [61] and found that higher-dose DCS exerted significant antidepressant effects as measured by the clinician-administered HAM-D and self-reported Beck Depression Inventory (BDI); more than half of the patients randomized to high-dose DCS had a greater than 50% reduction in HAM-D scores by the end of the trial.

2.3.3 GLYX-13 (Rapastinel)—The NMDA receptor glycine site functional partial agonist GLYX-13 (Rapastinel) has been in clinical development by Naurex, Inc (now acquired by Allergan). A Phase IIb safety and efficacy trial in unmedicated inpatients with treatment resistant MDD randomized to receive a single saline placebo (N=33) or intravenous GLYX-13 (1m/kg (N=25), 5mg/kg (N=20), 10 mg/kg (N=17), or 30 mg/kg (N=21)) over three to 15 minutes found that subjects randomized to the 5 and 10 mg/kg arms had a significant antidepressant response compared to placebo one week post-administration [62]. In addition, and 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 same research group recently published the results of a randomized, double-blind, clinical trial of adjunctive GLYX-13 in treatment-resistant MDD [63]. All participants were maintained on their current psychotropic medication regimen and randomized to 1, 5, 10, or 30 mg/kg intravenous GLYX-13 weekly for six weeks. At doses of 5 or 10 mg/kg IV, GLYX-13 reduced depressive symptoms at days 1 through 7 as assessed by the HAM-D17. Onset of action as assessed using the Bech-6 subscale of the HAM-D occurred within two hours. GLYX-13 elicited no psychotomimetic or other significant side effects.

2.3.4 Sarcosine—Sarcosine is a glycine transporter-I inhibitor that potentiates NMDA function. In a six-week, randomized, double-blind, citalopram-controlled study of 40 patients with MDD, sarcosine demonstrated superior antidepressant effects to citalopram (as assessed by the HAM-D, Clinical Global Impression (CGI), and Global Assessment of Function (GAF) rating scales). Sarcosine-treated patients had remission and response rates higher than those treated with citalopram and were less likely to drop out of the study. Sarcosine was also well-tolerated without significant side effects [64].

2.4 Group 1 Metabotropic Receptor Negative Allosteric Modulators

The Group 1 metabotropic receptors—mGluR1 and mGluR5—are generally stimulatory and activate protein kinase C (PKC)-coupled pathways. mGluR5 receptors are mostly post-synaptic and co-localize with NMDA receptors and, as such, modulate their function. Several mGluR5 antagonists have been studied in treatment-resistant MDD. AZD2066 was studied in a six-week randomized controlled trial with three treatment arms: AZD2066 (12-18 mg/day), oral placebo, and the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine (30-60mg/day) (NCT01145755); none of the arms statistically separated on any

efficacy measures and no ongoing studies in mood disorders with AZD2066 are currently listed on ClinicalTrials.gov.

An F. Hoffman-La Roche compound, RO4917523 (basimglurant, RG7090), has also been studied in individuals with treatment-resistant MDD [65]. The MARIGOLD phase IIb study compared adjunctive modified-release basimglurant (0.5 or 1.5 mg) to adjunctive placebo over nine weeks in individuals with treatment-resistant MDD (six weeks of double-blind treatment followed by three weeks of post-treatment follow-up) [66]. Patients were randomized to receive either adjunctive placebo (N=108), adjunctive basimglurant 0.5mg (N=112), or adjunctive basimglurant 1.5mg (N=111). While no statistically significant difference was observed on the primary endpoint (change in MADRS score from baseline to six weeks), promising results were observed on several exploratory secondary endpoints, including patient self-reported depression scores, at 1.5mg. The most common adverse events were dizziness (23%) and two self-resolving cases of mania at the 1.5mg dose.

3. The Cholinergic System

Cholinergic receptors are divided into the metabotropic muscarinic (M_1 to M_5) and ionotropic nicotinic (α and β) acetylcholine receptors. Acetylcholinesterase inhibitors—which increase central acetylcholine tone—have consistently been found to induce depressive symptoms in humans [67]. An early study found that the anticholinergic agent biperiden had antidepressant effects in severely depressed inpatients (N=10) [68]. Controlled pilot studies with the acetylcholinesterase inhibitor physostigmine found that either single or multiple injections of this agent rapidly but transiently decreased manic symptoms [69]. Similar studies conducted with the cholinesterase inhibitor donepezil in patients experiencing a manic episode found that no patient in the donepezil arm responded, whereas a few responded in the placebo arm [70]; however, at least one open series obtained promising preliminary results[71].

More recently, several randomized, double-blind, placebo-controlled studies have investigated intravenous doses of the anticholinergic agent scopolamine as add-on or monotherapy in individuals with either MDD or bipolar depression [72-74]. Notably, antidepressant effects were typically observed in the first week of treatment. A placebo-controlled, double-blind, crossover pilot study of participants with either MDD (N=9) or bipolar depression (N=9) found that scopolamine exerted rapid and robust antidepressant and anxiolytic effects, particularly at doses of 4 μg/Kg (compared to 2 or 3 μg/Kg) [75]; these antidepressant effects persisted for two weeks, and repeated dosing extended antidepressant response and yielded additional benefits. No significant increase in manic symptoms was noted.

Despite these promising results, it should be noted that few studies with anticholinergic drugs have been performed, and limited data therefore exist with regard to dose-response curves, pharmacodynamics, safety, or treatment duration. Scopolamine is also associated with several limitations that may restrict its broad clinical use, including anticholinergic side effects and risk of psychosis at higher doses [74].

4. The Glucocorticoid System

The glucocorticoid system and hypothalamic-pituitary-adrenal (HPA) axis are among the best studied areas in psychiatric research. Hypothalamic corticotropin-releasing hormone (CRH) is the principal central nervous system (CNS) stimulus to pituitary adrenal activation. CRH itself exerts many of the phenotypic features of melancholia, including anxiety-related behaviors, decreased appetite, decreased sleep, and decreased sexual activity, and it also has pronounced proinflammatory effects [76]. Multiple deleterious effects can occur when CRH is secreted excessively, including inhibited BDNF secretion, neuroplasticity, and subgenual prefrontal cortex function. Hypercortisolism also leads to behavioral hyperarousal, insomnia, and the desynchronization of critical biological rhythms; it also significantly interferes with sleep and sexual function [77]. In an attempt to limit the deleterious effects of hypercortisolism, a number of antiglucocorticoid agents have been studied in the treatment of mood disorders (reviewed in [78]).

Mifepristone (RU-486) is a synthetic, non-selective, glucocorticoid receptor antagonist. One study of inpatients with psychotic depression found that RU-486 (600 or 1200 mg/day) significantly decreased both Brief Psychiatric Rating Scale (BPRS) and HAM-D21 scores [79]. Another study of drug-free subjects with psychotic depression found that seven days of treatment with RU-486 followed by treatment as usual was both effective and well tolerated [80]. In contrast, one small study found that RU-486 had no antidepressant efficacy in psychotic depression [81], and another larger study (N=433 patients with psychotic depression) found that three different doses of RU-486 did not separate from placebo at study endpoint; however, the latter study noted a significant linear association between RU-486 plasma concentrations and clinical response [82]. RU-486 has also been tested in individuals with treatment-resistant bipolar depression. One six-week pilot study found that 600 mg/day of RU-486 improved depressive symptoms and cognition over placebo [83], and that this cognitive improvement was inversely associated with basal cortisol levels, suggesting an anti-glucocorticoid effect. Another placebo-controlled, double-blind, randomized study of 60 patients with bipolar depression evaluated RU-486 (600 mg/day for one week) as an adjunctive treatment. While no improvement in depressive symptoms was seen, RU-486 was associated with a time-limited increase in cortisol awakening response and sustained improvement in spatial working memory (the primary outcome measure); these effects were observable seven weeks after treatment ended [84]. Overall, the evidence suggests that RU-486 may have predominantly short-term benefits during acute depressive episodes. However, it should also be noted that long-term treatment with RU-486 could be associated with significant side effects that have yet to be properly assessed [85,86].

Pregnenolone is an endogenous steroid hormone and acts as a neurosteroid. A recent, randomized, placebo-controlled, double-blind, 12-week study of pregnenolone in individuals with bipolar depression (N=80) found that remission rates were higher for those receiving pregnenolone than for those receiving placebo (61% vs 37%, respectively), as assessed by the Inventory of Depressive Symptomatology (IDS) Self-Report, but not by the HAM-D [87]; moreover, pregnenolone was well tolerated and associated with only mild side effects.

Ketoconazole and metyrapone are both glucocorticoid synthesis inhibitors, agents thought to potentiate the efficacy of antidepressants. A controlled, randomized, double-blind trial in MDD patients found that adjunctive metyrapone therapy was superior to placebo, and accelerated the onset of antidepressant action [88]; metyrapone was well tolerated and associated with only mild side effects. A large, multi-center, placebo-controlled, randomized, Phase 3 trial evaluating the effects of metyrapone augmentation for individuals with treatment-resistant MDD was recently completed, but results are not yet available (NCT01375920).

Adjunctive ketoconazole (up to 800 mg/day) was also investigated in six patients with treatment-resistant BD [89]. Ketoconazole significantly improved depressive symptoms in three patients who received at least 400 mg/day, with no induction of manic symptoms. Another study found that, compared to placebo, ketoconazole improved depressive symptoms in individuals with hypercortisolemia, an effect that was not observed in nonhypercortisolemic patients [90]. Finally, one analysis looked at results from five trials conducted with ketoconazole in non-psychotic depression (either MDD or BD) and found a significant difference in favor of treatment (summarized in [91]). However, it should be noted that no recent trials have investigated this agent and, furthermore, that It should be noted, hthe relative risk for drug interactions associated with glucocorticoid synthesis inhibitors may limit their chronic use in mood disorders.

Dehydroepiandrosterone (DHEA) is an endogenous steroid hormone. A six-week, randomized, controlled trial of 22 MDD subjects found that DHEA (up to 90 mg/day) had significant antidepressant effects [92]. These findings were replicated in another six-week trial of DHEA as monotherapy that found significant improvement in depression rating scale scores for subjects taking DHEA compared to those receiving placebo; the drug was well tolerated and safe [93]. As with ketoconazole, no recent trials have investigated this agent.

In this drug category, studies have also explored the antidepressant properties of neuropeptides such as neurokinin 1 (NK1); vasopressin; orexin antagonists; and corticotropin releasing factor (CRF). Much of this work was specifically conducted in individuals with MDD. Despite promising preclinical evidence, particularly for CRF-1 antagonists, clinical results have been mixed and largely disappointing. For a review, see [94].

5. Inflammation Pathway

Inflammation is a core component of mood disorders. Patients with MDD were found to have increased plasma levels of cytokines, acute phase proteins, chemokines, and adhesion molecules, as well as inflammatory mediators such as prostaglandins and arachidonic acid metabolites [95]. Peripheral cytokines gain access to the brain and influence neurotransmitter and neuroendocrine function, and also lead to decreased neurogenesis, decreased neuroplasticity, and increased glutamate release, as well as oxidative stress [95,96]. These effects lead to the destruction or atrophy of neurons and loss of glial elements [96]. CNS-derived cytokines produce similar responses [97].

Preclinical studies have noted that stressed experimental animals have CNS inflammation characterized by the secretion of brain-derived cytokines into cerebrospinal fluid as well as evidence of neuronal inflammation (reviewed in [95]). This inflammation occurs in many areas of the brain thought to be involved in depressive disorders such as the subgenual prefrontal cortex and the amygdala. Studies have found that administering blockers to inflammatory compounds blocked the impact of the stressors on behavior and ameliorated a depressive-like picture. In addition, administering antidepressants prior to severe stress prevented any signs of neuroinflammation.

Multiple studies have shown elevated levels of plasma interleukin 1 (IL-1), tumor necrosis factor alpha (TNFa), and IL-6 in individuals with MDD[98]. Conversely, when cytokines have been given to treat hepatitis B and C, they induce a major depressive episode that responds to standard antidepressants [99]. Raison and Miller (2016) suggested that it might be possible to identify relevant populations based on degree of inflammation in depressive illness, thereby applying immune targeted therapies and monitoring therapeutic efficacy at the level of the immune system in addition to behavior [100].

In 37 MDD subjects, a placebo-controlled trial of the COX-2 inhibitor celecoxib (400mg/day as add-on therapy to fluoxetine, N=37) significantly decreased depression rating scale scores compared to placebo [101]. Another six-week study of MDD subjects found that celecoxib (400md/day adjunctive to reboxetine) was more effective than placebo [102]. An eight-week study of 30 first-episode women with MDD similarly found that celecoxib (200 mg/day as adjunctive therapy to sertraline) had significant antidepressant effects compared to placebo [103]. Finally, a six-week, placebo-controlled, double-blind study of celecoxib in patients with bipolar depression (400mg/day adjunctive to mood stabilizers) found that this agent had superior antidepressant efficacy during the first week of treatment [104]. Despite these promising preliminary findings, two caveats should be noted. First, the ability of celecoxib to enter the blood-brain barrier remains uncertain. Second, selective COX-2 inhibitors have been associated with higher risk of adverse cardiovascular effects, which may limit their long-term use [105].

The tumor necrosis factor antagonist infliximab has also been investigated in the treatment of mood disorders. A 12-week, placebo-controlled, randomized study of 60 subjects with MDD found that infliximab (5mg/kg infusion) had no antidepressant effects at baseline, at two weeks, or at four weeks compared to placebo [106].

Further studies are required to expand our knowledge of this class of agents. In addition, the complexity of the inflammatory pathway, the limited clinical evidence available to date, and the considerable risk for side effects associated with these agents suggests that care is needed before clinical application of these agents is possible.

6. Additional Targets of Interest

A number of other potential targets for further development in this field exist. These include N-acetyl cysteine (NAC), peroxisome proliferator-activated receptor gamma (PPAR-γ), and erythropoietin (EPO).

6.1 N-acetyl cysteine (NAC)

N-acetylcysteine (NAC) is a precursor of glutathione, the most abundant antioxidant protein in the brain, and increases its levels. Glutathione levels, in turn, have been found to be altered in individuals with BD [107,108]. Building on this finding, several studies have investigated NAC for the treatment of both acute episodes and maintenance in BD. One placebo-controlled, double-blind, randomized investigation evaluated adjunctive NAC (1g/twice daily) in 75 BD subjects and found that this agent was more effective than placebo after eight weeks, improving measures of depression, functionality, and quality of life [109]; however, results fluctuated over time and antidepressant efficacy did not separate from placebo post-discontinuation (after 24 weeks). Another study of 14 individuals with BD-II found that NAC improved both depressive and manic symptoms more consistently than placebo [110]. Finally, a large, open-label, eight-week trial of 149 patients with bipolar depression found that adjunctive use of NAC significantly improved depression rating scale scores, quality of life, and overall functioning [111]. In MDD, a large, 12-week, controlled, randomized, add-on trial of 252 patients found that those receiving NAC showed antidepressant improvements similar to the placebo group [112]; however, at week 12, scores on the Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) differed from placebo.

Taken together, the evidence suggests that NAC might improve depressive symptoms during mood episodes, but studies evaluating the frequency of cycling or mood stability are needed to clarify the effects of this agent. NAC has also been tested in other psychiatric disorders (eg, schizophrenia, obsessive compulsive disorder (OCD)), suggesting that it may have non-specific therapeutic effects.

6.2 Peroxisome proliferator-activated receptor gamma (PPAR-γ)

In the brain, PPAR-γ is a nuclear receptor found in neurons, glia and cerebrovascular vessels in the frontal cortex, nucleus accumbens, striatum, hippocampus, hypothalamus, and substantia nigra. Through multiple mechanisms, the PPAR-γ system rapidly senses CNS cellular stress and responds to ameliorate it; it also provides protection against multiple mediators of the innate immune system and promotes neurogenesis during periods of neuronal stress [113].

A recent trial investigated the use of adjunctive treatment with the PPAR-γ agonist pioglitazone [114]. Thirty-seven individuals with treatment-resistant, non-psychotic MDD who were being treated with a standard psychiatric regimen for MDD were randomized in a 12-week double-blind, controlled trial of pioglitazone or placebo. The investigators found that improvement in depression rating scale scores was associated with improved glucose metabolism, but only in patients with insulin resistance. Pioglitazone also appeared to be more beneficial in younger patients. Another double-blind, placebo-controlled study of 40 MDD patients randomized subjects to receive either citalopram plus pioglitazone (15 mg every 12 hours) (N=20) or citalopram plus placebo (N=20) for six weeks [115]. Pioglitazone was superior to placebo over the course of the trial, with patients in the pioglitazone group demonstrating significantly lower HAM-D scores at all time points than the placebo group. Finally, another parallel, randomized, double-blind, placebo-controlled trial evaluated six

weeks of treatment with either pioglitazone (30 mg/day) or placebo as adjunctive to treatment with lithium in 44 patients with bipolar depression [116]. Pioglitazone significantly reduced depressive symptoms (as assessed by the HAM-D) at weeks 2, 4, and 6, and no serious adverse effects were observed.

Taken together, the findings suggest that differential improvement in response to pioglitazone may depend on both glucose metabolic status and level of depression at baseline. This, in turn, suggests that elucidating the reciprocal links between depression and insulin resistance may alter the manner in which we both conceptualize and treat MDD.

6.3 Erythropoietin (EPO)

The hormone erythropoietin (EPO), which controls red blood cell production, has neurotrophic effects. In a randomized, double-blind, placebo-controlled, parallel group study, 40 subjects with treatment-resistant MDD were randomized to eight weeks of treatment with either EPO (40,000 IU) or saline infusion [117]. EPO had no effect on HAM-D (the primary outcome) or Global Assessment of Function (GAF) scores, or on remission rates at nine weeks; however, EPO did improve Beck Depression Inventory-21 (BDI-21) and World Health Organization Quality of life-BREF (WHOQOL-BREF) scores at nine weeks, an effect that was maintained at follow-up (14 weeks). EPO also appeared to enhance both verbal recall (P=0.02) and recognition (P=0.03) at nine and 14 weeks and reduced depression composite scores at those time points, suggesting that further investigation into this agent for treatment-resistant MDD is warranted.

6.4. Silexan

Silexan, a substance derived from *Lavandula angustifolia* flowers, is a voltage-operated calcium channel (VOCC) inhibitor [118] that has also been shown significantly reduce 5-HT_{1A} binding potential in brain [119], thereby increasing extracellular serotonin levels. At doses of 80 mg/day, it has been approved in Germany since 2009 for the treatment of restlessness related to anxious mood. Randomized, double-blind, controlled studies found that Silexan has pronounced anxiolytic effects in patients suffering from generalized anxiety disorder [120,121] as well as subsyndromal anxiety disorder [122] and anxiety-related restlessness and agitation [123]. The antidepressant effects of this substance were tested in a double-blind, randomized, placebo-controlled, parallel-group, multi-center study of 318 patients with mixed anxiety and depressive disorder [124]. Silexan (80mg/day) significantly reduced both MADRS and Hamilton Anxiety Rating Scale (HAM-A) scores compared to placebo; antidepressant effects were noted after two weeks, became statistically significant at four weeks, and remained significant through study endpoint (10 weeks).

7. Conclusions and Perspectives

As this paper has reviewed, diverse new agents with therapeutic potential for mood disorders have recently been tested in clinical proof-of-concept trials. Promising targets for the development of new, improved therapeutics for mood disorders include the glutamatergic system, the cholinergic system, the glucocorticoid system, and the inflammation pathway, as well as several additional targets of interest. Presently, none of these new pharmacological

approaches are FDA-approved for the treatment of mood disorders. As noted above, although a good number of placebo-controlled studies have been carried out—particularly with glutamatergic agents—most of the clinical evidence to date has come from case reports, case series, or early proof-of-concept studies, most with relatively small samples. Nevertheless, the novel therapeutics reviewed in this paper may prove clinically useful in treating mood disorders, particularly treatment-resistant cases.

8. Expert Commentary

The preliminary findings described in this paper are encouraging, clearly worthy of ongoing exploration, and may help guide future directions in drug development for the millions of individuals worldwide who suffer from these devastating disorders. As this paper has highlighted, a number of novel avenues for the development of rapid-acting antidepressants are presently being explored. Of these novel targets, the most promising—and the ones for whom the most evidence exists—appear to be the ionotropic glutamate receptors. However, despite their promise, ketamine and related glutamatergic modulators cannot presently be routinely recommended outside of a research milieu due to the dearth of multi-site, randomized, placebo-controlled trials with much larger sample sizes (n>100); these are necessary to better assess the efficacy, safety, and tolerability of ketamine and related agents. It is notable, however, that some experts now consider ketamine as a late option in the treatment algorithm for temporary symptom relief, and/or as a bridge to alternative therapies in specialized clinics for individuals with treatment-resistant mood disorders.

Clearly, continued research is necessary to better define the utility and safety of the agents reviewed in this paper in larger samples and the related mechanisms of action responsible for their clinical efficacy. These advances will support further studies focused on refining the most promising therapeutic targets and developing new, effective treatments within those targets, as well as identifying new, as yet unexplored areas of research.

However, making strides towards truly rapid and effective treatments for mood disorders will involve more than a simple paradigm shift towards expecting that such treatments could and should exert antidepressant effects within hours or days instead of weeks. Moving forward will require us to fully embrace the goal of personalized medicine and will require health professionals to pre-emptively identify potential responders. Towards this end, the search for the unique biosignatures of rapid-acting antidepressants—those whose validity has been tested in larger samples—is urgent, and will require researchers to use target engagement tools to comprehensively and consistently assess drug kinetics, the ability of various agents to pass through the blood-brain barrier, and brain distribution data. As a next step, future trials comprising enriched samples would thus be likely to be more efficient, given that participants would be more likely to receive the potentially most effective agent available based on their biomarker signatures. Relatedly, continued efforts to improve our understanding of the neurobiological underpinnings of mood disorders remain absolutely key to developing system-targeted approaches that act more rapidly, whose effects last longer, and whose overall efficacy is superior to those of currently available therapeutics.

9. Five-Year View

As this review has underscored, while the glutamatergic system currently seems the most promising in terms of developing novel, rapid-acting antidepressants, other systems also hold considerable potential, particularly the cholinergic and inflammatory systems, and we expect that research in these areas will grow exponentially over the next five years. The most promising research avenue is currently the ionotropic glutamate receptors. In this regard, ketamine is a powerful proof-of-concept agent and we expect that work appearing in the next year or two exploring the mechanisms of action of ketamine metabolites—*2R*,6*R*-HNK in particular—may lead to another paradigm shift in this already rapidly growing field. In addition, there is much we do not know about the effects of ketamine, other glutamatergic modulators, or other novel agents on dimensions such as anhedonia, suicidality, and fatigue; research into these areas is likely to increase in the next five years as we refine our understanding of these agents. Finally, recent studies are currently attempting to identify the relevant biomarkers and predictors of response that may help us identify biosignatures and design future studies with enriched samples to inform this valuable area of research.

Acknowledgments

The authors thank the 7SE research unit and staff for their support.

Funding: Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIA MH002927), by a NARSAD Independent Investigator Award to CA Zarate, and by a Brain and Behavior Mood Disorders Research Award to CA Zarate.

References

*-Papers of interest

1*. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006; 163(1):28–40. [PubMed: 16390886]

2*. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med. 2007; 356:1711–1722. [PubMed: 17392295]

3*. Machado-Vieira R, Salvadore G, Ibrahim LA, Diaz-Granados N, Zarate CA Jr. Targeting glutamatergic signaling for the development of novel therapeutics for mood disorders. Curr Pharm Des. 2009; 15(14):1595–1611. [PubMed: 19442176]

4. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013; 15:1–44. [PubMed: 23237061]

5. Machado-Vieira R, Salvadore G, Luckenbaugh DA, Manji HK, Zarate CAJ. Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depressive disorder. J Clin Psychiatry. 2008; 69:946–958. [PubMed: 18435563]

6. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000; 47(4):351–354. [PubMed: 10686270]

7*. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006; 63(8):856–864. [PubMed: 16894061]

8. Valentine GW, Mason GF, Gomez R, et al. The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS. Psychiatry Res. 2011; 191(2):122–127. [PubMed: 21232924]

9. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry. 2013; 170(10): 1134–1142. [PubMed: 23982301]
10*. Diazgranados N, Ibrahim L, Brutsche N, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry. 2010; 67:793–802. [PubMed: 20679587]
11. Zarate CA, Brutsche N, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry. 2012; 71:939–946. [PubMed: 22297150]
12. Permoda-Osip A, Kisielewski J, Bartkowska-Sniatkowska A, Rybakowski JK. Single ketamine infusion and neurocognitive performance in bipolar depression. Pharmacopsychiatry. Oct 27.2014 [Epub ahead of print].
13. Niciu MJ, Luckenbaugh D, Ionescu DF, Mathews D, Richards EM, Zarate CA. Subanesthetic dose ketamine does not induce an affective switch in three independent samples of treatment-resistant major depression. Biol Psychiatry. 2013; 74:e23–e24. [PubMed: 23726512]
14. Newport DJ, Carpenter LL, McDonald WM, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry. 2015; 172:950–966. [PubMed: 26423481]
15. Ribeiro CM, Sanacora G, Hoffman R, Ostroff R. The use of ketamine in the treatment of depression in the context of psychotic symptoms: to the editor. Biol Psychiatry. 2016; 79:65–66.
16. Lee EE, Della Selva MP, Himelhoch S. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. Gen Hosp Psychiatry. 2015; 37:178–184. [PubMed: 25698228]
17*. Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum Psychopharmacol. 2015; 30:152–163. [PubMed: 25847818]
18. Diamond PR, Farmery AD, Atkinson S, et al. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. J Psychopharmacol. 2014; 28(6):536–544. [PubMed: 24699062]
19. aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry. 2010; 67(2):139–145. [PubMed: 19897179]
20. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013; 74(4): 250–256. [PubMed: 22840761]
21. Rasmussen KG, Lineberry TW, Galardy CW, et al. Serial infusions of low-dose ketamine for major depression. J Psychopharmacol. 2013; 27(5):444–450. [PubMed: 23428794]
22. Singh NS, Zarate CAJ, Moaddel R, Bernier M, Wainer IW. What is hydroxynorketamine and what can it bring to neurotherapeutics? Expert Rev Neurother. 2014; 14:1239–1242. [PubMed: 25331415]
23. Wan LB, Levitch CF, Perez AM, et al. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. J Clin Psychiatry. 2015; 76:247–252. [PubMed: 25271445]
24. Romeo B, Choucha W, Fossati P, Rotge JY. Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. Psychiatry Res. 2015; 230:682–688. [PubMed: 26548981]
25. Mathew SJ, Shah A, Lapidus KA, et al. Ketamine for treatment-resistant unipolar depression: current evidence. CNS Drugs. 2012; 26:189–204. [PubMed: 22303887]
26. Lapidus KA, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry. 2014
27. Luckenbaugh D, Niciu MJ, Ionescu DF, et al. Do the dissociative side effects of ketamine mediate its antidepressant effects. J Affect Disord. 2014; 159:56–61. [PubMed: 24679390]
28. Glue P, Gulati A, Le Nedelec M, Duffull S. Dose- and exposure-response to ketamine in depression. Biol Psychiatry. 2011; 70(4):e9–10. author reply e11-12. [PubMed: 21481846]

29. Chilukuri H, Reddy NP, Pathapati RM, Manu AN, Jollu S, Shaik AB. Acute antidepressant effects of intramuscular versus intravenous ketamine. Indian J Psychol Med. 2014; 36(1):71–76. [PubMed: 24701015]
30. Irwin SA, Iglewicz A. Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care. J Palliat Med. 2010; 13(7):903–908. [PubMed: 20636166]
31. Paslakis G, Gilles M, Meyer-Lindenberg A, Deuschle M. Oral administration of the NMDA receptor antagonist S-ketamine as add-on therapy of depression: a case series. Pharmacopsychiatry. 2010; 43(1):33–35. [PubMed: 20013614]
32. Irwin SA, Iglewicz A, Nelesen RA, et al. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. J Palliat Med. 2013; 16(8):958–965. [PubMed: 23805864]
33. De Gioannis A, De Leo D. Oral ketamine augmentation for chronic suicidality in treatment-resistant depression. Aust N Z J Psychiatry. 2014; 48(7):686. [PubMed: 24452289]
34. Lara DR, Bisol LW, Munari LR. Antidepressant, mood stabilizing and procognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression. Int J Neuropsychopharmacol. 2013; 16(9):2111–2117. [PubMed: 23683309]
35*. DiazGranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry. 2010; 71(12):1605–1611. [PubMed: 20673547]
36. Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry. 2009; 66(5): 522–526. [PubMed: 19545857]
37. Price RB, Iosifescu DV, Murrough JW, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety. 2014; 31(4):335–343. [PubMed: 24668760]
38. Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int J Neuropsychopharmacol. 2011:1–5.
39. Ballard ED, Ionescu DF, Vande Voort JL, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res. 2014; 58:161–166. [PubMed: 25169854]
40. Niciu MJ, Henter ID, Luckenbaugh DA, Zarate CAJ, Charney DS. Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. Annu Rev Pharmacol Toxicol. 2014; 54:119–139. [PubMed: 24392693]
41. Singh JB, Fedgchin M, Daly E, et al. Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. Biol Psychiatry. 2016; 80:424–431. [PubMed: 26707087]
42. Daly, E., Singh, JB., Fedgchin, M., et al. 54th Annual Meeting of the American College of Neuropsychopharmacology. Hollywood, Florida: 2015. Intranasal esketamine in treatment-resistant depression, a dose response study – double-blind and open-label extension data; p. 74
43. Canuso, CM., Singh, JB., Fedgchin, M., et al. American Society of Clinical Psychopharmacology (ACSP). Scottsdale, Arizona: 2016. PeRSEVERe: a study of esketamine for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in patients assessed to be at imminent risk for sucide.
44. Johnson and Johnson. Esketamine receives Breakthrough Therapy Designation from Food and Drug Administration for major depressive disorder with imminent risk for suicide. 2016
45*. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidpressant actions of ketamine metabolites. Nature. May 4.2016 [Epub ahead of print].
46. Nagele P, Duma A, Kopec M, et al. Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. Biol Psychiatry. 2015; 78:10–18. [PubMed: 25577164]
47. Lauterbach EC. Dextromethorphan as a potential rapid-acting antidepressant. Medical Hypotheses. 2011; 76(5):717–719. [PubMed: 21367535]
48. Lauterbach EC. An extension of hypotheses regarding rapid-acting, treatment-refractory, and conventional antidepressant activity of dextromethorphan and dextrorphan. Medical Hypotheses. 2012; 78(6):693–702. [PubMed: 22401777]

49. Lee SY, Chen SL, Chang YH, et al. The DRD2/ANKK1 gene is associated with response to add-on dextromethorphan treatment in bipolar disorder. J Affect Disord. 2012; 138:295–300. [PubMed: 22326841]
50. Kelly TF, Lieberman DZ. The utility of the combination of dextromethorphan and quinidine in the treatment of bipolar II and bipolar NOS. J Affect Disord. 2014; 167:333–335. [PubMed: 25016490]
51. Messias E, Everett B. Dextromethorphan and quinidine combination in emotional lability associated with depression: a case report. Prim Care Companion CNS Disord. 2012; 14 PCC. 12I01400.
52. Zarate CA, Mathews D, Ibrahim L, et al. A randomized trial of a low-trapping nonselective N-methyl-D-aspartate channel blocker in major depression. Biol Psychiatry. 2013; 74:257–264. [PubMed: 23206319]
53. Sanacora, G., Johnson, M., Khan, A., Atkinson, S., Riesenberg, R., Schronen, J. 53rd Meeting of the ACNP. Hollywood, FL, USA: 2014. Adjunctive lanicemine (AZD6765) in patients with major depressive disorder and a history of inadequate response to antidepressants: primary results from a randomized, placebo controlled study (PURSUIT).
54. Sanacora G, Schatzberg AF. Ketamine: promising path or false prophecy in the development of novel therapeutics for mood disorders? Neuropsychopharmacology. 2015; 40(2):259–267. [PubMed: 25257213]
55. Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. J Clin Psychopharmacol. 2008; 28:631–637. [PubMed: 19011431]
56. Hashimoto KJ. Comments on “An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606 in patients with treatment-refractory major depressive disorder. J Clin Psychopharmacol. 2009; 29:411–412. [PubMed: 19593196]
57. Ibrahim L, Diazgranados N, Jolkovsky L, et al. A randomized, placebo-controlled, crossover pilot trial of the oral selective NR2B antagonist MK-0657 in patients with treatment-resistant major depressive disorder. J Clin Psychopharmacol. 2012; 32:551–557. [PubMed: 22722512]
58. MacDougall Biomedical Communications. Cerecor provides update on CERC-301 development in major depressive disorder. MacDougall Biomedical Communications; 2015.
59. Millan MJ. N-methyl-D-aspartate receptor-coupled glycineB receptors in the pathogenesis and treatment of schizophrenia: a critical review. Curr Drug Targets CNS Neurol Disord. 2002; 1(2): 191–213. [PubMed: 12769627]
60. Heresco-Levy U, Javitt DC, Gelfin Y, et al. Controlled trial of D-cycloserine adjuvant therapy for treatment-resistant major depressive disorder. J Affect Disord. 2006; 93(1-3):239–243. [PubMed: 16677714]
61. Heresco-Levy U, Gelfin G, Bloch B, et al. A randomized add-on trial of high-dose D-cycloserine for treatment-resistant depression. Int J Neuropsychopharmacol. 2013; 16(3):501–506. [PubMed: 23174090]
62. Moskal JR, Burch R, Burgdorf JS, et al. GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. Expert Opin Investig Drugs. 2014; 23:243–254.
63. Preskorn S, Macaluso M, Mehra DO, et al. Randomized Proof of Concept Trial of GLYX-13, an N-Methyl-D-Aspartate Receptor Glycine Site Partial Agonist, in Major Depressive Disorder Nonresponsive to a Previous Antidepressant Agent. J Psychiatr Pract. 2015; 21(2):140–149. [PubMed: 25782764]
64. Huang CC, Hua Wei I, Huang CL, et al. Inhibition of glycine transporter-I as a novel mechanism for the treatment of depression. Biol Psychiatry. 2013; 74:734–741. [PubMed: 23562005]
65. Kagedal M, Cselenyi Z, Nyberg S, et al. A positron emission tomography study in healthy volunteers to estimate mGluR5 receptor occupancy of AZD2066 - estimating occupancy in the absence of a reference region. Neuroimage. 2013; 82:160–169. [PubMed: 23668965]

66. Quiroz JA, Tamburri P, Deptula D, et al. Efficacy and safety of basimglurant as adjunctive therapy for major depression: a randomized clinical trial. JAMA Psychiatry. 2016; 73:675–684. [PubMed: 27304433]

67. van Enkhuizen J, Janowsky DS, Olivier B, et al. The catecholaminergic-cholinergic balance hypothesis of bipolar disorder revisited. Eur J Pharmacol. 2015; 753:114–126. [PubMed: 25107282]

68. Kasper S, Moises HW, Beckmann H. The anticholinergic biperiden in depressive disorders. Pharmacopsychiatria. 1981; 14:195–198. [PubMed: 7323139]

69. Khouzam HR, Kissmeyer PM. Physostigmine temporarily and dramatically reversing acute mania. Gen Hosp Psychiatry. 1996; 18:203–204. [PubMed: 8739014]

70. Eden Evins A, Demopulos C, Nierenberg A, Culhane MA, Eisner L, Sachs GS. A double-blind, placebo-controlled trial of adjunctive donepezil in treatment-resistant mania. Bipolar Disord. 2006; 8:75–80. [PubMed: 16411983]

71. Burt T, Sachs GS, Demopoulos C. Donepezil in treatment-resistant bipolar disorder. Biol Psychiatry. 1999; 45:959–964. [PubMed: 10386177]

72*. Drevets WC, Zarate CAJ, Furey ML. Antidepressant effects of the muscarinic cholinergic receptor antagonist scopolamine: a review. Biol Psychiatry. 2013; 73:1156–1163. [PubMed: 23200525]

73. Jaffe RJ, Novakovic V, Peselow ED. Scopolamine as an antidepressant: a systematic review. Clin Neuropharmacol. 2013; 36:24–26. [PubMed: 23334071]

74. Khajavi D, Farokhnia M, Modabbernia A, et al. Oral scopolamine augmentation in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2012; 73:1428–1433. [PubMed: 23146150]

75. Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: A randomized, placebo-controlled clinical trial. Arch Gen Psychiatry. 2006; 63:1121–1129. [PubMed: 17015814]

76. Khairova RA, Machado-Vieira R, Du J, Manji HK. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. Int J Neuropsychopharmacol. 2009; 12:561–578. [PubMed: 19224657]

77. Valiengo LL, Soeiro-de-Souza MG, Marques AH, et al. Plasma cortisol in first episode drug-naive mania: differential levels in euphoric versus irritable mood. J Affect Disord. 2012; 138:149–152. [PubMed: 22305430]

78*. Quiroz JA, Singh J, Gould TD, Denicoff KD, Zarate CA Jr, Manji HK. Emerging experimental therapeutics for bipolar disorder: clues from the molecular pathophysiology. Mol Psychiatry. 2004; 9:756–776. [PubMed: 15136795]

79. Belanoff JK, Rothschild AJ, Cassidy F, et al. An open label trial of C-1073 (mifepristone) for psychotic major depression. Biol Psychiatry. 2002; 52(5):386–392. [PubMed: 12242054]

80. DeBattista C, Belanoff J, Glass S, et al. Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. Biol Psychiatry. 2006; 60(12):1343–1349. [PubMed: 16889757]

81. Carroll BJ, Rubin RT. Mifepristone in psychotic depression? Biol Psychiatry. 2008; 63(1):e1. author reply e3. [PubMed: 17919458]

82. Blasey CM, Block TS, Belanoff JK, Roe RL. Efficacy and safety of mifepristone for the treatment of psychotic depression. J Clin Psychopharmacol. 2011; 31:436–440. [PubMed: 21694614]

83. Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. Neuropsychopharmacology. 2004; 29:1538–1545. [PubMed: 15127079]

84. Watson S, Gallagher P, Porter RJ, et al. A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. Biol Psychiatry. 2012; 72:943–949. [PubMed: 22770649]

85. Rothschild AJ. Challenges in the treatment of depression with psychotic features. Biol Psychiatry. 2003; 53(8):680–690. [PubMed: 12706954]

86. Grunberg SM, Weiss MH, Russell CA, et al. Long-term administration of mifepristone (RU486): clinical tolerance during extended treatment of meningioma. Cancer Invest. 2006; 24(8):727–733. [PubMed: 17162554]

87. Brown ES, Park J, Marx CE, et al. A randomized, double-blind, placebo-controlled trial of pregnenolone for bipolar depression. Neuropsychopharmacology. 2014; 39:2867–2873. [PubMed: 24917198]

88. Jahn H, Schick M, Kiefer F, Kellner M, Yassouridis A, Wiedemann K. Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. Arch Gen Psychiatry. 2004; 61(12):1235–1244. [PubMed: 15583115]

89. Brown ES, Bobadilla L, Rush AJ. Ketoconazole in bipolar patients with depressive symptoms: a case series and literature review. Bipolar Disord. 2001; 3:23–29. [PubMed: 11256460]

90. Wolkowitz OM, Reus VI, Chan T, et al. Antiglucocorticoid treatment of depression: double-blind ketoconazoleAntiglucocorticoid treatment of depression: double-blind ketoconazole. Biol Psychiatry. 1999; 45:1070–1074. [PubMed: 10386195]

91. Gallagher P, Malik N, Newham J, Young AH, Ferrier IN, Mackin P. Antiglucocorticoid treatments for mood disorders. Cochrane Database Syst Rev. Jan.2008 23(1) CD005168.

92. Wolkowitz OM, Reus VI, Keebler A, et al. Double-blind treatment of major depression with dehydroepiandrosterone. Am J Psychiatry. 1999; 156:646–649. [PubMed: 10200751]

93. Schmidt PJ, Daly RC, Bloch M, et al. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. Arch Gen Psychiatry. 2005; 62:154–162. [PubMed: 15699292]

94*. Dale E, Bang-Andersen B, Sanchez C. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. Biochem Pharmacol. 2015; 95:81–97. [PubMed: 25813654]

95. Gold PW, Machado-Vieira R, Pavlatou MG. Clinical and biochemical manifestations of depression: relation to the neurobiology of stress. Neural Plast. 2015

96. Khairova R, Machado-Vieira R, Du J, Manji HK. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. Int J Neuropsychomarmacol. 2009; 12:561–578.

97. Barbosa IG, Machado-Vieira R, Soares JC, Teixeira AL. The immunology of bipolar disorder. Neuroimmodulation. 2014; 21:117–122.

98. Barbosa IG, Bauer ME, Machado-Vieira R, Teixeira AL. Cytokines in bipolar disorder: paving the way for neuroprogression. Neural Plast. 2014

99. Teixeira AL, Barbosa IG, Machado-Vieira R, Rizzo LB, Wieck A, Bauer ME. Novel biomarkers for bipolar disorder. Expert Opin Med Diagn. 2013; 7:147–159. [PubMed: 23530885]

100. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016; 16:22–34. [PubMed: 26711676]

101. Akhondzadeh S, Jafari S, Raisi F, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress Anxiety. 2009; 26:607–611. [PubMed: 19496103]

102. Muller N, Schwarz MJ, Dehning S, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. Mol Psychiatry. 2006; 11(7):680–684. [PubMed: 16491133]

103. Majd M, Hashemian F, Hosseini SM, Vahdat Shariatpanahi M, Sharifi A. A randomized double-blind, placebo-controlled trial of celecoxib augmentation of sertraline in treatment of drug-naive depressed women: a pilot study. Iran J Pharm Res. 2015; 14:891–899. [PubMed: 26330878]

104. Nery FG, Monkul ES, Hatch JP, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Hum Psychopharmacol. 2008; 23(2):87–94. [PubMed: 18172906]

105. Velentgas P, West W, Cannuscio CC, Watson DJ, Walker AM. Cardiovascular risk of selective cyclooxygenase-2 inhibitors and other non-aspirin non-steroidal anti-inflammatory medications. Pharmacoepidemiol Drug Saf. 2006; 15(9):641–652. [PubMed: 16392153]

106. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013; 70(1):31–41. [PubMed: 22945416]

107. Andreazza AC, Cassini C, Rosa AR, et al. Serum S100B and antioxidant enzymes in bipolar patients. J Psychiatr Res. 2007; 41(6):523–529. [PubMed: 16956621]
108. Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkilinc N. Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. Cell Biochem Funct. 2002; 20(2):171–175. [PubMed: 11979513]
109. Berk M, Copolov DL, Dean O, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. Biol Psychiatry. 2008; 64(6):468–475. [PubMed: 18534556]
110. Magalhaes PV, Dean OM, Bush AI, et al. N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. J Affect Disord. 2011; 129:317–320. [PubMed: 20800897]
111. Berk M, Dean O, Cotton SM, et al. The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: An open label trial. J Affect Disord. 2011; 135(1-3):389–394. [PubMed: 21719110]
112. Berk M, Dean OM, Cotton SM, et al. The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2014; 75:628–636. [PubMed: 25004186]
113. Gold PW, Licinio J, Pavlatou MG. Pathological parainflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, klotho and PPAR-γ systems. Mol Psychiatry. 2013; 18:154–165. [PubMed: 23183489]
114. Lin KW, Wroolie TE, Robakis T, Rasgon NL. Adjuvant pioglitazone for unremitted depression: clinical correlates of treatment response. Psychiatry Res. 2015; 230:846–852. [PubMed: 26602230]
115. Sepanjnia K, Modabbernia A, Ashrafi M, Modabbernia MJ, Akhondzadeh S. Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: randomized double-blind placebo-controlled trial. Neuropsychopharmacology. 2012; 37:2093–2100. [PubMed: 22549115]
116. Zeinoddini A, Sorayani M, Hassanzadeh E, et al. Pioglitazone adjunctive therapy for depressive episode of bipolar disorder: a randomized, double-blind, placebo-controlled trial. Depress Anxiety. 2015; 32:167–173. [PubMed: 25620378]
117. Miskowiak KW, Vinberg M, Christensen EM, et al. Recombinant human erythropoietin for treating treatment-resistant depression: a double-blind, randomized, placebo-controlled phase 2 trial. Neuropsychopharmacology. 2014; 39:1399–1408. [PubMed: 24322509]
118. Schuwald AM, Noldner M, Wilmes T, Klugbauer N, Leuner K, Muller WE. Lavender oil-potent anxiolytic properties via modulating voltage dependent calcium channels. Plos One. 2013; 8:e59998. [PubMed: 23637742]
119. Baldinger P, Hoflich AS, Mitterhauser M, et al. Effects of Silexan on the serotonin-1A receptor and microstructure of the human brain: a randomized, placebo-controlled, double-blind, cross-over study with molecular and structural neuroimaging. Int J Neuropsychopharmacol. 2014; 18 pii:pyu063.
120. Kasper S, Gastpar M, Muller WE, et al. Lavender oil preparation Silexan is effective in generalized anxiety disorder -- a randomized, double-blind comparison to placebo and paroxetine. Int J Neuropsychopharmacol. 2014; 17:859–869. [PubMed: 24456909]
121. Woelk H, Schlafke S. A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder. Phytomedicine. 2010; 17:94–99. [PubMed: 19962288]
122. Kasper S, Gastpar M, Muller WE, et al. Silexan, an orally administered Lavendula oil preparation, is effective in the treatment of ‘subsyndromal’ anxiety disorder: a randomized, double-blind, placebo controlled trial. Int Clin Psychopharmacol. 2010; 25:277–287. [PubMed: 20512042]
123. Kasper S, Anghelescu I, Dienel A. Efficacy of orally administered Silexan in patients with anxiety-related restlessness and disturbed sleep--a randomized, placebo-controlled trial. Eur Neuropsychopharmacol. 2015; 25:1960–1967. [PubMed: 26293583]
124. Kasper S, Volz HP, Dienel A, Schlafke S. Efficacy of silexan in mixed anxiety-depression--A randomized, placebo-controlled trial. Eur Neuropsychopharmacol. 2016; 26:331–340. [PubMed: 26718792]

Key Issues

- Overall antidepressant efficacy is limited with current standard approaches
- Clinical studies using glutamatergic modulators have shown that these agents exert rapid antidepressant effects, especially the high-trapping glutamatergic modulators
- Cholinergic and glucocorticoid system antagonists are promising antidepressant agents but remain understudied
- New research approaches with these novel agents may yield important insights to advance the field of personalized medicine.

Table 1
New agents in the treatment of mood disorders ranked by evidence of efficacy

Evidence drawn from replicated double-blind (DB), randomized controlled trials (RCTs) that include a placebo arm, or from meta-analyses

	Target	Mechanism of Action
Ketamine	Glutamatergic system	Broad glutamatergic modulation
Esketamine	Glutamatergic system	Non-competitive and subtype non-selective activity-dependent NMDA receptor antagonism
Scopolamine	Cholinergic system	Anticholinergic
Dehydroepiandrosterone (DHEA)	Hormone regulation	Unknown
Pioglitazone	Metabolic pathways	PPAR-γ agonism

Evidence drawn from one double-blind, randomized controlled trial that includes a placebo arm or from a trial with an active comparator

	Target	Mechanism of Action
Nitrous oxide	Glutamatergic system	Non-competitive NMDA receptor inhibition
AZD6765	Glutamatergic system	Broad glutamatergic modulation
CP-101,606	Glutamatergic system	Subunit (NR2B)-specific N-methyl-D-aspartate (NMDA) receptor antagonism
D-cycloserine (DCS)	Glutamatergic system	Glycine-site partial agonism
GLYX-13 (Rapastinel)	Glutamatergic system	Glycine-site partial agonism
Sarcosine	Glutamatergic system	Glycine transporter-I inhibition
Metyrapone	Glucocorticoid system	Glucocorticoid synthesis inhibition
Ketoconazole	Glucocorticoid system	Cortisol modulation
Celecoxib	Inflammation pathway	COX-2 inhibition
N-acetyl cysteine (NAC)	Oxidative stress	Increase in glutathione levels
Silexan	Serotonergic system	5-TH_{1A} receptor inhibition

Evidence from prospective, non-controlled trials with 10 or more subjects or secondary measures assessed in double-blind, randomized controlled trials

	Target	Mechanism of Action
Basimglurant (RO4917523 or RG7090)	Glutamatergic system	Metabotropic (mGluR5) glutamate receptor modulation
Biperiden	Cholinergic system	Anticholinergic
Mifepristone (RU-486)	Glucocorticoid system modulation	Non-selective glucocorticoid receptor antagonism
Pregnenolone	Glucocorticoid system modulation	Downstream hormone regulation
Erythropoietin (EPO)	Neurotrophins	Neurotrophism

Anecdotal reports or expert opinion

	Target	Mechanism of Action
Dextromethorphan	Glutamatergic system	Non-competitive NMDA receptor antagonism
MK-0657 (CERC-301)	Glutamatergic system	Subunit (NR2B)-specific N-methyl-D-aspartate (NMDA) receptor antagonism
Donepezil	Cholinergic system	Cholinesterase inhibition