

Novel glutamatergic drugs for the treatment of mood disorders

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Abstract: Mood disorders are common and debilitating, resulting in a significant public health burden. Current treatments are only partly effective and patients who have failed to respond to trials of existing antidepressant agents (eg, those who suffer from treatment-resistant depression [TRD]) require innovative therapeutics with novel mechanisms of action. Although neuroscience research has elucidated important aspects of the basic mechanisms of antidepressant action, most antidepressant drugs target monoaminergic mechanisms identified decades ago. Glutamate, the major excitatory neurotransmitter in the central nervous system, and glutamatergic dysfunction has been implicated in mood disorders. These data provide a rationale for the pursuit of glutamatergic agents as novel therapeutic agents. Here, we review preclinical and clinical investigations of glutamatergic agents in mood disorders with a focus on depression. We begin with discussion of evidence for the rapid antidepressant effects of ketamine, followed by studies of the antidepressant efficacy of the currently marketed drugs riluzole and lamotrigine. Promising novel agents currently in development, including *N*-methyl-D-aspartate (NMDA) receptor modulators, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) receptor modulators, and drugs with activity at the metabotropic glutamate (mGlu) receptors are then reviewed. Taken together, both preclinical and clinical evidence exists to support the pursuit of small molecule modulators of the glutamate system as novel therapeutic agents in mood disorders. It is hoped that by targeting neural systems outside of the monoamine system, more effective and perhaps faster acting therapeutics can be developed for patients suffering from these disabling disorders.

Keywords: glutamate, mood disorders, major depressive disorder, ketamine, NMDA, AMPA

Introduction

Mood disorders represent a tremendous worldwide public health burden. According to the World Health Organization (WHO), unipolar depressive disorders account for 65.5 million disability-adjusted life years (DALYs) lost and rank third among leading causes of global disease burden.¹ Among all brain-based disorders, unipolar depressive disorders rank first; bipolar disorder (BPD) ranks fourth, accounting for 14.4 million DALYs lost.¹ Compounding this large disease burden, current treatments for mood disorders remain only partially effective and are associated with a long lag time to onset of therapeutic efficacy.² It is estimated that more than one-third of patients with major depressive disorder (MDD) suffer from treatment-resistant depression (TRD), defined as a failure to achieve antidepressant response to one or more antidepressant treatments of adequate dose and duration.³ For this group of patients in particular,

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current monoaminergic antidepressant agents are inadequate and innovative therapeutics with novel mechanisms of action are urgently needed.

Current pharmacological options for MDD include the serotonin-selective reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants (eg, bupropion, mirtazapine), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Treatment options for BPD include lithium, anticonvulsants (eg, valproic acid), and antipsychotic agents. Remission (defined as resolution of symptoms) is the ultimate therapeutic goal in the treatment of mood disorders and it is associated with improved long-term outcomes and lower relapse rates.⁴ Patients with MDD who have failed to respond to two treatments experience significantly reduced remission rates (10%–20%) following the next treatment trial and no specific treatment option appears superior to alternatives.⁵ Depressive symptoms and episodes represent the predominant source of disability associated with BPD and are often particularly difficult to treat.^{6,7} When mood disorder symptoms persist despite an optimized trial with a first-line therapeutic agent, there is no clear guidance on the next best treatment steps. The standard of care for MDD consists of a trial and error approach involving sequential monotherapy trials with antidepressant agents and augmentation or combination strategies. A similar approach represents the standard of care for BPD. Careful assessment, re-evaluation of diagnosis, a high suspicion for occult substance or general medication problems, attendance to environmental factors, and consideration of psychotherapy all constitute important aspects of the clinical management of mood disorders.

Although neuroscience research has elucidated important aspects of the basic mechanisms of antidepressant action,⁸ the majority of antidepressant drugs target monoaminergic mechanisms identified decades ago. After several unsuccessful attempts by the industry to develop drugs active at new molecular targets for mood disorders, several major pharmaceutical companies have recently eliminated or reduced R&D investment in neuroscience therapeutics.⁹ The remaining programs tend to focus on ‘safe’ targets rather than potentially paradigm-shifting therapies, although there exist important exceptions. There is an undeniable public health imperative to develop new therapies for TRD to address persistent mood symptoms, promote sustained remission, and improve quality of life.

Herein, we provide a narrative review of preclinical and clinical investigations of glutamatergic agents in mood

disorders with a focus on depression and agents with antidepressant activity. Our literature review included searches of PubMed, NCBI, and ClinicalTrials.gov databases and the search terms, ‘depression’, ‘major depression’, ‘major depressive disorder’, ‘mood disorder’, ‘bipolar disorder’, ‘treatment’, ‘antidepressant treatment’, ‘mood stabilizers’, and ‘glutamate’, as well as each specific class and drug name discussed in the manuscript. We begin by reviewing the glutamate system and the evidence supporting the rapid antidepressant effects of ketamine. Subsequently, we review evidence concerning the antidepressant efficacy of the currently marketed drugs riluzole and lamotrigine. We then discuss novel agents currently in development, including *N*-methyl-D-aspartate (NMDA) and 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) modulators and drugs with activity at the metabotropic glutamate receptors (mGluRs). We conclude with a discussion of the current state of glutamatergic antidepressant agents and future directions for therapeutic development. The scope of this review precludes detailed discussion regarding the efficacy and off-target effects of each agent and the reader is therefore referred to the relevant primary publications for additional details.

Glutamatergic neurotransmission as an emerging therapeutic target in mood disorders

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS) and plays a central role in synaptic plasticity, learning, and memory.¹⁰ Glutamate is packaged into synaptic vesicles for calcium-dependent release, which enables binding to ionotropic and metabotropic receptors (see Figure 1). The ionotropic glutamate receptors include NMDA, AMPA, and kainate receptors. Metabotropic glutamate receptors all initiate signal transduction cascades via G-protein coupling and are divided into three groups: Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3), and Group III (mGluR4, mGluR6, mGluR7, mGluR8). Glutamate is not significantly degraded extracellularly and instead is transported into glia by excitatory amino acid transporters (EAATs) and is the primary mechanism by which clearance occurs. The glial cell – together with the pre-synaptic and post-synaptic neurons – make up the ‘tripartite synapse’ which functions to exert tight regulatory control over levels of synaptic and extra-synaptic glutamate. Excessive levels of glutamate result in the well described phenomenon for neuronal excitotoxicity. The extensive molecular machinery

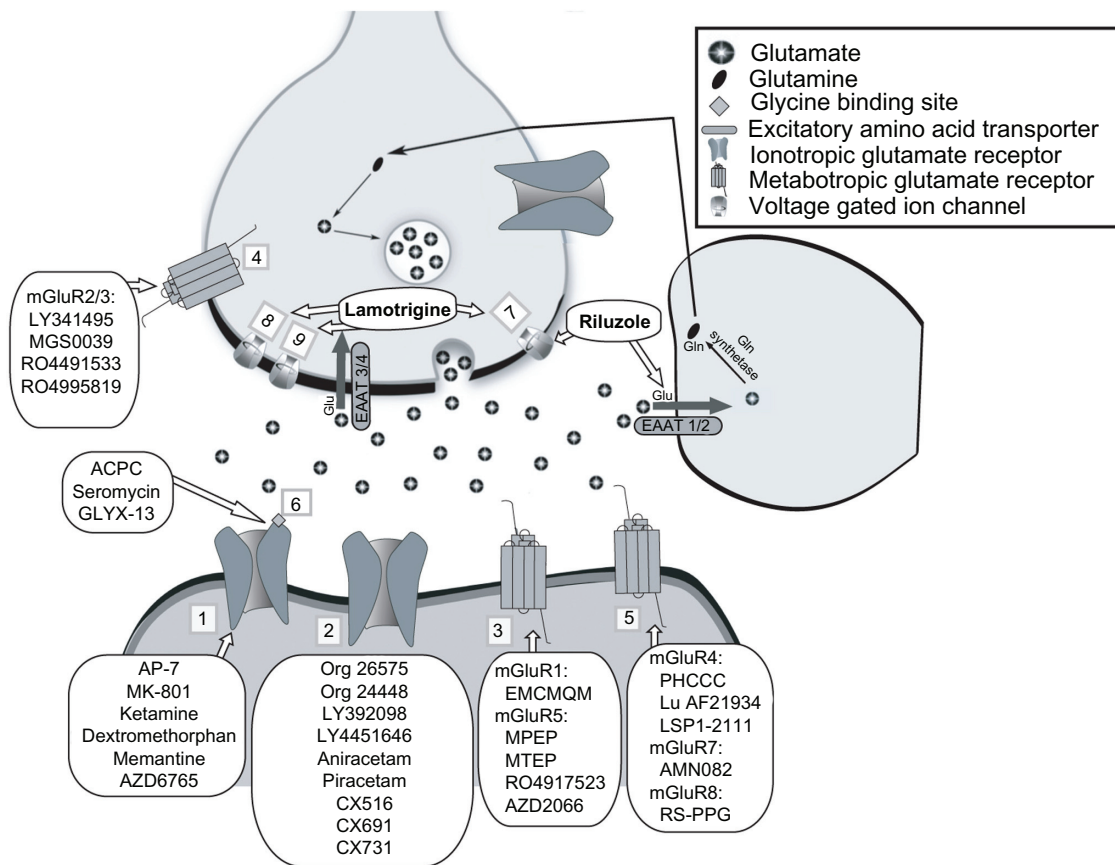


Figure 1 Molecular targets of glutamatergic drugs for mood disorders.

Notes: Sites of action and regulation for glutamate neurotransmission are shown, and drugs that target each specific site/mechanism are indicated. The specific locations depicted here are representative, though ionotropic and metabotropic glutamate receptors may be located on both presynaptic and postsynaptic cells. Numbers indicate the following targets: (1) NMDAR; (2) AMPAR; (3) Group I mGluR; (4) Group II mGluR; (5) Group III mGluR; (6) Glycine site of NMDAR; (7) Na⁺ Channel; (8) Ca²⁺ Channel; (9) K⁺ Channel.

Abbreviations: AMPAR, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid receptor; EAAT, excitatory amino acid transporter; Gln, glutamine; mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptor; MTEP, 3-((2-methyl-4-thiazolyl)ethynyl)pyridine; PHCCC, (-)-N-phenyl-7-(hydroxyimino) cyclopropa[b]chromen-1a-carboxamide; EMCMQM, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate; Glu, glutamate; ACPC, L-aminocyclo-propanecarboxylic acid.

regulating glutamate signaling provides multiple targets of glutamatergic drug development (Figure 1).

Evidence from postmortem and in vivo brain imaging studies implicates amino acid neurotransmitter systems in the pathophysiology of MDD. Increased cortical glutamate levels were detected in postmortem samples from patients with bipolar and unipolar depression.¹¹ Imaging studies with magnetic resonance spectroscopy (MRS) have demonstrated abnormalities in regional glutamate, glutamine, and GABA in patients with depression.^{12,13} For example, Sanacora et al reported an increase in cortical glutamate along with decreases in GABA in depression.¹³ These brain abnormalities are consistent with observed alterations in peripheral blood and cerebrospinal fluid glutamate levels as well as postmortem studies of glutamate receptors.¹⁴ One postmortem study demonstrated altered NMDA receptor (NMDAR) binding and used in situ hybridization to identify cortical decreases in a variety of

glutamate receptor components in both BPD and MDD.¹⁵ Notably, traditional monoamine-based antidepressants have been found to regulate glutamate receptor expression and function.¹⁶ Taken together, these data implicate altered glutamate signaling in mood disorders and provide a rationale for the pursuit of glutamatergic agents as novel therapeutic agents.^{17–19}

Ketamine

Ketamine is a non-competitive glutamate NMDAR antagonist currently approved as an anesthetic agent. Ketamine is classified as a dissociative anesthetic and produces an anesthetic state characterized by preserved pharyngeal reflexes and cardiovascular and respiratory stimulation when administered intravenously (IV) at doses of 1–3 mg/kg.²⁰ While IV is the typical route of administration, additional routes include intramuscular (IM), intranasal (IN), epidural, subcutaneous, transdermal, and oral.

Table I Glutamatergic agents in depression-like animal models

Target	Drug	Major mechanism of action	Treatment effect	Reference numbers
NDMAR	Ketamine	Non-competitive antagonist	Antidepressant effects in CS, TST, FST, LH, and NSFT; increases in synaptic density	30, 74, 120
NMDAR glycine	Memantine	Non-competitive low-affinity antagonist	Antidepressant effects in FST and CS	116, 121
	GLYX-13	Partial agonist at glycine site	Antidepressant effects in FST and LH	72
NMDAR GluN2B	Ro25-6981	GluN2B selective antagonist	Antidepressant effects in FST and CS	73–76
AMPA	Aniracetam	PAM	Mixed antidepressant effects in FST	88, 89
	CX516; CX691; CX731; piracetam	PAMs	Possible anxiolytic vs antidepressant effects on submissive behavior	88
	LY392098	PAM	Antidepressant effects in FST and TST, but no effect in CS	85, 87, 122
	LY451646	PAM	Mixed antidepressant effects in FST and TST	86
Group I mGluR1	EMQMCM	mGluR1 antagonist	Antidepressant effects in FST and TST	97, 98
Group I mGluR5	GRN-529	mGluR5 NAM	Antidepressant effects in FST	96
	MPEP; MTEP	mGluR5 antagonists	Antidepressant effects in FST and TST	92–95, 98
Group II mGluR	LY341495	mGluR2/3 antagonist	Antidepressant effects in TST, FST, and nicotine-withdrawal-related ICSS elevation	101–104
	MG50039	mGluR2/3 antagonist	Antidepressant effects in LH, TST, and FST; anxiolytic effects in conditioned fear	99–101
Group III mGluR	RO4491533	mGluR2/3 NAM	Antidepressant effects in TST and FST	103
	ACPT-1	mGluR group III agonist	Antidepressant effects in FST	105, 106, 108
			No antidepressant effects in FST and TST following peripheral administration	107
Group III mGluR4	Lu AF21934	mGluR4 PAMs	No effect in FST and TST	109, 110
	LSPI-2111			
	PHCCC	mGluR4 PAM	No antidepressant effect in FST alone; antidepressant effects in FST when given with mGluR Group III antagonist, ACPT-1	108
Group III mGluR7	AMN082	mGluR7 agonist	Antidepressant effects in FST and TST	111
Group III mGluR8	RS-PPG	mGluR8 agonist	Antidepressant effects in FST	106
Other	Riluzole	Reduces extra-synaptic glutamate by inhibiting presynaptic release, enhances astroglial uptake	Antidepressant effects in FST, CS, and bulbectomy	33–35
	Lamotrigine	Inhibits voltage-dependent channels to reduce glutamate release	Antidepressant effects in FST and CS	45–47
	Acamprosate	NMDA and mGluR5 antagonist	Antidepressant effects in FST	112

Note: Summary of evidence from animal models of depression and selected references are provided for drugs, grouped by class.

Abbreviations: NMDAR, N-methyl-D-aspartate receptor; CS, chronic stress; TST, tail suspension test; FST, forced swim test; LH, learned helplessness; NSFT, novelty-suppressed feeding test; GLYX-13, (S)-N-[(2S,3R)-1-amino-3-hydroxy-1-oxobutan-2-yl]-1-[(S)-1-((2S,3R)-2-amino-3-hydroxybutanoyl)pyrrolidine-2-carbonyl]pyrrolidine-2-carboxamide; GluN2B, isoform of a regulatory NMDAR subunit; AMPAR, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid receptor; PAM, positive allosteric modulator; EMQMCM, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate; mGluR, metabotropic glutamate receptor; GRN-529, (4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl)(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)methanone; MPEP, 2-methyl-6-(phenylethynyl)pyridine; MTEP, 3-((2-methyl-4-thiazolyl)ethynyl)pyridine; LY341495, 2-[(1S,2S)-2-carboxycyclopropyl]-3-(9H-xanthen-9-yl)-D-alanine; MG50039, (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; RO4491533, 4-[3-(2,6-dimethylpyridin-4-yl)phenyl]-7-methyl-8-trifluoromethyl-1,3-dihydrobenzo[b][1,4]diazepin-2-one; NAM, negative allosteric modulator; ACPT-1, (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid; LSPI-2111, (2S)-2-amino-4-[hydroxy(hydroxy(4-hydroxy-3-methoxy-5-nitro-phenyl)methyl)phosphoryl]butanoic acid; PHCCC, (-)-N-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide; AMN082, N,N'-dibenzhydrylethane-1,2-diamine dihydrochloride; RS-PPG, (RS)-4-phosphonophenylglycine; NMDA, N-methyl-D-aspartate.

The first report of the antidepressant effects of ketamine utilizing a controlled design in patients with MDD described a rapid onset antidepressant effect within hours following a single IV dose of 0.5 mg/kg (approximately one-fourth of the anesthetic dose).²¹ A second study – specifically conducted in patients with TRD – replicated the finding of a rapid antidepressant effect of ketamine compared to saline in a cross-over design and found a 70% response rate at 24 hours following a single infusion.²² Since these initial reports,

several open-label studies and case reports have added to the evidence base for ketamine as a novel glutamatergic antidepressant.^{23–25} These findings were also extended to BPD; ketamine added to a mood stabilizer exerted a rapid antidepressant effect in BPD patients who were in a refractory depressive episode at the time of randomization.^{26,27}

Despite the promise of an effective and mechanistically novel antidepressant, several hurdles remain before ketamine may be considered as a treatment for mood disorders outside

Table 2 Clinical trials of glutamatergic agents in MDD

Target	Drug	Major mechanism of action	Treatment effect	Reference numbers
NMDAR	AZD6765	Low–moderate affinity open-channel antagonist	Limited evidence for antidepressant efficacy to date	66
	Dextromethorphan	Non-competitive antagonist	No clinical evidence for antidepressant efficacy to date	65
	Ketamine	Non-competitive antagonist	Good evidence for antidepressant efficacy	17, 18, 22, 23
	Memantine	Non-competitive low affinity antagonist	Controlled data does not support antidepressant efficacy	117
NMDAR Glycine	D-cycloserine	Partial agonist at glycine site	Limited evidence for antidepressant efficacy	69, 70
NMDAR GluN2B	CP-101,606	GluN2B selective antagonist	Preliminary evidence for antidepressant efficacy	77
	MK-0657	GluN2B selective antagonist	Preliminary evidence for antidepressant efficacy	78
AMPA	Org 26575	PAM	No clinical evidence for antidepressant efficacy to date	84
Other	Acamprosate	NMDA and mGluR5 antagonist	Controlled data does not support antidepressant efficacy	113, 114
	Lamotrigine	Inhibits voltage-dependent channels to reduce glutamate release	Limited evidence for antidepressant efficacy	53–56, 123–125
	Riluzole	Reduces extra-synaptic glutamate by inhibiting presynaptic release, enhances astroglial uptake	Preliminary evidence for antidepressant efficacy	36–38

Note: Summary of evidence from clinical trials and selected references are provided for drugs, grouped by class.

Abbreviations: NMDAR, N-methyl-D-aspartate receptor; AZD6765, lanicemine; GluN2B, isoform of a regulatory NMDAR subunit; CP-101,606, Traxoprodil; D-cycloserine, Seromycin; AMPAR, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid receptor; PAM, positive allosteric modulator; mGluR5, metabotropic glutamate receptor 5; NMDA, N-methyl-D-aspartate; MDD, major depressive disorder

of the research setting. Regarding the question of efficacy, a degree of uncertainty remains regarding the specificity of ketamine's antidepressant effects since prior studies used only an inert placebo (ie, saline) as a control condition. A study comparing a single dose ketamine to an anesthetic control condition – the benzodiazepine anesthetic agent midazolam – in patients with TRD has recently been completed (NCT00768430) and data from this trial will provide a more rigorous assessment of ketamine's antidepressant efficacy. Additionally, therapeutic strategies designed to maintain the antidepressant effects of ketamine will need to be identified.^{28,29} A schedule of repeated doses of ketamine given three times a week for 2 weeks has demonstrated promise, but further controlled studies are necessary.^{24,29} The glutamate release inhibitor riluzole (see opposite) was found to be ineffective as a relapse prevention strategy following ketamine.^{23,28}

Concerning safety, ketamine is a potential drug of abuse and has been associated with cognitive impairments and alterations in brain imaging measures when abused for prolonged periods of time.³⁰ Likewise, high doses of ketamine and other NMDAR antagonists have been associated with neurotoxic effects in animal models.^{31,32} Interestingly, lower doses of ketamine and other NMDAR antagonists have been associated with neuroprotection and neurotrophic effects.^{33,34} Recently, ketamine was found to rapidly increase synaptic density and signaling in cortical neurons in conjunction with

rapid antidepressant effects in animal models and to reverse stress-induced trophic deficits following chronic mild stress.³⁴ Differences in dose and duration of exposure are likely critical variables accounting for the apparent paradoxical cellular effects of NMDARs and warrant a watchful approach to study and development of ketamine as a potential antidepressant treatment.

Riluzole

Riluzole, a glutamate modulator with neuroprotective and plasticity-enhancing properties, is FDA-approved for the treatment of amyotrophic lateral sclerosis (ALS).³⁵ Riluzole reduces extra-synaptic glutamate by (1) inhibiting glutamate release via presynaptic inhibition of voltage-gated sodium channels, (2) enhancing astroglial uptake of glutamate, and (3) increasing AMPA receptor trafficking.³⁶ The antidepressant effect of riluzole has been demonstrated in several animal models including forced swim test (FST),³⁷ unpredictable stress,³⁸ and bulbectomy models of depression.³⁹

To date, no randomized controlled trials (RCTs) of riluzole have been published in patients with mood disorders. Following several case reports on riluzole in unipolar and bipolar depression, a 6-week, open-label monotherapy study of riluzole (mean daily dose 100–200 mg/day) in TRD found significant antidepressant effects with remission and response rates of 21% and 32% for completers, respectively.⁴⁰ Another open-label study of riluzole in BPD reported changes in

glutamate metabolites and significant improvements in depressive symptoms.⁴¹ An 8-week augmentation trial of riluzole (50–200 mg/day) with lithium in bipolar depression reported significant improvements in depression ratings at weeks 5–8, without evidence of hypomania or mania.⁴² Another open-label trial of riluzole augmentation of ongoing medications in TRD demonstrated significant decreases in depression and anxiety severity that reached significance by the end of the first riluzole treatment week and persisted for the 12-week duration of the study.⁴³ Ongoing RCTs of riluzole versus placebo augmentation of SSRI therapy in TRD will provide more definitive information regarding riluzole's potential antidepressant efficacy (NCT01204918, NCT01703039).

Lamotrigine

Lamotrigine is a glutamate release inhibitor FDA-approved for partial and tonic-clonic seizure and for BPD. Lamotrigine inhibits voltage-dependent sodium channels, calcium channels, and potassium channels;⁴⁴ this is thought to decrease glutamate release and increase the AMPA receptor expression. Lamotrigine also weakly inhibits serotonin reuptake⁴⁵ and may exert neuroprotective effects.^{46,47}

Rodent studies of the antidepressant effects of lamotrigine have yielded mixed results,⁴⁸ though most have reported decreased immobility time in the FST.^{49,50} In rats subjected to chronic unpredictable stress, chronic administration of lamotrigine ameliorated behavioral deficits in both the sucrose preference test (SPT) and novelty-suppressed feeding test (NSFT).⁵¹ In patients with BPD, lamotrigine has shown both antimanic and antidepressant properties.^{52–55} In contrast to the strength of data for lamotrigine in BPD, human studies of lamotrigine's efficacy in unipolar depression have been less consistent.

In TRD patients (≥ 2 antidepressant failures), open-label treatment with lamotrigine resulted in significant reductions in symptoms of depression by 8 weeks and a significant improvement in social and occupational functioning at 6 months.⁵⁶ Several RCTs in TRD also demonstrated efficacy. In one, comparable results were found between lamotrigine versus lithium augmentation.⁵⁷ Another RCT in treatment refractory unipolar and bipolar depression found lamotrigine monotherapy to be superior to both gabapentin and placebo.⁵⁸ Extending these results, Obrocea et al followed unipolar and bipolar patients, reporting improvement in both groups with a more robust effect in those with bipolar disorder.⁵⁹ In contrast, several RCTs failed to show any benefit of lamotrigine on primary outcome measures.^{60–63} While lamotrigine is currently approved by the FDA for use in bipolar disorder, there is

less support for its efficacy in unipolar depression. To date, it is unclear why divergent results have been obtained from different trials, so further studies are indicated.

NMDA receptor modulators other than ketamine

The reports of ketamine's rapid antidepressant effects coupled with preclinical reports from a variety of other agents acting at the NMDA receptor have fueled increasing interest in the development of NMDA modulators as novel therapeutics in mood disorders.^{64–66} Initial interest in NMDA antagonists derived from a study of a variety of NMDAR antagonists including a competitive NMDAR antagonist (2-amino-7-phosphonoheptanoic acid [AP-7]), a noncompetitive NMDAR antagonist (dizocilpine [MK-801]), and a partial agonist at the NMDAR-GLY site (1-aminocyclopropanecarboxylic acid [ACPC]), were all found to mimic the effects of clinically effective antidepressants in animal models of depression-like behavior.⁶⁷

Dextromethorphan is an NMDAR antagonist initially used as a cough suppressant; more recently, the combination of dextromethorphan + quinidine (Nuedexta[®], Avanir Pharmaceuticals, Aliso Viejo, CA, USA) has been approved by the FDA for the treatment of pseudobulbar affect. Quinidine is a potent inhibitor of the CYP2D6 enzymatic pathway and thereby functions to raise the blood levels of dextromethorphan. In addition to NMDAR antagonism, dextromethorphan is an agonist at mu (μ) and sigma-1 opioid receptors and blocks calcium channels, serotonin transporters, and muscarinic receptors (reviewed by Lauterbach⁶⁸). Based on the efficacy of ketamine in depression, dextromethorphan may possess antidepressant activity, although to our knowledge, no clinical research investigating this question has been conducted to date. In the single published study, valproate augmentation with dextromethorphan versus placebo did not result in significant differences in manic or depressive symptom severity in BPD.⁶⁹ Further studies are needed to determine whether dextromethorphan may provide benefit in depressive symptoms associated with MDD and BPD.

A number of novel NMDAR modulators have been developed and currently show promise as potential antidepressant agents. AZD6765 (Lanicemine, AstraZeneca, London, UK) is a low-to-moderate affinity open-channel NMDA antagonist, that has been reported in a RCT to rapidly provide short-lived relief of depressive symptoms without eliciting dissociative or psychotomimetic symptoms in a single-site clinical trial.⁷⁰ This study included 22 subjects with TRD and demonstrated significant but transient differences in improvement of depressive symptom severity with AZD6765. Improvement

was evident within 80 minutes, but significant difference from placebo only persisted until the 110-minute time point. Several other trials of AZD6765 have been completed but are not yet published and a multi-site RCT seeking to extend the period of antidepressant efficacy is currently active and recruiting patients with TRD (NCT01482221).

The NMDA receptor's glycine binding site has also been targeted for potential antidepressant drugs, partly because standard antidepressant treatments have been shown to modulate binding at this site.^{16,71} D-cycloserine (Seromycin®, Eli Lilly and Co., Indianapolis, IN, USA), an antibiotic that has been used for decades to treat infections, has shown antidepressant efficacy. Initial reports suggesting possible antidepressant effects in tuberculosis patients treated with ≥ 500 mg/day D-cycloserine included improved mood, sleep, and appetite.⁷² A 6-week RCT of D-cycloserine 250 mg/day augmentation of ongoing antidepressant treatment failed to show superiority over placebo augmentation.⁷³ In contrast, a 6-week RCT of D-cycloserine 1000 mg/day augmentation was well tolerated and elicited significant benefit over placebo (54% versus 15% response at endpoint) in antidepressant response.⁷⁴ Newer drugs targeting the glycine site are also under investigation.

A new glycine site targeting agent, GLYX-13, is an antibody-derived tetra-peptide with partial agonist activity.⁷⁵ GLYX-13 showed potential antidepressant efficacy in rats by reducing immobility on FST and ameliorated symptoms of learned helplessness.⁷⁶ A Phase II trial was performed, but the results have not yet been published (NCT01234558). The company is testing other compounds in this class, and has the intention of testing these compounds in clinical trials, though no preclinical studies have yet been published or clinical trials launched. Currently a clinical RCT of low- and high-dose GLYX-13 is recruiting (NCT01684163).

The NMDAR is a tetrameric complex consisting of two NR1 and two NR2 subunits, which are available in multiple splice variants. NR2B subunit specific (GluN2B) antagonists have also shown promise as rapidly acting antidepressants. In several preclinical studies, the GluN2B antagonist Ro25-6981 demonstrated antidepressant efficacy by reducing immobility on the FST^{77–79} and increasing sucrose preference following chronic unpredictable stress (CUS).⁸⁰ These findings further motivated clinical trials of GluN2B antagonists CP-101,606 (traxoprodil), and MK-0657. In a small trial, CP-101,606 augmentation of paroxetine demonstrated antidepressant superiority over placebo with dose-related dissociative side effects.⁸¹ Although sample size may have limited statistical power, the large proportion of responders who maintained response for 1 week following a single dose,

was noted. Results from a clinical trial of the orally-active compound, MK-0657, suggested potential antidepressant efficacy but the study was stopped after only five subjects were enrolled because the manufacturer discontinued compound development before the trial could be completed.⁸² A RCT in TRD of the NR2B antagonist EVT-101 was recently terminated though data are not yet published (NCT01128452).

AMPA-targeting agents

AMPA receptor (AMPA) positive allosteric modulators (AMPA-PAMs; also known as AMPA potentiators or 'AMPAkines') slow the rate of AMPAR deactivation or desensitization. These agents have mainly been studied for cognitive enhancement in dementia and schizophrenia. Interest in these agents as potential antidepressants stems in part from the observation that traditional antidepressants regulate AMPARs^{83,84} and the ability of signaling through AMPARs to increase BDNF,^{85,86} in addition to glutamatergic effects. Several AMPAR potentiators have also shown promise in preclinical studies of mood disorders. To our knowledge, the only published placebo-controlled clinical trials of an AMPA-PAM in mood disorder patients involve Org 26575.^{87,88} A Phase II study of Org 26575 failed to show a significant separation from placebo, although efficacy was not the primary endpoint of this study.⁸⁸ The study did demonstrate tolerability, suggesting that further, well-powered studies are indicated to assess efficacy of this agent. Another agent from this class, the AMPAR potentiator Org 24448, was previously studied in major depression, but the RCT was discontinued (Clinicaltrials.gov identifier: NCT00113022). In this context, the tolerability demonstrated for Org 26575 is important for motivating further studies of AMPA acting agents.

LY392098 and LY451646 – biarylsulphonamide AMPAR potentiators – reduced immobility in the forced swim and tail suspension tests (FST, TST), and LY392098's effects were blocked by an AMPAR antagonist.^{89,90} Bidirectional antidepressant synergism was also reported between LY392098 and traditional antidepressants on FST.⁹¹ In a less common model of depression, two benzoylpyrrolidinones (aniracetam and piracetam) and three benzoylpyrrolidines (Ampakines; CX516, CX691, and CX731) all reduced submissive behavior regarding a rewarding food source.⁹² In this study, more rapid and greater action was reported for these compounds than fluoxetine. Aniracetam has also been found to reduce immobility time on FST in aged but not young rats.⁹³ The preclinical promise of these AMPA specific agents warrants further exploration in controlled clinical trials.

Metabotropic glutamate receptor-targeting agents

G-protein coupled metabotropic glutamate receptors (mGluRs) exert modulatory effects on neuronal function through signal transduction and have shown promise for the treatment of depression and anxiety in preclinical studies. Notably, Group I mGluRs (mGluR1, mGluR5) are functionally coupled to NMDARs and may regulate NMDAR-stimulated synaptic plasticity among other cellular functions.^{94,95} mGluR5 antagonists MPEP and MTEP have been repeatedly found to reduce immobility on TST and FST, independently and synergistically with imipramine.^{96–98} Antidepressant-like effects of MTEP on FST were found to depend on NMDAR but not on AMPAR signaling.⁹⁹ Similarly, the mGluR5 negative allosteric modulator (NAM) GRN-529 results in antidepressant-like effects, reducing immobility time on FST.¹⁰⁰ Results have not been published from two RCTs of mGluR5 negative modulators in MDD, RO4917523 (NCT00809562) and AZD2066 (NCT1145755). However, a follow-up study of RO4917523 versus placebo augmentation in MDD is currently recruiting (NCT1437657). The mGluR1 antagonist EMQMCM also decreased immobility on TST and FST.¹⁰¹ Other approved treatments synergized the FST effects of MTEP and EMQMCM.¹⁰²

Selective antagonists of group II mGluR2/3, LY341495 and MGS0039 and the NAM group II modulator RO4491533 variably reduced depressive-like behavior on TST, FST, and foot shock-related learned helplessness, and these effects were found to be AMPAR-dependent.^{103–107} LY341495 also reduced nicotine withdrawal-related anhedonia as assessed by intracranial self-stimulation.¹⁰⁸ An ongoing RCT of RO4995819 in major depression (NCT1457677) will provide human data for antidepressant efficacy of a related mGluR2/3 negative allosteric modulator.

The group III mGluR agonist, ACPT-1 and the mGluR8 specific agonist (RS)-4-phosphonophenylglycine (RS-PPG), showed antidepressant-like effects on FST, which were reversed through mGluR group III antagonism,^{109,110} though effects on FST and TST were not replicated when ACPT-1 was peripherally administered.¹¹¹ Moreover, the effect of ACPT-1 was facilitated by a positive allosteric modulator of mGluR4, (-)-N-phenyl-7-(hydroxyimino) cyclopropa[b]chromen-1a-carboxamide (PHCCC).¹¹² However, when administered alone, the mGluR4 positive allosteric modulators, Lu AF21934 and LSP1-2111, failed to exhibit antidepressant-like activity on TST and FST.^{113,114} The mGluR7 selective agonist, N,N'-dibenzylhydrazyl-ethane-1,2-diamine dihydrochloride (AMN082), also was reported

to decrease immobility on FST and TST, and similar effects were not seen in animals lacking mGluR7, though high doses impaired locomotor activity.¹¹⁵

Conclusion

The limited efficacy and delayed onset of action of standard monoaminergic antidepressants compels the search for new therapeutics with novel mechanisms of action. A growing body of evidence implicates dysregulation of the glutamate system as a key pathophysiological feature of mood disorders, thereby making the glutamate system a prime target for innovative treatments. The data reviewed herein suggest that agents directly targeting glutamatergic transmission show promise for expanding the scope and efficacy of antidepressant treatments. Ketamine in particular offers a proof of principal for modulation of the NMDAR as a novel antidepressant strategy. In the future, ketamine may provide a hospital-based treatment option for patients with refractory forms of depression or in cases where rapid treatment is required, for example, in the case of acute suicidal ideation. Much more research investigating the longer-term safety and efficacy of ketamine, however, is necessary before this can be recommended as a treatment. While lamotrigine is currently approved by the FDA for use in BPD, its efficacy in unipolar depression or TRD is less compelling. Riluzole possesses limited evidence for efficacy in unipolar and bipolar depression but larger definitive studies are required before widespread clinical use can be recommended.

Additional glutamatergic agents marketed for non-mood disorder conditions are under consideration as potential antidepressant agents. For example, acamprosate, used for the treatment of alcohol abuse, which also has antagonist activity at both NMDAR and mGluR5 receptors, has shown antidepressant-like activity on the TST¹¹⁶ along with trends but not statistically significant improvements in underpowered studies of depressive symptoms in patients with comorbid depression and alcohol dependence.^{117,118} However, another NMDA modulator – memantine – has not demonstrated efficacy in depression. Memantine (Namenda) is an amantadine derivative and voltage-dependent non-competitive low-affinity NMDAR antagonist, and is approved for the treatment of moderate-to-severe Alzheimer's disease.¹¹⁹ While memantine demonstrated antidepressant effects in multiple animal models of depression including FST and chronic mild stress,¹²⁰ results from RCTs of memantine in human depression have failed to demonstrate antidepressant benefit.¹²¹ Memantine's low-affinity and fast off-rate have been suggested as possible explanations for

the lack of antidepressant efficacy.¹²² Substantially more research is required on these compounds before they can be recommended for clinical use in mood disorders.

Innovative experimental agents with significant therapeutic promise in mood disorders based on preclinical data include novel NMDAR modulators (including NR2B subtype-selective agents), AMPA-PAMs, and selective mGluR PAMs and NAMs. Additional components of the glutamate regulatory machinery may be suitable for future drug development, including EAATs. Glutamate uptake by EAATs is the primary means by which glutamate is removed from the extracellular space, thereby limiting the potential for excitotoxicity caused by excessive glutamate signaling. Compounds capable of increasing the activity of EAATs may have antidepressant properties and a series of small molecules that may enhance EAAT levels have recently been described.¹²³ Future preclinical studies will be needed to test the hypothesized antidepressant effect of these agents.

Taken together, both preclinical and clinical evidence exists to support the pursuit of small molecule modulators of the glutamate system as novel therapeutic agents in mood disorders. This effort represents a critical departure from reliance on developing compounds that target the monoamine system, yielding so called 'me too' drugs which do not typically differ in clinically meaningful ways from previously marketed antidepressants. It is hoped that by targeting neural systems outside of the monoamine system, more effective and perhaps faster acting therapeutics can be developed for patients suffering from these disabling disorders.

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