HHS Public Access

Author manuscript

Drug Discov Today. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Drug Discov Today. 2019 February ; 24(2): 606–615. doi:10.1016/j.drudis.2018.11.007.

A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems

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Abstract

Mood disorders represent the largest cause of disability worldwide. The monoaminergic deficiency hypothesis, which has dominated the conceptual framework for researching the pathophysiology of mood disorders and the development of novel treatment strategies, cannot fully explain the underlying neurobiology of mood disorders. Mounting evidence collected over the past two decades suggests the amino acid neurotransmitter systems (glutamate and GABA) serve central roles in the pathophysiology of mood disorders. Here, we review progress in the development of compounds that act on these systems as well as their purported mechanisms of action. We include glutamate-targeting drugs, such as racemic ketamine, esketamine, lanicemine (AZD6765), traxoprodil (CP-101,606), EVT-101, rislenemdaz (CERC-301/MK-0657), AVP-786, AXS-05, rapastinel (formerly GLYX-13), apimostinel (NRX-1074/AGN-241660), AV-101, NRX-101, basimglurant (RO4917523), decoglurant (RG-1578/RO4995819), tulrampator (CX-1632/S-47445), and riluzole;and GABA-targeting agents, such as brexanolone (SAGE-547), ganaxolone, and SAGE-217.

Introduction

Mood disorders, including major depressive disorder (MDD) and bipolar disorder, represent the most common mental illnesses and the largest cause of disability worldwide. For decades, the monoaminergic deficiency hypothesis dominated the conceptual framework for researching the pathophysiology of mood disorders. Although this approach has brought many advances, including the majority of currently available treatments for MDD, it is increasingly clear that it cannot completely explain the underlying neurobiology of mood disorders [1]. The shortcomings of the monoamine deficiency hypothesis are reflected in the large proportion of patients that do not adequately respond to first- or second-line therapies and the lag in therapeutic response with to physiological actions of the drugs [2]. Given the prevalence of mood disorders and the limitations of our current therapeutic armamentarium,

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there is an urgent need for development of novel therapeutic strategies that are better informed by our improved understanding of the disease pathophysiology.

Glutamate/GABA neurotransmitter systems

The amino acid neurotransmitter systems (GABA and glutamate) have emerged as active targets of investigation in the pathophysiology of mood disorders. Several lines of research point to the crucial role of these systems [3,4]. Several studies report abnormal levels of glutamate/glutamine in plasma, serum, cerebrospinal fluid (CSF), and brain tissue of individuals with mood disorders [5]. Imaging studies have consistently detected abnormalities in the levels and ratios of the amino acid neurotransmitters in several key brain regions [6]. Another line of research suggests that several NMDAR (NMDAR) antagonists have antidepressant effects and that conventional antidepressant treatments [e.g., tricyclic antidepressants, other monoamine-based drugs, and electroconvulsive therapy (ECT)] converge upon NMDAR function and expression as a final common pathway [1]. Finally, glial cells have a crucial role in glutamate regulation, including: (i) the clearance of glutamate from the synaptic cleft through excitatory amino acid transporters; (ii) the synthesis and release of the NMDAR coagonist D-serine; (iii) metabolism of glutamate to glutamine; and (iv) expression of metabotropic glutamate receptors (mGluRs). In postmortem studies, reductions and alteration in glial cell structure and function have been demonstrated in the medial prefrontal cortex of individuals with depression [7], and following periods of stress in rodent models of mood disorders [8].

Emerging pipeline of potential antidepressants

Inspired by advances in our understanding of the pathophysiology of mood disorders, the growing series of generally consistent clinical trials demonstrating rapid-onset antidepressant effects of ketamine, and the profound unmet need for improved therapeutics in treatment-resistant depression, several pharmaceutical companies have launched programs to discover and develop compounds that target different aspects of the amino acid neurotransmitter systems. Such compounds include nonselective NMDAR antagonists, selective NR2B site NMDAR antagonists, allosteric modulators at the NMDAR, allosteric modulators of metabotropic glutamate receptors and AMPA receptors (AMPARs), modulators of glutamate clearance, and drugs targeting GABA receptors. These clinical development programs have helped to provide renewed enthusiasm for the area of central nervous system (CNS) drug development. Here, we review these programs based on the published literature (from MEDLINE), published abstracts at citable conferences, clinical trials from the US Clinical Trials registry (www.clinicaltrials.gov), and press releases. We systematically searched these resources using the following key words (or their corresponding compound number/name): esketamine; lanicemine; traxoprodil; EVT-101; rislenemdaz; AVP-786; AXS-05; rapastinel; apimostinel; AV-101; NRX-100/101; basimglurant; decoglurant; tulrampator; riluzole; brexanolone; ganaxolone; and SAGE-217. We also briefly review the purported mechanisms of action of many of these compounds in development (Table 1 [9–30]). We have limited the scope of this review to reports from Phase II or III human trials.

Ketamine

Ketamine is a noncompetitive, channel-blocking NMDAR antagonist. Although its exact mechanism of antidepressant action remains under debate [31,32], mounting evidence suggests that it involves region-specific increases in local protein synthesis and neuroplasticity [33]. Preclinical evidence suggests that ketamine causes a dose-dependent surge in glutamate release at the tripartite synapse, which leads to enhanced signaling through AMPARs, downstream upregulation of synaptic proteins, and increased BDNF activity [34]. Another model suggests that blockade of NMDARs that are stimulated at rest has effects that increase the function of eukaryotic elongation factor 2, causing regionally increased local protein and BDNF expression, and increased signaling through AMPARs that results in enhanced synaptic plasticity [35]. Other models propose that ketamine increases glutamate release and postsynaptic AMPA activation independent of its effects on the NMDAR [36] or by activation of opioid neurotransmission [37].

In 2000, a small randomized trial showed that subanesthetic doses of ketamine have rapid antidepressant properties [38]. Since then, several additional randomized trials have confirmed these effects in MDD or bipolar disorder (reviewed in [6]). Unfortunately, ketamine is unlikely to gain the financial sponsorship that is crucial to supporting a possible path to US Food and Drug Administration (FDA) approval as an antidepressant because of patent restrictions; furthermore, currently published trials are too small and lack the rigor required to lead to approval. Nonetheless, ketamine continues to be a compound of interest.

Most randomized trials of racemic ketamine are single-dose protocols. The largest multidose, randomized study (sponsored by Janssen Pharmaceuticals) was designed to address the question of the optimal dose schedule. This study of 68 participants with treatment-resistant depression (TRD) found that dosing three times per week was no better than dosing twice per week [39]. A few small, open-label trials have investigated multiple-dosing protocols (reviewed in [6]). A rapidly growing number of mental health care providers have begun to offer ketamine as an off-label treatment for mood disorders [40]; however, there is no organized registry that is documenting safety outcomes from the large numbers of patients who are receiving ketamine off-label. Overall, there remains a paucity of data on the safety and efficacy of long-term use and concerns remain about the effects of long-term exposure on cognitive outcomes, abuse liability, delusions, and interstitial cystitis.

(S)-ketamine (esketamine, Janssen)

Esketamine is the *S*-enantiomer of ketamine that is being developed by Janssen Pharmaceuticals. With few exceptions, all of Janssen's registered trials with esketamine use an intranasal formulation. The first published results of the intranasal formulation were from a randomized, placebo-controlled, multiple-dose study of 67 participants with TRD [10]. The study revealed a dose-response relationship, favoring the highest intranasal dose of 84 mg.

A series of recently completed studies investigated the use of esketamine in individuals with MDD who have not responded to conventional antidepressants (TRANSFORM studies). In the TRANSFORM-2 study, 227 patients with TRD were randomly assigned to receive either

a flexible dose of esketamine plus initiation of a new oral antidepressant or an intranasal placebo plus initiation of a new oral antidepressant. The study was positive in its primary outcome, showing significant differences between the groups on the primary outcome measure, showing a greater decrease in depression severity [Montgomery-Åsberg Depression Rating Scale (MADRS) score] in the arm receiving esketamine + antidepressant compared with placebo + antidepressant at 4 weeks ($P < 0.05$) [11]. The TRANSFORM-3 study had a very similar design in older patients ($N = 138$). This study did not demonstrate a statistically significant difference between groups on the primary outcome, but statistically significant effects were seen for patients aged 65−74 in secondary analyses [13]. To our knowledge, results from the TRANSFORM-1 study have not yet been presented.

The SUSTAIN series of studies is investigating longer-term efficacy and safety (Table 2). The SUSTAIN-1 study was a double-blind, randomized withdrawal of patients who remitted ($N = 176$) or responded ($N = 121$) to esketamine; results demonstrated that both remitters and responders who continued esketamine had a lower risk of relapse compared with those who discontinued the drug [41]. The SUSTAIN-2 study, a long-term, open-label study, showed a general sustaining of response in 603 subjects that received esketamine weekly or every other week during the maintenance phase, with 76.5% retaining response by the maintenance phase endpoint [42].

Another series of studies is investigating the potential of esketamine as a rapid antidepressant and antisuicidal agent in patients with MDD who are at imminent risk of suicide. The Phase II trial ($N = 68$) recruited patients presenting to emergency departments or similar settings for MDD with suicidal ideation. Participants were randomized to receive intranasal esketamine or saline placebo twice weekly for 4 weeks (a total of eight treatments);all participants received standard of care [except ECT or a monoamine oxidase inhibitor (MAOI) antidepressant] and initiated a new antidepressant at study entry. The study demonstrated statistically significant group differences in its primary outcome measure: depression severity 4h after the first dose ($P < 0.05$) [12]. Two Phase III trials are ongoing with very similar study designs (ASPIRE studies, Table 2).

Esketamine was granted Breakthrough Therapy Designation by the FDA in 2013 for TRD and was granted the same status in 2016 for the treatment of MDD with imminent risk of suicide.

Lanicemine (AZD-6765, AstraZeneca)

Lanicemine is a low-trapping NMDAR antagonist that was under development as a therapy for TRD as an intravenous formulation by AstraZeneca. Lanicemine was successful in an initial Phase IIb trial of 152 participants [14] but did not meet primary endpoints in a subsequent Phase IIb trial [15]. Notably, the active arm in both phases achieved similar improvements in depression, but the placebo response rate was considerably higher in the later Phase IIb trial compared with the initial Phase IIb trial. Recently, Bio-Haven Pharmaceuticals licensed an orally available compound, BHV-5000, from AstraZeneca. Lanicemine is the active metabolite of BHV-5000;the company plans to explore the development of BHV-5000 in TRD and other potential indications [43].

Traxoprodil (CP-101,606, Pfizer)

Traxoprodil is an NMDAR antagonist that is selective for the NR2B subunit. In a small Phase II trial ($N = 30$), traxoprodil showed significantly greater improvement compared with placebo on the primary outcome measure at day 5 following a single intravenous infusion, with a 60% response rate versus 20% for placebo [44]. To our knowledge, there has been no further activity in the development of this compound.

EVT-101 (Evotec/La Roche)

EVT-101 is an orally bioavailable compound that is a selective NR2b subunit, NMDAR antagonist. A Phase II trial was terminated early because of a clinical hold issued from the FDA (www.clinicaltrials.gov; NCT01128452). No further investigation of this compound has been conducted according to the US Clinical Trials Registry.

Rislenemdaz (CERC-301/MK-0657, Cerecor)

Rislenemdaz/CERC-301 is an orally bioavailable antagonist at the 2B subunit of the NMDAR. An NIH-sponsored, small pilot, crossover trial ($N = 5$) was completed with an oral formulation of the drug [45], which failed to show a statistically significant difference on the primary outcomes measure (MADRS score); however, some secondary outcome measures showed a difference. Notably, the study was not adequately powered. Since being acquired by Cerecor, the drug has been tested in two Phase II trials. One of these trials, which utilized a sequential parallel comparison design, did not meet its primary endpoint as reported in a press release [18,46]. To our knowledge, no further trials using this compound have been registered.

AVP-786 (Avanir/Otsuka)

AVP-786 is an oral formulation of a combination of dextromethorphan hydrobromide and quinidine sulfate. Dextromethorphan is a weak antagonist of the NMDAR and might have antidepressant properties [47]; quinidine is used to increase the bioavailability of the compound by decreasing the metabolism of dextromethorphan via cytochrome P450–2D6. This compound is a next-generation version of Nuedexta, which is approved for the treatment of pseudobulbar affect. The compound differs from Nuedexta in that AVP-786 contains deuterium, a heavier isotope of hydrogen. This alteration might further slow the metabolism of the drug, leading to a longer half-life [48]. As per www.clinicaltrials.gov, a single Phase II study in subjects with MDD/ TRD ($N = 206$) was completed in February 2016, but to our knowledge results have not yet been published (NCT02153502). At this point, the compound is principally being pursued as a therapeutic for agitation in individuals with Alzheimer's dementia, where it is in Phase III trials (NCT02446132, NCT03393520, NCT02442765, and NCT02442778) and has received FDA Fast Track Designation [49]. No additional trials for MDD have been registered on clinicaltrials.gov at this time.

AXS-05 (Axsome)

AXS-05 is a combination of dextromethorphan and bupropion. The purpose of adding bupropion, in addition to its antidepressant effects, is to increase the bioavailability of dextromethorphan through inhibition of CYP2D6. Axsome is currently recruiting for an

ongoing Phase III clinical trial in patients with TRD ($N \sim 350$), where the active comparator is bupropion. The compound is also in Phase III trials for the treatment of agitation in Alzheimer's disease (AD). The compound has received FDA Fast Track Designation for both TRD [19] and agitation in AD [50].

Rapastinel (Glyx-13, Allergan)

Rapastinel (Glyx-13) is a polypeptide that appears to serve as a partial functional agonist at the glycine site of the NMDAR. Rapastinel is delivered intravenously, with most ongoing studies investigating once-weekly dosing schedules. Results from a Phase II study were published in 2015, where 116 subjects who had failed at least one trial of a standard antidepressant were randomized to one of four doses of rapastinel or placebo [17]. This trial was positive and appeared to show a nonlinear dose-response relationship. An additional Phase II study was completed in 2014 (NCT01684163). Unlike ketamine or esketamine, rapastinel appears to have no appreciable psychotomimetic or dissociative effects [17]. Several Phase III trials are underway and are expected to be completed by the end of 2018;most of these trials have set a primary outcome at 24 h after initial dosing (Table 2). Rapastinel was granted Fast Track Designation by the FDA for the adjunctive treatment of MDD in 2014 and Breakthrough Therapy Designation in 2016.

Apimostinel (NRX-1074/AGN-241660, Allergan)

NRX-1074/Apimostinel is an orally bioavailable compound that is purportedly analogous to, but more potent than, rapastinel/ GLYX-13 in its inhibition of NMDAR activity [51]. Its NMDAR antagonism is believed to be mediated through binding to the glycine B site. Two Phase I, ascending-dose studies have been completed in healthy controls (NCT01856556 and NCT02366364). One Phase II study of the intravenous formulation has also been completed, but results have not been reported publicly to our knowledge. At this time, no additional studies have been registered.

AGN-241751 (Allergan)

AGN-241751 is an orally bioavailable NMDAR modulator that was acquired from Aptinyx, Inc. The compound is in a Phase II, dose-finding trial expected to be completed in mid-2019 (NCT03586427) and has received FDA Fast Track Designation [23].

AV-101 (VistaGen)

AV-101 (L-4-chlorokyurenine or 4-CI-KYN) is a potent selective antagonist at the glycine-binding site of the NMDAR NR1 subunit, and has been designed as a once-daily oral formulation [52]. A randomized crossover trial sponsored by the National Institutes of Health is currently ongoing (expected enrollment of 25). A larger, Phase II industry-funded study is planned with an expected enrollment of 180. AV-101 has shown antidepressant-like effects in several animal models [53], but there are no published results in humans. AV-101 received Fast Track Designation by the FDA in 2018 for the treatment of MDD [22].

NRX-101/NRX-100 (NeuroRx)

NeuroRx is developing a sequential treatment regimen comprising single-dose intravenous ketamine (NRX-100) followed by an oral formulation of D-cycloserine and lurasidone (NRX-101), for the treatment of bipolar disorder with acute suicidal ideation and behavior. D-cycloserine is an NMDAR partial agonist and lurasidone is a serotonin 2a receptor antagonist. NRX-100/NRX-101 is in Phase II/III trials, wherein subjects with bipolar disorder and recent suicidal ideation or behavior receive a single dose of intravenous ketamine and those who achieve response are randomized to receive NRX-101 or lurasidone alone.

Basimglurant (RO4917523, Roche)

Basimglurant is a negative allosteric modulator of mGluR5 and is being developed by Roche as a therapy for TRD. The drug showed promise in a Phase IIa study (NCT00809562, unpublished) but failed to separate from placebo in a larger Phase IIb ($N = 319$; NCT01437657) [24]. Notably, the placebo response in the latter trial was particularly robust, with a mean 14.6-point improvement in the MADRS score from baseline to week 6. Currently, no additional studies are registered on clinicaltrials.gov for mood disorders.

Decoglurant (RO4995819/RG-1578, Roche)

Decoglurant is a negative allosteric modulator of mGluR2 and mGluR3. A four-arm, fixed-dose study was completed in June 2014 and reported as negative [54]. The compound was removed from the Roche pipeline as reported by the company during early 2015 [25]. To our knowledge, no further trials using this compound are currently registered for mood disorders.

Tulrampator (CX-1632, RespireRx, formerly S-47445 by Cortex, Servier)

Tulrampator is an orally bioavailable compound that acts as a positive allosteric modulator of the AMPAR. The compound has undergone a Phase II trial with 400 participants, with TRD patients being randomized to one of two doses of the compound or to placebo (NCT02805439). To our knowledge, no additional trials have been registered at this time.

Riluzole

Riluzole is believed to modulate glutamate neurotransmission through a variety of actions, including inhibiting glutamate release, facilitating glutamate uptake, and possibly even as a direct NMDAR antagonist [55]. It is approved by the FDA for the treatment of amyotrophic lateral sclerosis. Small, open-label trials showed significant improvement in patients with mood and anxiety disorders (reviewed in [56]). However, several subsequent randomized trials showed no separation from placebo (see results on clinicaltrials.gov, NCT00376220) [26,27]. Notably, one randomized study of 64 inpatients with MDD using riluzole as an adjunctive therapy to citalopram found a significant effect of treatment ($P < 0.01$) [28].

Brexanolone (SAGE-547, SAGE)

Brexanolone is an exogenous formulation of allopregnanolone, an endogenous neuroactive steroid, that is being investigated for the treatment of postpartum depression (PPD).

Allopregnanolone is the major metabolite of progesterone and its levels rise rapidly during pregnancy, peaking during the third trimester. The precipitous drop in these levels following parturition has been hypothesized as being a major factor driving the pathophysiology of PPD [57,58]. Allopregnanolone modulates neuronal activation of GABAA receptors. Brexanolone is currently delivered intravenously over a slow, 60-h infusion period and has been tested in two Phase II trials. The first trial was an open-label trial with just four patients with PPD, but results were impressive, with an 81% improvement in HAM-D score 84 h following initiation of the infusion [58]. A subsequent, randomized trial of 21 participants showed a clear separation from placebo. Notably, effects lasted for 4 weeks following cessation of the treatment [57]. SAGE recently completed two Phase III trials, both of which achieved their primary outcome measures [29,59]. The compound has been granted a Breakthrough Therapy Designation by the FDA for the treatment of PPD.

Ganaxolone (Marinus)

Ganaxolone is a neuroactive steroid that modulates the $GABA_A$ receptor and is under development for the treatment of PPD. Currently, two Phase II studies are recruiting, with the last trial expected to end in January 2019. The first trial uses an intravenous formulation, while Marinus is also developing an orally bioavailable form, which is being used in the other trial.

SAGE-217 (SAGE)

SAGE-217 is an oral compound designed for once-daily dosing. Similar to brexanolone, SAGE-217 is a positive allosteric modulator of the $GABA_A$ receptor. This compound has completed a Phase II trial in patients with MDD (N=89). The study achieved its primary endpoint (P = 0.0005), which was 2 weeks post randomization [30]. Phase III trials are underway, and the compound received Fast Track Designation by the FDA in 2017.

Future challenges

The clinical pipeline for novel treatments for mood disorders is improved compared with 10 years ago. Nonetheless, several challenges remain in the further development of these potential therapies. Many compounds in development are being evaluated for rapid-acting antidepressant properties. Although this would be a substantial improvement above currently available therapies, several questions remain about the pharmacokinetics, optimal dosing schedule, and ideal outcome measures for clinical trials that evaluate these compounds. Traditionally, standard antidepressants are delivered to achieve a near-constant serum drug level. By contrast, some compounds in development are delivered in a pulsatile fashion. Ketamine, which has an elimination half-life of 2–4 h, appears to exert downstream effects several hours after most of the drug has left the body. Thus, understanding the optimal pharmacokinetic patterns and dosing schedule is a complex issue requiring further study.

Another issue is the optimal outcome measures used to assess the efficacy of rapid-acting antidepressants. Currently used scales, such as the Hamilton Depression Rating Scale (HDRS) and MADRS, were developed several decades ago and designed to measure change over weeks to months (as opposed to hours to days). For example, changes in symptoms,

such as insomnia and lack of appetite, cannot reasonably be assessed over a period of hours. Yet, each of these symptoms represents core items of the standard rating scales used in most trials of rapid-acting antidepressants (HDRS or MADRS). How accurately these existing scales capture the clinical effects of rapid-acting antidepressant compounds bears further study.

Finally, mood disorders constitute a heterogenous group of disorders and our understanding of their pathophysiology remains incomplete. As such, recruiting a well-characterized sample of patients for participation in clinical trials is not a trivial challenge. Placebo response rates are highly variable [60], difficult to predict, and can hinder drug development. Constraining the heterogeneity of patient samples has been one strategy to try and limit the placebo response. One of the most common approaches for doing this involves limiting subjects to those who have failed to adequately respond to previous treatment trials; however, it is not clear that this strategy consistently limits placebo response. Furthermore, placebo response rates when medications are administered parenterally might also present special challenges. For example, placebo response rates seen in a Phase Ilb lanicemine study (administered intravenously) were particularly robust, even in samples of patients with severe depression with some level of treatment resistance [15]. Very high placebo response rates were also seen in the basimglurant study, which also required patients to have some level of treatment resistance [24]. There is not sufficient agreement on how to design clinical trials of antidepressants to limit the placebo response rate. Finally, parenterally administered, rapid-acting antidepressants can produce unusually high placebo response rates because of nonspecific factors associated with the route of administration of the drug.

Concluding remarks

Despite the challenges described earlier, the current pipeline of potential compounds for use in mood disorders, based on an improved understanding of the relevance of the glutamate and GABA neurotransmitter systems, should engender hope for patients and enthusiasm among clinicians. Although it is unlikely that racemic ketamine will ever receive FDA approval as a mono-therapeutic treatment for mood disorders, several glutamate- and GABA-targeting compounds might become available as approved clinical treatments in the near future.

Acknowledgments

This project was supported, in part, by grant number K12HS023000 from the Agency for Healthcare Research and Quality (S.T.W.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. The authors also acknowledge support from the Brain and Behavior Research Foundation (formerly NARSAD), the Robert E. Leet and Clara Guthrie Patterson Trust, the American Foundation for Suicide Prevention (S.T.W.), as well as the West Haven VA National Center for PTSD, State of CT Department of Mental Health and Addiction Services, and Yale-New Haven Hospital (G.S.). The authors would like to thank Mayra Ortiz for her invaluable editorial assistance and for assistance in preparing the tables.

Disclosures

S.T.W. reports receiving research support from Janssen (administered through Yale) to conduct clinical trials as well as consulting fees from Janssen. G.S. has received consulting fees from Allergan, Alkermes, AstraZeneca, Avanier Pharmaceuticals, Axsome Therapeutics, BioHaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Hoffman La-Roche, Intra-Cellular Therapies, Janssen, Merck, Naurex, Navitor

Pharmaceuticals, Novartis, Noven Pharmaceuticals, Otsuka Pharmaceuticals, Praxis Therapeutics, Sage Pharmaceuticals, Servier Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, and VistaGen therapeutics over the past 36 months. He has also received additional research contracts from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Hoffman La-Roche, Merck, Naurex, and Servier over the past 36 months. Free medication was provided to G.S. for an NIH-sponsored study by Sanofi-Aventis. In addition, he holds shares in BioHaven Pharmaceuticals Holding Company and is a co-inventor on a patent 'Glutamate agents in the treatment of mental disorders' (Patent number: 8778979), for which he has received royalties.

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TABLE 1

Potential antidepressant compounds in development[a]

Compound, route of administration	Pharmacology	Sponsor	Phase	Comments	Refs
Ketamine, various	Nonselective, noncompetitive NMDAR antagonist	Multiple	N/A	Several small trials from academia; unlikely to be studied as a monotherapy in Phase III clinical trials required to receive FDA approval	[6]
Esketamine, intranasal	Nonselective, noncompetitive NMDAR antagonist	Janssen	III	Breakthrough Therapy Designation in 2013 for TRD and Breakthrough Therapy Designation in 2016 for MDD with imminent risk of suicide; 4–5 × NMDAR-binding potency compared with (*R*)-ketamine; several positive studies reported, with one study among older patients that did not meet statistical significance for its primary endpoint	[9–13]
Lanicemine/AZD-6765, intravenous	Low trapping NMDAR antagonist	AstraZeneca/BioHaven	IIb	Mixed results in two Phase II studies	[14–16]
Traxoprodil/CP-101,606, intravenous	NMDAR antagonist at NR2B subunit	Pfizer	II	Positive Phase II study reported; no additional studies registered	[17]
EVT-101	NMDAR antagonist at NR2B subunit	Evotec/La Roche	II	Phase II trial terminated early, placed on clinical hold by FDA (clinicaltrials.gov)	
Rislenemdaz/CERC-301/MK-0657, oral	NMDAR antagonist at NR2B subunit	Cerecor	II	At least one Phase II trial did not show separation from placebo	[18]
AVP-786, oral	Nonselective antagonist of NMDAR	Avanir/Otsuka	II	Combination of dextromethorphan and quinidine. Phase II trial completed in February 2016; no additional studies for mood disorders registered as of March 2018.	
AXS-05, oral	Nonselective antagonist of NMDAR	Axsome	III	Combination of dextromethorphan/bupropion; Fast Track Designation by FDA	[19]
Rapastinel/GLYX-13, intravenous	Partial functional agonist at glycine site of NMDAR	Allergan	III	Fast Track Designation for MDD in 2014; Breakthrough Therapy designation in 2016	[20]
Apimostinel/NRX-1074/AGN-241660, oral	Reported to be a functional antagonist at Glycine B site of NMDAR	Allergan	II	Company press release reports that NRX-1074 showed rapid antidepressant efficacy in initial single-dose Phase II study in patients with MDD	[21]
AV-101, oral	Selective agonist at glycine site of NMDAR NR1 subunit	VistaGen	II	Fast Track Designation for MDD in 2018	[22]
NRX-100/NRX-101, oral	Partial NMDAR agonist at glycine site	NeuroRx	III	Ketamine (NRX-100) followed by D-cycloserine plus lurasidone (NRX-101) to sustain effects in suicidal bipolar depression	
AGN-241751	NMDAR modulator	Allergan	II	Fast Track Designation by FDA in 2018	[23]
Basimglurant/RO4917523, oral	Negative allosteric modulator of $mGluR_5$	Hoffmann-La Roche	IIb	Phase IIb study did not show separation from placebo	[24]
Decoglurant/RG1578/RO4995819	Negative allosteric modulator of $mGluR_{2/3}$	Hoffmann-La Roche	II	Removed from Roche pipeline as reported by company in 2015	[25]
Tulrampator/CX-1632/S-47445	Positive allosteric modulator of AMPAR	RespireRx	II	Completed Phase 2 trial in TRD; no results reported to date.	
Riluzole, oral	Glutamate release inhibitor/up take facilitator	Multiple	II	Mixed results, among randomized clinical trials: three negative studies (incl. NCT00376220); one positive study	[26–61]

Compound, route of administration	Pharmacology	Sponsor	Phase	Comments	Refs
Brexanolone/SAGE-547, intravenous	Positive allosteric modulator of $GABA_A$ receptor	Sage	III	PPD with two positive Phase III trials; Breakthrough Designation for MDD	
Ganaxolone, intravenous	Positive allosteric modulator of $GABA_A$ receptor	Marinus	II	Treatment of PPD	[29]
SAGE-217, oral	Positive allosteric modulator of $GABA_A$ receptor	Sage	II	Fast Track Designation by FDA in 2017 with a positive Phase II trial	[30]

Abbreviations: NMDAR, N-methyl-D-aspartate receptor; FDA, Food and Drug Administration; TRD, treatment-resistant depression; PPD, post-partum depression; GABA, gamma-aminobutyric acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; mGluR, metabotropic glutamate receptor; NAM, negative allosteric modulator; PAM, positive allosteric modulator.

[a]Drugs are grouped according to purported mechanism of action.

TABLE 2

Phase II/III trials of glutamate/GABA-based compounds in development for the treatment of mood disorders[a]

NCT identifier/trial acronym	Trial design	Condition	Expected/actual completion date	Projected/actual recruitment	Phase	Primary outcome measure and results if reported	Refs
Esketamine (Janssen Pharmaceuticals); delivered intranasally in referenced studies unless otherwise noted							
NCT03185819	4-arm RCT, fixed dose	Suicidal MDD, ages 12–17	Feb 2022	145	II	Change from baseline in CDRS-R at 24 h	
NCT02782104; SUSTAIN-3	Open label, single group	TRD	Sep 2021	1150	III	Safety outcomes	
NCT03434041	RCT, 2-arm plus initiation of new oral antidepressant	TRD, Chinese	Apr 2021	234	III	Change from baseline in MADRS at 4 weeks	
NCT03039192; ASPIRE-1	RCT, recruiting from emergency settings	Suicidal MDD	Sep 2019	224	III	Change from baseline in MADRS at 24 h post dose	
NCT03097133 ASPIRE-II	RCT, recruiting from emergency settings	Suicidal MDD	Sep 2019	224	III	Change from baseline in MADRS at 24 h post dose	
NCT02918318	RCT, multiple fixed-dose, 4-arm, study	TRD, Japanese	Feb 2019	183	II	Change from baseline in MADRS at 4 weeks	
NCT02493868; SUSTAIN-1	Randomized withdrawal study	TRD in remission	Aug 2018	718	III	Time to relapse in remitters: remitters and responders who continued esketamine had a lower risk of relapse compared with those who discontinued drug	[41]
NCT02417064 TRANSFORM-1	3-arm RCT, fixed dose study	TRD	Aug 2018	346	III	Change from baseline in MADRS at 4 weeks; results not publicly available	

NCT identifier/trial acronym	Trial design	Condition	Expected/actual completion date	Projected/actual recruitment	Phase	Primary outcome measure and results if reported	Refs
NCT02422186 TRANSFORM-3	2-arm RCT, flexible dose	TRD, elderly	Aug 2017	139	III	Change from baseline in MADRS at 4 weeks: did not meet statistical significance in primary endpoint	[13]
NCT02497287; SUSTAIN-2	Open label, single group	TRD	Oct 2017	802	III	Safety outcomes: general sustaining of response in those who continued to receive esketamine weekly or every other week; 9.5% of subjects discontinued esketamine because treatment emergent adverse events	[41]
NCT02418585 TRANSFORM-2	2-arm RCT, flexible dose	TRD	Nov 2017	227	III	Change from baseline in MADRS at 4 weeks: positive study	[11]
NCT02133001	RCT, recruiting from emergency settings	Suicidal MDD	Feb 2016	68	II	Change from baseline in MADRS at 4 h post dose; primary outcome positive	[12]
NCT01998958 SYNAPSE	RCT, 5-arm, multiple dose titration study	TRD	Sep 2015	108	II	Change from baseline in MADRS at 1 week; positive study	[10]
NCT01640080	RCT, multiple-dose, 3-arm study of IV esketamine	TRD	Jun 2013	30	II	Change from baseline in MADRS at 24 h; both doses (0.2 mg/kg and 0.4 mg/kg) showed significant improvement	[61]

NCT identifier/trial acronym	Trial design	Condition	Expected/actual completion date	Projected/actual recruitment	Phase	Primary outcome measure and results if reported	Refs
						compared with placebo	
Lanicemine/AZD-6765 (AstraZeneca), intravenous formulation							
NCT01482221	3-arm, fixed-dose RCT	TRD	Aug 2013	302	IIb	Change in MADRS at 6 weeks; no separation from placebo	[14]
NCT00986479	Randomized crossover trial	TRD	Dec 2011	22	IIa	MADRS total score at 60 min, 80 min, 110 min, 230 min, 1 day, 2 days, 3 days, and 7 days post dose; rapid but transient effect seen (d = 0.40)	[16]
NCT00491686	RCT	TRD	Nov 2007	34	IIa	Change in MADRS from baseline, trends on prespecified criteria for this exploratory study	[15]
NCT00781742	3-arm, fixed-dose RCT	TRD	Mar 2010	152	IIb	Change in MADRS from baseline at 3 weeks; positive study	[15]
Traxoprodil/CP-101,606 (Pfizer), intravenous formulation							
NCT00163059	RCT	TRD	Dec 2005	30	II	Traxoprodil produced greater improvement in MADRS by day 5 (8.6 mean difference, $P < 0.10$, prespecified outcome); response rate was 60% for active versus 20% for placebo	[44]
EVT-101 (Roche/Evotec) NCT01128452	2-arm RCT	MDD	NA	8	II	Discontinued because of a clinical hold	

NCT identifier/trial acronym	Trial design	Condition	Expected/actual completion date	Projected/actual recruitment	Phase	Primary outcome measure and results if reported	Refs
						issued by the FDA	
Rislenemdaz/CERC-301 (Cerecor),formerlyMK-0657(Merck)							
NCT02459236	3-arm, fixed-dose RCT	MDD	Dec 2016	115	II	Change in Bech-6 from baseline at 2 and 4 days post treatment; results not publicly available	
NCT01941043	3-arm, SPCD	MDD with recent SI	Oct 2014	137	II	HAM-D after 7 days of dosing; study did not meet primary endpoint	[18,46]
AVP-786 (Avanir/Otsuka); oral formulation							
NCT02153502	2-arm RCT	TRD	Feb 2016	206	II	MADRS score at week 10; results not publicly available	
AXS-05 (Axsome Therapeutics) NCT02741791; STRIDE-1	2-arm RCT (active comparator: bupropion)	TRD	Dec 2018	350	III	MADRS scores at week 6	
Rapastlnel (GLYX-13, Allergan); delivered Intravenously unless otherwise noted							
NCT03002077	Open label, single group	MDD	Feb 2020	500	III	Safety outcomes over 52 weeks	
NCT03352453	2-arm RCT, recruiting from emergency settings	Suicidal MDD	Jan 2020	300	II	Change from baseline in MADRS at 1 day	
NCT02192099	Open-label extension, single group	MDD	Oct 2019	61	II	Safety outcomes	
NCT02951988	3-arm, randomized withdrawal	MDD	Sep 2019	600	III	Time to first relapse during 52 weeks after randomization	
NCT02943564; RAP-MD-02	3-arm, fixed-dose RCT	MDD	Dec 2018	1050	III	Change from baseline in MADRS at 1 day	
NCT02943577; RAP-MD-03	2-arm RCT	MDD	Dec 2018	700	III	Change from baseline in MADRS at 1 day	

NCT identifier/trial acronym	Trial design	Condition	Expected/actual completion date	Projected/actual recruitment	Phase	Primary outcome measure and results if reported	Refs
NCT02932943; RAP-MD-01	2-arm RCT	MDD	Nov 2018	700	III	Change from baseline in MADRS at 1 day	
NCT01684163	3-arm, fixed-dose RCT	MDD	Jun 2014	369	II	Change in HAM-D at 6, 12, and 16 weeks; results not publicly available	
NCT01234558	4-arm, fixed-dose RCT	MDD	Jul 2012	115	II	Change in depression score at 14 days; clear dose-response relationship observed and primary outcome measures were positive	[17]
Apimostinel/NRX-1074/AGN-241660 (Naurex/Allergan); oral formulation							
NCT02067793	4-arm, fixed-dose RCT	MDD	Feb 2015	151	II	Change from baseline in HAM-D (multiple time points); results not publicly available	
AV-101 (VistaGen); oral formulation designed for once-daily dosing							
NCT02484456	2-week crossover RCT	MDD	Dec 2019	25	II	Change from baseline in HAM-D (sponsored by NIMH)	
NCT03078322; ELEVATE	2-arm RCT	MDD	Mar 2019	180	II	MADRS at 2 weeks	
NRX-100 (single-dose IV Ketamine) followed by NRX-101 (D-cycloserine and lurasidone, NeuroRx)							
NCT03395392	2-arm RCT, control arm is placebo + lurasidone	Suicidal BPD	Mar 2019	150	II/III	Change in MADRS from baseline at 6 weeks	
NCT03396068; SBP-ASIB	2-arm RCT, control arm is placebo + lurasidone	Suicidal BPD	Mar 2019	72	II/III	Change in MADRS from baseline at 6 weeks	

NCT identifier/trial acronym	Trial design	Condition	Expected/actual completion date	Projected/actual recruitment	Phase	Primary outcome measure and results if reported	Refs
NCT03396601; SevereBD	2-arm RCT of NRX-100 (ketamine) versus saline	Suicidal BPD	Mar 2019	150	III	Suicidal ideation at 24 h	
NCT02974010; STABIL-B	2-arm RCT, control arm is placebo + lurasidone	Suicidal BPD	Dec 2018	120	III	Change in MADRS from baseline at 6 weeks	
AGN-241751 (Allergan), oral formulation							
NCT03586427	5-arm, fixed-dose RCT	MDD	May 2019	250	II	Change in MADRS at 1 day	
Baslmglurant/RO4917523 (Roche); oral formulation							
NCT01437657; MARIGOLD	3-arm, fixed-dose RCT	MDD	Sep 2013	319	II	Change in MADRS at 6 weeks; no separation from placebo	[24]
NCT00809562	2-arm RCT	MDD	Feb 2011	46	II	Safety and tolerability outcomes, results not publicly available	
Decoglurant/RO4995819/RG-1578 (Roche); oral formulation							
NCT01457677; ARTEDeCo	4-arm, fixed-dose RCT	TRD	Jun 2014	357	II	Change in MADRS at week 6; no separation from placebo seen	[54]
Tulrampator/CX-1632/S-47445 (RespireRx/Servier, formerly of Cortex)							
NCT02805439	3-arm, fixed-dose RCT	TRD	Apr 2017	400	II	Change In HAM-D at 8 weeks; results not publicly available	
Riluzole, oral NCT01703039	2-arm RCT (riluzole plus sertraline versus placebo plus sertraline)	MDD	Sep 2019	120	II	Mean change In HAM-D from baseline to week 8; proportion of patients with response; proportion of patients with remission	

NCT identifier/trial acronym	Trial design	Condition	Expected/actual completion date	Projected/actual recruitment	Phase	Primary outcome measure and results if reported	Refs
NCT01204918	Sequential parallel comparison design	TRD	Aug 2015	104	II	Treatment groups did not differ in mean MADRS scores, response rate, or any secondary outcome measures	[26]
IRCT201307181556N54 (Iranian registry)	2-arm RCT	MDD	Mar 2015	64 (60 analysed)	-	HAM-D at weeks 2, 4, and 6: significant treatment × time interaction with large effect sizes (Cohen's d = 0.87–1.06)	[28]
NCT00054704	2-arm RCT	BPD	Dec 2014	19	II	MADRS: no separation from placebo	[27]
NCT00805493	2-arm RCT	Pediatric BPD	Jun 2012	6	II	Terminated early because of insufficient recruitment	
NCT00376220	2-arm RCT	BPD	May 2010	94	II	Mean changes in MADRS at week 8; no meaningful difference in MADRS noted (per clinicaltrials.gov)	
Brexanolone (SAGE-547); delivered intravenously over 60 h unless otherwise noted							
NCT02942017	2-arm RCT	PPD	Oct 2017	108	III	Change from baseline in HAM-D at 3 days; study was reported as positive	[59]
NCT02942004	2-arm RCT	PPD	Oct 2017	138	III	Change from baseline in HAM-D at 3 days; study was reported as positive	[59]
NCT02614547	2-arm RCT	PPD	Jul 2016	21	II	Change from baseline in	[57]

NCT identifier/trial acronym	Trial design	Condition	Expected/actual completion date	Projected/actual recruitment	Phase	Primary outcome measure and results if reported	Refs
						HAM-D at 3 days; trial was positive, with effect size of d = 1.2	
NCT02285504	Open label, single group	PPD	Jun 2015	4	II	Safety measures were primary outcomes; descriptive efficacy measures showed large improvements in symptoms of depression and anxiety	[58]
Ganaxolone (Marinus); oral and intravenous formulations							
NCT03460756	2-arm RCT, oral	PPD	Jan 2019	58	II	HAM-D scores at 38 days, safety outcomes	
NCT03228394	2-arm RTC, IV	PPD	Aug 2018	60	II	Safety outcomes; results not publicly available	
SAGE-217 (SAGE); oral formulation designed for once-dally dosing							
NCT02978326	2-arm RCT	PPD	Dec 2018	60	II	Change from baseline in HAM-D at 14 days	
NCT03000530	Part A: open-label (N = 14); part B: 2-arm RCT (N = 89)	MDD	Oct 2017	102	II	Efficacy: HAM-D score at 14 days; primary outcome (Part B) positive [30]; safety: adverse events, laboratory values, vital signs, ECG, and suicidal ideation (C-SSRS)	

Abbreviations: BPD, bipolar depression; MDD, major depressive disorder; PPD, post-partum depression; TRD, treatment-resistant depression; RCT, randomized controlled trial; SPCD, sequential parallel comparison design; MADRS, Montgomery-Åsberg Depression Rating Scale; CDRS-R, Children-s Depression Rating Scale, Revised; HAM-D, Hamilton Depression Rating Scale; ECG, electrocardiogram; C-SSRS, Columbia Suicide Severity Rating Scale.

[a]Unless otherwise noted, the data here are from clinicaltrials.gov. Compounds are grouped by purported mechanism of action and are listed in the same order as in Table 1; different studies for the same compound are listed in chronological order of estimated or actual completion date. Some completed studies did not have publicly available data.