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Targeting the Glutamatergic System to Treat Major Depressive Disorder:

Rationale and Progress to Date

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Abstract

Major depressive disorder (MDD) is a severe, debilitating medical illness that affects millions of individuals worldwide. The young age of onset and chronicity of the disorder has a significant impact on the long-term disability that affected individuals face. Most existing treatments have focused on the 'monoamine hypothesis' for rational design of compounds. However, patients continue to experience low remission rates, residual subsyndromal symptoms, relapses and overall functional impairment.

In this context, growing evidence suggests that the glutamatergic system is uniquely central to the neurobiology and treatment of MDD. Here, we review data supporting the involvement of the glutamatergic system in the pathophysiology of MDD, and discuss the efficacy of glutamatergic agents as novel therapeutics. Preliminary clinical evidence has been promising, particularly with regard to the *N*-methyl-D-aspartate (NMDA) antagonist ketamine as a 'proof-of-concept' agent. The review also highlights potential molecular and inflammatory mechanisms that may contribute to the rapid antidepressant response seen with ketamine.

Because existing pharmacological treatments for MDD are often insufficient for many patients, the next generation of treatments needs to be more effective, rapid acting and better tolerated than currently available medications. There is extant evidence that the glutamatergic system holds considerable promise for developing the next generation of novel and mechanistically distinct agents for the treatment of MDD.

1. Background

Investigation of the mechanisms of action of the earliest effective therapeutic agents for major depressive disorder (MDD) – including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs) and electroconvulsive therapy (ECT)[1,2] –led researchers to adopt the initial 'monoamine hypothesis' of MDD and other affective disorders.[3–5] Although TCAs became the initial standard treatment for depression, usage was limited by

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the large number of adverse effects associated with their use and by the danger of overdose rather than by their lack of efficacy.[6] Subsequent drug discovery efforts focused on the rational design of compounds with similar efficacy, but improved tolerability; the most notable example is selective serotonin reuptake inhibitors (SSRIs).[7]

Despite the widespread use of SSRIs, the World Health Organization (WHO) Global Burden of Disease analysis projected that MDD will be the second leading cause of disability worldwide by 2020.[8] Furthermore, marked limitations associated with the use of currently available antidepressants were observed in the 7-year Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which encompassed nearly 3000 outpatients aged 18–75 years. The study concluded with the sobering observation that fewer than one-third of patients with MDD achieved remission after a standard antidepressant trial.[9] Additional controversy and debate have surrounded the efficacy of currently available anti-depressants, and a recent meta-analysis suggested a weaker than expected effect compared with placebo.[10] The methodology of these findings has been challenged,[11,12] and another analysis demonstrated that available antidepressants were clinically superior to placebo;[13] nevertheless, the issue of heterogeneity in treatment response remains.

In recent years, a growing body of evidence has implicated the glutamatergic system in the pathogenesis of depression. While much of the early impetus in this area came from preclinical models,[14,15] recent remarkable clinical observations[16,17] – particularly with the *N*-methyl-D-aspartate (NMDA) antagonist ketamine – have driven increased interest in the aetiological framework and search for potential targets within this complex regulatory system. The fact that so many individuals with MDD continue to struggle in their efforts to find effective treatments underscores the clearly urgent need to develop innovative and mechanistically distinct agents to further reduce the burden of mental illness. This next generation of treatments needs to be more effective, rapid acting and better tolerated than currently available medications.[18] In this context, considerable research suggests that the glutamatergic system may provide key insights into the pathophysiology of MDD, and in the development of novel therapeutics to treat this devastating disorder. Given the scope of this topic, this article focusses primarily on current relevant therapeutics and potential mechanisms underlying ketamine's rapid antidepressant effect.

2. Rationale for Investigating Glutamate

High concentrations of glutamate were first observed in the brain in the 1930s, suggesting to researchers that this amino acid likely played a neurophysiological role.[19] As a neurotransmitter, glutamate was largely considered nonspecific until experiments in mammalian vertebrates in 1979 used specific agonists and antagonists to identify glutamate receptors in the brain.[20,21] Glutamate is found in substantially higher concentrations than monoamines and in more than 80% of neurons, cementing its role as a major excitatory synaptic neurotransmitter.[22] Accumulating research shows that glutamate plays a key role in regulating neuroplasticity, learning and memory.[23]

Given that glutamate is so widely distributed in the brain, strict regulation is necessary to prevent undue excitotoxicity. This is critical, as glutamate excitotoxicity has been implicated in a number of central nervous system (CNS) disorders, including Alzheimer's disease, Huntington's disease and Amyotrophic Lateral Sclerosis (ALS).[24–27] The delicate balance of glutamate with the major inhibitory neurotransmitter γ-aminobutyric acid (GABA) is essential for all physiological homeostasis in the CNS.[28] Given the ubiquitous nature of glutamate in the brain, and the fact that it acts on a number of different receptors – including glial cell receptors – it is not surprising that the underlying mechanisms of glutamate signalling are quite complex.

Evidence that glutamate is involved in the pathophysiology of mood disorders is indirect and drawn from imaging and post-mortem studies. Changes in glutamate levels have been noted in plasma,[29–31] serum,[32] cerebrospinal fluid (CSF)[33,34] and brain tissue[35] of individuals with mood and psychotic disorders, as well as in suicide victims.[36,37] Most studies reported that serum levels of glutamate in depressed patients were significantly higher than in healthy controls. However, interpreting glutamate levels in plasma, serum and CSF studies is challenging, given confounds such as medication exposure, post-mortem metabolic effects, and the inability to distinguish the source of glutamate (central vs peripheral).[38,39]

In recent years, however, new techniques, such as proton magnetic resonance spectroscopy (^{1}H-MRS), have provided non-invasive *in vivo* brain imaging methods that can be used to study the mechanism of action of psychotropic drugs. Resonances in the ^{1}H-MR spectrum can be reliably measured for several metabolites with brain concentrations in the millimolar range, including *N*-acetyl-aspartate (NAA), glutamate, glutamine, the combined measure of glutamate and glutamine (Glx), creatine + phosphocreatine (Cr), choline-related compounds (Cho) and myo-inositol.[40]

In the study of mood disorders, several investigators have focused on measuring Glx and GABA in various and specific brain regions. At its simplest, Glx reflects the total glutamatergic pool available for synaptic/metabolic activity in the form of glutamate or glutamine. One study found decreased Glx levels in the dorsomedial/dorsoanterolateral prefrontal cortex (PFC) of subjects with MDD,[41] echoing findings from prior post-mortem histopathological studies.[36] Elevated levels of glutamate have also been noted in the occipital cortex of MDD patients,[42] and decreased levels in the anterior cingulate cortex (ACC) in individuals with bipolar disorder.[43] A recent review of the MRS literature in mood disorders found reduced Glx levels in the ACC, left dorsolateral PFC (DLPFC), dorsomedial PFC (DMPFC), ventromedial PFC (VMPFC), amygdala and hippocampus of MDD patients.[44] In bipolar disorder, Glx levels were elevated in the grey matter areas of the ACC, medial PFC, DLPFC, parieto-occipital cortex, occipital cortex, insula and hippocampus.[44] However, it is important to consider the methodological heterogeneity across MRS studies; these include, but are not limited to, subject selection, sample size, MRS sequences, field strength and anatomical placement of the voxel of interest.[45] Combining MRS with other imaging techniques – such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) or magnetoencephalography (MEG) – is already helping investigators integrate data across multiple sources and may ultimately help identify glutamatergic abnormalities that could serve as key biomarkers for diagnosis or antidepressant response.[45]

Lastly, dendritic/structural remodelling in key regions (e.g. PFC, hippocampus, amygdala) of the CNS is thought to play a role in depression and anxiety.[46–49] Given that glutamate is necessary for the normal development of dendritic branching,[50] it has been speculated that excessive glutamatergic neurotransmission (via exposure to chronic stress) causes dendritic retraction and loss of spines.[46] Such changes would effectively limit the number of exposed glutamate receptors and as a result, drugs thought to reduce glutamatergic neurotransmission may prevent dendritic retraction and protect brain synapses.[46,51] Interestingly, glutamatergic neurotransmission may further be altered at the genetic level, where genetic variations in key enzymes could influence the presumed *in vivo* index of glutamatergic neurotransmission.[52]

Taken together, the evidence presented above suggests that the glutamatergic system likely plays a significant role as a ‘primary mediator of psychiatric pathology’.[53] Our increasing knowledge of this system underscores its potential as an alternative or complementary

pathway for developing novel treatments for MDD and other mood disorders. Ongoing studies that augment our understanding of the glutamatergic system –and the subsequent application of this information – may ultimately enhance neural plasticity and cellular resilience in patients with mental illness.[54] Table I and table II and the text that follows provide a summary of glutamate targets for drug development and the evidence in support of specific agents.

3. The Physiology of Glutamate

Glutamate acts on three key cell compartments: presynaptic neurons, postsynaptic neurons and glia. Often characterized as the 'tripartite glutamatergic synapse', this system functions in the uptake, release and inactivation of glutamate via two major subtypes of glutamate receptors in the CNS: ionotropic and metabotropic.[64] In addition, high-affinity excitatory amino acid transporters (EAATs) provide glutamate clearance from extracellular space, and soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) complexes are thought to play a role in the structural aspects of synaptic vesicle exocytosis.[65] Lastly, vesicular glutamate transporters (VGLUTs) are responsible for the uptake of glutamate into the synaptic vesicle.[65] Because of limited current therapeutic applications with many of the above targets, most of the following discussion pertains to the ionotropic receptor subtypes: NMDA and α-amino-3-hydroxy-5methyl-4-isoxazole propionic acid (AMPA).

The NMDA receptor channel comprises NR1, NR2 (NR2A–NR2D) and NR3 (NR3A and NR3B) subunits. NMDA receptor antagonists have demonstrated antidepressant-like effects in many animal models of depression, including inescapable stressors, the forced swim test, the tail suspension test, learned helplessness models of depression, and exposure to chronic mild stress procedures.[14,66–69] Other studies noted adaptive changes in NMDA receptor expression in response to both TCAs and ECT.[70–73]

The AMPA receptor is stimulated by the presence of glutamate and typically produces a fast excitatory synaptic signal. Its activation allows for the inward flow of sodium, causing depolarization of the neuronal membrane. The change in the intracellular charge frees the magnesium cation from the NMDA receptor, allowing the influx of calcium.[74] This channel is composed of four functionally diverse AMPA receptor subunits (GluR1–GluR4), and at mature synapses is co-expressed with NMDA receptors.[75–77] The presence of these receptors at synapses is carefully regulated to ensure proper neuronal communication.[78] Consequently, the trafficking of AMPA receptors into and out of synapses is a dynamic process and considered a significant mechanism underlying activity-induced changes in synaptic transmission[79] and plasticity, which are particularly instrumental in learning and memory.[23,76,77]

In animal models, AMPA receptor subunit 1 (GluR-A)-knockout mice (GluR-A$^{-/-}$) displayed increased learned helplessness, decreased serotonin and noradrenaline (norepinephrine) levels, and disturbed glutamate homeostasis with increased glutamate levels and increased NMDA receptor expression. Bleakman et al.[80] reviewed preclinical models with antidepressant-like behavioural effects and found that AMPA potentiators produced neuronal effects (e.g. brain-derived neurotrophic factor [BDNF] induction) similar to those produced by currently available antidepressants. This is in line with research suggesting that antidepressants exert their effects via a cascade of AMPA-mediated and NMDA-mediated events ultimately promoting synaptic plasticity.[75] In addition, compounds that augment AMPA receptor signalling or decrease NMDA receptor function may have antidepressant effects.[81]

Further evidence of AMPA's role in mood disorders comes from studies of medications with antidepressant properties that significantly enhance GluR1 and GluR2 expression in a dose-

dependent manner in hippocampal neurons.[80] AMPA receptor expression was also recently reported to be increased in post-mortem ACC samples from subjects with MDD.[82] Interestingly, animal models using an AMPA antagonist (NBQX) prior to infusion found that it selectively attenuated ketamine's antidepressant-like effects.[83] These results suggest that the antidepressant effects of ketamine are in part mediated by AMPA activation[83] and that enhanced AMPA receptor throughput may likely account for the uniquely rapid onset of action of ketamine[84] (ketamine is discussed in greater detail in section 4.1.1 and 4.1.2).

With regard to drug development, several compounds are being developed to allosterically modulate AMPA receptors, including pyrrolidones (piracetam, aniracetam), benzothiazides (cyclothiazide), benzylpiperidines and biarylpropylsulfonamides (for more complete reviews see Bleakman et al.,[80] Alt et al.[85] and O'Neill and Witkin[86]). Accordingly, these compounds do not directly activate AMPA receptors themselves, but slow the rate of receptor desensitization in the presence of an agonist.[87,88] Preclinical research with behavioural despair paradigms found that biarylpropylsulfonamide AMPA receptor potentiators (LY392098 and LY451616) had antidepressant-like effects.[89] In another animal study, CX-516 (Ampalex™), an AMPA potentiator, had more rapid antidepressant-like effects (during the first week of treatment) than fluoxetine.[90] More recently, the AMPA receptor potentiator LY451646 was found to mimic the effects of antidepressants in preclinical tests with high predictive validity. Interestingly, this particular compound – along with ketamine – demonstrated that BDNF signalling does not play a role in its antidepressant effects[91] (discussed in greater detail in section 5.1). It is also interesting to note that recent preliminary research was conducted with a rat-human translational pharmacokinetic-pharmacodynamic (PK-PD) model of AMPA receptor modulation, with the goal of predicting human target engagement and informing ideal dose selection in future efficacy clinical trials.[92]

Figure 1 illustrates general glutamatergic neuro-transmission and potential sites for novel drug development. The interested reader is referred to several recent reviews[93–95] for more detailed information regarding glutamate metabolism, clearance, cycling and other glutamate receptor functions/applications (e.g. metabotropic receptors).

4. Therapeutics

4.1 Ketamine and Other *N*-Methyl-D-Aspartate (NMDA) Antagonists

4.1.1 Ketamine—Ketamine, a phencyclidine (PCP) derivative, is a noncompetitive, high-affinity NMDA antagonist that prevents excess calcium influx and cellular damage.[96] Its primary mechanism of action is blocking the NMDA receptor at the PCP site within the ionotropic channel. Ketamine also has a high affinity to the NMDA receptor, slower open channel blocking/unblocking kinetics, 'trapping block versus partial-trapping' channel closure properties,[97] and different NMDA subunit selectivity than other NMDA antagonists such as memantine, active remacemide, AZD6765.[98–101] Several pre-clinical studies found that ketamine demonstrated antidepressant- or anxiolytic-like behaviours in various animal behaviour models of depression (e.g. forced swim test, tail suspension test, etc.).[73,83,102–112] An early dose-response preclinical study further demonstrated that low doses of ketamine increased glutamate outflow in the PFC.[113]

In regard to safety, ketamine has been widely used as an anaesthetic agent for children for decades.[114] Literature reviews also note that significant cardiorespiratory adverse events are rare, but dysphoric emergence phenomena (psychotomimetic effects) occur in up to 20% of cases[115,116] in paediatric/adult populations. A single dose of ketamine in rats (up to 20 mg/kg, subcutaneously) did not exert neuronal toxicity.[117]

The first report of ketamine's potential to alleviate depressive symptoms was a small, randomized, double-blind study demonstrating that a single subanaesthetic (0.5 mg/kg) ketamine infusion improved depressive symptoms within 72 hours in seven patients with treatment-resistant MDD.[16] Subsequently, a larger double-blind, placebo-controlled, crossover study found that a single ketamine infusion (0.5 mg/kg over 40 minutes) had fast and relatively sustained antidepressant effects (lasting 1–2 weeks) in patients with treatment-resistant MDD.[17] In this study, subjects had on average failed six prior antidepressant trials and were medication free at least 2 weeks prior to infusion. Notably, criteria for significant antidepressant response were found in 50% of subjects within 2 hours after ketamine infusion, and 71% within 24 hours. None of the subjects randomized to placebo met response criteria. The magnitude of the effect at this early timepoint was similar to that observed after many weeks of treatment with currently available antidepressants. Adverse effects included perceptual disturbances, confusion, elevations in blood pressure, euphoria, dizziness and increased libido, but most of these peaked within 40 minutes and ceased within 80 minutes post-infusion. In no case did euphoria or derealization/depersonalization persist beyond 80 minutes.[17] This finding of significant antidepressant effects associated with a single ketamine infusion has since been reported in several other studies of individuals with MDD; the magnitude and timeframe of onset and duration of response to ketamine appears remarkably similar across studies.[118–121]

Building on this work, the antidepressant effects of ketamine for the treatment of bipolar depression were examined. In the first such study, a single ketamine infusion was found to have rapid anti-depressant effects in 18 patients (maintained on therapeutic levels of lithium or valproate) with treatment-resistant bipolar depression. Within 40 minutes, depressive symptoms significantly improved in subjects receiving ketamine compared with those receiving placebo; the drug difference effect size was largest at day 2. A total of 71% of subjects responded to ketamine and 6% responded to placebo at some point during the trial. Ketamine was generally well tolerated, with the most common adverse effect being dissociative symptoms, which were observed only at the 40-minute point.[55] This study was recently replicated in another double-blind, randomized, crossover, placebo-controlled study.[56] Fifteen subjects with bipolar type I or II depression (also maintained on therapeutic levels of lithium or valproate) received a single intravenous infusion of either ketamine hydrochloride 0.5 mg/kg or placebo on two test days 2 weeks apart. Within 40 minutes, depressive symptoms as well as suicidal ideation significantly improved in subjects receiving ketamine compared with placebo (d = 0.89, 95% CI 0.61, 1.16; and 0.98, 95% CI 0.64, 1.33, respectively); this improvement remained significant through day 3. The most common side effect was again dissociative symptoms, occurring only at the 40-minute timepoint.[56] Notably, this second study was also the first controlled study to show that ketamine had rapid anti-suicidal effects in bipolar depression.

Other studies – albeit uncontrolled – similarly demonstrated that open-label ketamine had significant and rapid anti-suicidal effects in MDD patients. One study of 26 patients with treatment-resistant MDD found significantly reduced Montgomery-Åsberg Depression Rating Scale (MADRS) suicide subscale scores 24 hours after a single ketamine infusion.[122] In another study of 33 subjects with treatment-resistant MDD who received a single ketamine infusion, suicidal ideation scores decreased significantly within 40 minutes, an effect that remained significant for 4 hours post-infusion.[123] One study conducted in a naturalistic setting (e.g. emergency room) showed similar results.[124] Due to the enormous public health implications of these findings, future large-scale prospective studies are warranted.

Although these initial ketamine trials were greeted with considerable enthusiasm, the use of this agent remains highly investigational. Furthermore, due to its associated sedative and

psychotomimetic effects, it is unlikely that ketamine will be adopted for widespread clinical use. Despite ketamine's tolerability and safety profile,[114] long-term safety data are presently also limited, and well designed trials are needed to evaluate effective safety and relapse prevention strategies for the repeated use of ketamine. Additional studies are also needed to assess optimal dosing, alternative delivery routes and the risk of psychosis in patient populations.[125] Thus, considerable research efforts are aimed at developing therapeutic strategies to maintain ketamine's initial antidepressant effects. Some of the strategies under consideration include the administration of repeated doses of ketamine, or augmentation with other drugs that are better tolerated than ketamine; the latter strategy permits the administration of a single ketamine infusion followed by treatments that do not induce psychotomimetic effects, with the goal of obtaining a rapid and sustained antidepressant effect.

One small study evaluated the therapeutic benefit of repeated ketamine infusions by administering six open-label intravenous ketamine infusions over 12 days in ten medication-free symptomatic patients with treatment-resistant MDD. The study found that ketamine was associated with both an initial and a sustained antidepressant effect. The mean reduction in MADRS scores after the sixth infusion was 85% (SD ± 12%). Post-ketamine, eight of nine patients relapsed, on average 19 days after the sixth infusion (range 6–45 days). One patient remained antidepressant-free with minimal depressive symptoms for over 3 months. Ketamine was fairly well tolerated, with only mild side effects; however, the small sample size and lack of a control group limit the extent to which these findings can be generalized.[120]

4.1.2 Ketamine Augmentation Strategies—A recent pilot randomized, double-blind study (n = 14)[60] evaluated the ability of riluzole – a glutamatergic modulator with antidepressant and synaptic plasticity-enhancing properties[126–128] –to prevent post-ketamine relapse (for an in-depth review of riluzole in psychiatric disorders, see Zarate and Manji[129]). The study also investigated whether pretreatment with lamotrigine might attenuate ketamine's psychotomimetic effects and enhance antidepressant activity. Lamotrigine, a presynaptic glutamate-release inhibitor[130] and anticonvulsant is currently approved by the US FDA for maintenance treatment of bipolar type I disorder and as an antiepileptic for seizure disorders.[131] Trials have demonstrated that lamotrigine has beneficial effects on depressive symptoms in the depressed phase of bipolar disorder[132] and an earlier study demonstrated attenuation of psychotomimetic side effects to ketamine in healthy volunteers.[133] The pilot study by Mathew et al.[60] found that lamotrigine failed to reduce the transient psychotomimetic or dissociative side effects associated with ketamine use, and did not enhance its antidepressant effects. In addition, an interim analysis found no significant differences in post-ketamine time to relapse between the riluzole and placebo groups.

Building on this work, a larger 4-week, double-blind, randomized, placebo-controlled study evaluated riluzole use after a single ketamine infusion. Four to six hours after a single infusion of ketamine 0.5 mg/kg, 42 subjects with treatment-resistant MDD were randomized to double-blind treatment with either riluzole (100–200 mg/day; n = 21) or placebo (n = 21) for 4 weeks. The effect size of improvement with ketamine was initially large and remained moderate throughout the 28-day trial. Overall, 27% of ketamine responders had not relapsed by 4 weeks following a single ketamine infusion, underscoring ketamine's enduring antidepressant effects in patients with treatment-resistant MDD. The average time to relapse was 13.2 days. However, the difference between the riluzole and the placebo treatment groups was not significant, suggesting that the combination of riluzole with ketamine treatment did not significantly alter the course of antidepressant response to ketamine alone.[61] Taken together, evidence from these two studies[60,61] suggests that riluzole did

not maintain ketamine's antidepressant response. Nevertheless, this does not imply that riluzole lacked significant antidepressant effects; the above studies were conducted in treatment-resistant MDD patients, and it is possible that an antidepressant signal could be detected in less refractory patients.

4.2 NMDA NR2B Antagonists

Non-competitive NMDA receptor antagonists like ketamine and PCP can produce psychotomimetic effects when used acutely. This observation led researchers to investigate whether subtype-selective, rather than pan blockers of the NMDA receptor, could maintain an efficacious profile while minimizing the adverse effects associated with blocking this receptor. In this regard, NR2B receptors are of particular interest. In preclinical models, the NR2B antagonist Ro 25-6981 reversed stress-induced hippocampal long-term potentiation (LTP) [via foot shock stress][134] and had behavioural antidepressant-like effects in the forced swim test.[83] For a detailed review of the properties of NR2B receptors and possible approaches to their use in the development of glutamate-based therapeutics see Loftis and Janowsky[135] and Gogas.[136]

An older clinical trial studying traumatic brain injury first identified an NR2B-selective NMDA antagonist (CP-101,606) that was well tolerated and did not produce psychotropic side effects.[137] In a recent randomized, placebo-controlled, double-blind study, Preskorn et al.[62] evaluated the anti-depressant efficacy of the NR2B subunit-selective NMDA receptor antagonist CP-101,606 in treatment-refractory MDD subjects. Non-responders (n = 30) to a 6-week open-label trial of paroxetine (up to 30 mg/day) and a single intravenous placebo infusion were then randomized to a double-blind single infusion of CP-101,606 or placebo plus continued treatment with paroxetine for up to an additional 4 weeks. Of the patients receiving CP-101,606, 60% responded to the treatment versus 20% for placebo; 78% of treatment responders maintained response status for at least 1 week after infusion. However, the dose was reduced for the rest of the study because several of the research subjects experienced dissociative symptoms. Dosing was clearly an issue in this study, which led the authors to also speculate that lower doses of ketamine that do not cause psychotomimetic states may nevertheless be antidepressive, and that allosteric modulation of the NR2B antagonist "may yield a bona fide greater therapeutic index for CP-101,606 compared with ketamine."[62]

Subsequently, another small randomized, double-blind, placebo-controlled, crossover pilot study evaluated the potential antidepressant efficacy and tolerability of an oral formulation of the selective NMDA NR2B antagonist MK-0657 in patients with treatment-resistant MDD. MDD subjects underwent a 1-week drug-free period and were subsequently randomized to receive either MK-0657 monotherapy (4–8 mg/day) or placebo for 12 days. Due to recruitment challenges and the discontinuation of the compound's development by the manufacturer, only five patients completed both periods of the crossover administration of MK-0657 and placebo. Significant antidepressant effects were observed as early as day 5 in patients receiving MK-0657 compared with placebo as assessed by the Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory (BDI), the secondary efficacy scales; however, no improvement was noted when symptoms were assessed with the MADRS, the primary efficacy measure.[63] It is interesting to note that differential sensitivity to drug effects between the HAM-D and the MADRS has been well recognized in controlled clinical trials.[138] MK-0657 also significantly increased plasma BDNF levels compared with placebo after 9 days of treatment, demonstrating a biological effect typically observed with most other antidepressants.[139] No serious or dissociative adverse effects were observed in patients receiving this oral formulation of MK-0657. Despite the small sample size, the pilot study suggested that an oral formulation of the NR2B antagonist MK-0657 may have anti-depressant properties in MDD patients without psychotomimetic

effects.[63] Further studies with larger sample sizes are necessary to confirm these preliminary findings, and additional studies are necessary to further demonstrate the efficacy and safety of compounds selective for the NR2B receptor.

4.3 Other Non-Competitive NMDA Antagonists: Memantine and Amantadine

Memantine is a low-affinity, non-competitive, open-channel NMDA receptor antagonist.[140–144] This drug is FDA approved for the treatment of moderate to severe Alzheimer's disease,[145,146] with a recent extended-release formulation. In contrast to ketamine, memantine has essentially no psychotomimetic effects at therapeutic doses (5–20 mg/day); a detailed review of the associated preclinical data can be found in Parsons et al.[147]

In 2006, an 8-week, double-blind, placebo-controlled trial (n = 32) of memantine (5–20 mg/day) failed to improve depressive symptoms in patients with MDD.[57] The authors speculated that perhaps compounds such as ketamine – which have a higher affinity for NMDA receptors, stronger open-channel blocking/unblocking kinetics and slower off rates[97] – provide more antidepressant efficacy than lower affinity compounds such as memantine, which are also weaker open channel-blockers with faster off rates.[148] Another recent 8-week, proof-of-concept study (n = 29) similarly failed to show a statistically significant benefit for memantine augmentation (5–20 mg/day) of lamotrigine (stable dose of at least 100 mg/daily for 4 weeks prior to randomization) for patients with bipolar depression. However, memantine had a significant antidepressant effect early during the course of treatment (up to 4 weeks), during its titration. The authors speculated that these effects might be due to a plateau effect from compensatory mechanisms within the glutamate system, or to dose-related effects.[58] Another 12-week, double-blind, placebo-controlled pilot study (n = 35) evaluated memantine (10 mg twice daily) for late-life depression and apathy after a disabling medical event and found that it did not improve affective or functional outcome compared with placebo.[59]

In contrast, a larger Finnish study (n = 80) evaluated alcohol-dependent patients with MDD who were randomized to memantine 20 mg/day or escitalopram 20 mg/day.[149] Memantine has been shown to reduce alcohol cravings in pre-clinical studies,[150–153] and alcohol dependence is known to be co-morbid with MDD.[154,155] In the Finnish study, abstinence was not required and both treatments significantly reduced depression and anxiety (primary outcome measures) without significant differences in treatment groups or in cognitive functioning scores.[149] It should be noted that long-term alcohol use increases the number,[156] and alters the function, of glutamate NMDA receptors.[157] Alcohol dependence might therefore be involved in the antidepressant response of NMDA receptor antagonists, given that treatment with glutamate antagonists decreased ethanol seeking and relapse behaviour in rats.[158] Interestingly, a 7-day, placebo-controlled, randomized, single-blind psychopharmacology study (n = 127) that used three different antiglutamatergic strategies (lamotrigine 25 mg 4 times per day, memantine 10 mg 3 times per day or topiramate 25 mg 4 times per day) for ethanol detoxification found that all three significantly improved alcohol withdrawal symptoms and dysphoric mood.[159]

Amantadine, another NMDA receptor antagonist,[160] has been used as an antiviral agent since 1996 against influenza-A viral infections. It should be noted that amantadine appears to act through several pharmacological mechanisms (e.g. serotonergic, dopaminergic, monamine-oxidase, etc.) and has also shown effectiveness in Parkinson's disease, traumatic head injury and other neurological conditions.[161] Preclinical models have shown synergistic antidepressant-like behavioural effects and influence on immuno-endocrine parameters (e.g. plasma corticosterone levels, interleukin [IL]-10 production) with amantadine combination treatment.[162–164] Clinically, interest in its antidepressant qualities

were piqued because of its remarkable effect in depressed patients with Borna disease virus (BDV) infection; one study (n = 25) demonstrated a 68% reduction in depressive symptoms in 2.9 weeks (100–300 mg/day).[165,166] Other clinical trials have been quite limited and have primarily used amantadine as an augmentation strategy (up to 300 mg/daily) in treatment-resistant MDD, with some modest effects. Side effects included dry mouth and sedation.[167,168] Larger and better designed studies are needed to evaluate the anti-depressant effects of amantadine.

5. Neurobiology of Ketamine

5.1 Molecular Mechanisms Associated with Ketamine's Antidepressant Effects

Building on the remarkable clinical observations described above, both preclinical and human studies are exploring the cellular and molecular mechanisms associated with ketamine's antidepressant actions. In particular, recent well designed experiments[105,108,169] have demonstrated that ketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway, leading to increased synaptic signalling proteins, spine plasticity (maturation/shape formation) in the PFC, and antidepressant-like behaviours in rodents. mTOR is a multi-effector serine/threonine protein kinase involved in translation control and long-lasting synaptic plasticity; dysregulation of its signalling cascade has been hypothesized to be a common pathophysiological feature of neuropsychiatric disorders.[170] Phosphorylation of Akt (or protein kinase B) is thought to more directly activate mTOR. Akt, in turn, is activated by neurotrophic factor signalling cascades, including phosphoinositide-3 kinase (PI3K)-phosphoinositide-dependent kinase 1 (PDK1) and by extracellular signal-regulated protein kinase (ERK) pathways.[170,171]

Specifically, ketamine was found to transiently increase the phosphorylated and activated forms of eukaryotic initiation factor 4E binding protein 1 (4E-BP1), p70S6 kinase (p70S6K) and mTOR.[105] These proteins are all involved in the mTOR-signalling pathway and serve as prominent regulators of protein translation. The same study further demonstrated that inhibition of the kinases Akt and ERK – both of which are ubiquitous mediators of synaptic plasticity – eliminated ketamine's ability to stimulate the phosphorylation of mTOR, p70S6 kinase and 4E-PB.[105] Interestingly, the mTOR pathway showed specificity, as it was not activated by single or repeated doses of two commonly used antidepressant drugs or by ECT.[105,172] While acute activation of mTOR might be related to the rapid antidepressant effects of ketamine, it should be noted that the extant literature suggests that chronic mTOR activation may lead to deleterious effects, particularly inhibition of autophagy (the ability of a cell to manage build-up of aggregate proteins and toxic substances), ultimately leading to reduced cellular resilience.[173,174]

Beurel et al.[175] recently showed that GSK-3 inhibition also contributed to the rapid anti-depressant-like effects of ketamine in a model of learned helplessness and knock-in preclinical models. Considerable previous evidence implicates deficient GSK-3 serine-phosphorylation in vulnerability to mood-related behavioural disturbances.[176–179] Consequently, modulating GSK-3 by serine-phosphorylation has been suggested as an important mechanism for mood regulation.[180] Beurel et al.[175] showed that GSK-3 inhibition was evident in the hippocampus and the PFC 30 and 60 minutes after ketamine infusion, echoing prior studies of the antidepressant effects of ketamine.[105] Other studies have noted the potential involvement of Akt,[171] which is activated by ketamine[105] and known to regulate GSK-3.[181] These findings may encourage the application of specific GSK-3 inhibitors or small molecular compounds to this site for rapid antidepressant effects.[175] Nevertheless, GSK-3 inhibition may have limitations because of its involvement in diverse pathways that contain multiple substrates, which may lead to side effects or toxicity.[182]

Another recent study demonstrated that the antidepressant effects of ketamine were associated with the rapid synthesis of BDNF in the hippocampus of mice. The results demonstrated that ketamine blockade of NMDA receptors at rest deactivated eukaryotic elongation factor 2 (eEF2) kinase (a key mediator of ribosomal translocation) resulting in reduced eEF2 phosphorylation and increased BDNF translation.[169] More importantly, eEF2 inhibitors in the study exerted antidepressant-like effects in the forced swim test after 30 minutes, a timescale comparable to that of ketamine. No such response was observed in the BDNF knockout mice, which suggests that BDNF expression following eEF2 inhibition is required to produce an antidepressant-like response. Interestingly, the study was not able to detect ketamine-induced mTOR signalling, or rapamycin (an mTOR inhibitor) blockade of the behavioural actions of ketamine.[169] Some reasons explaining the lack of ketamine-induced mTOR signalling[169] compared with earlier findings[105] include differences in measurement (homogenates of hippocampus vs synaptosome-enriched fractions of PFC), earlier time of analysis (30 minutes after ketamine infusion) and systemic administration of an mTOR inhibitor versus intra-cerebroventricular (ICV) administration.[171] Given that the prior mTOR study[105] examined molecular effects 2 hours after drug treatment and behavioural effects 24 hours after drug treatment,[105] Autry et al.[169] concluded that the role of mTOR in the antidepressant effects of ketamine may be one of maintenance rather than rapid induction.

Another study demonstrated that knock-in mice with the (BDNF) Val66Met polymorphism – particularly those expressing the BDNF Met allele –had loss of synaptogenic and antidepressant actions in pyramidal cells in the PFC with low-dose ketamine.[108] The Val66Met single nucleotide polymorphism (SNP) is found in approximately 20–30% of humans[183] and results in decreased trafficking into the regulated secretion pathway and impaired activity-dependent release of BDNF.[184] The $BDNF_{Met}$ allele has also been linked with select learning and memory impairments[185] as well as vulnerability to psychiatric disorders.[186–191]

Despite the work described above, and an earlier finding demonstrating that acute administration of ketamine increases BDNF levels in rodent models,[104] the role of BDNF expression and ketamine is decidedly mixed. For example, other studies using repeated daily dosing of ketamine found no alterations in hippocampal BDNF levels.[103,107] Clinically, one recent study (responders vs non-responders) found that ketamine's rapid initial antidepressant effects were not mediated by peripheral measures of BDNF,[192] while another study evaluating chronic ketamine drug users showed elevated levels of peripheral BDNF;[193] however, it should be noted that in the latter study, most of the ketamine users were also polydrug users. Also, as discussed earlier, studies conducted with both ketamine and the AMPA receptor potentiator LY 451646 demonstrated that BDNF signalling or TrkB phosphorylation did not play a role in its antidepressant effects.[91] These findings[91] are not consistent with the hypothesis that BDNF, via TrkB (tyrosine kinase), activates the mTOR pathway.[194–196]

Lastly, a recent study[197] (n = 62) demonstrated that patients carrying a BDNF Met substitution (Val/Met and Met/Met) had an attenuated anti-depressant response to ketamine infusion compared with Val/Val patients. The study specifically examined whether the rs6265 (Val66Met SNP) was associated with response to ketamine in patients experiencing a major depressive episode. Results showed a 24% (SD ± 31) improvement for Met carriers versus 41% (SD ± 24) for Val carriers from baseline HAM-D score to 210/230 minutes post-infusion. While limitations of the results include the inability to correct for population stratification and the small sample size, this study builds on prior preclinical data,[108] with Liu et al.[198] showing that homozygous Val/Val mice exhibited a stronger neural response

(prefrontal cortex synaptogenesis) and antidepressant effect to ketamine on the basis of this single polymorphism.

It is also interesting to note that – although data are mixed – three studies[89,105,169] reported that the molecular and behavioural effects of ketamine were blocked by an AMPA receptor antagonist.[199] A recent human study corroborates the importance of enhanced non-NMDA receptor-mediated synaptic potentiation as central to the mechanism of action of ketamine as demonstrated by MEG.[200] These findings highlight the significance of AMPA receptor signalling for enhancement of synaptic plasticity,[54,79] where novel classes of AMPA potentiators (allosteric modulation) may play a key role in future treatments.[201] Finally, continued and improved understanding of the complex regulatory mTOR translational system and its role in synaptogenesis may continue to elucidate the underlying mechanisms of future rapid-acting and efficacious antidepressant treatments.

5.2 The Role of Inflammation and Ketamine

Given that MDD is a heterogeneous condition with differing underlying aetiologies, the disorder has also been associated with chronic, low-grade inflammation and cell-mediated immune (CMI) activation (the part of the immune system that involves interactions between different immune cells).[202–206] Paralleling the above research are continued findings of reduced neurogenesis, increased neurodegeneration and the overall neuro-progressive nature of MDD that is likely enhanced by these inflammatory processes.[207–210] These effects appear to be in part mediated by increased levels of interferon (IFN)-γ, IL-2 and pro-inflammatory cytokines (e.g. IL-1, IL-6 and tumour necrosis factor [TNF]-α),[211] as well as newer pathways, such as the activation of indoleamine 2,3-dioxygenase (IDO), which can indirectly lower brain concentrations of tryptophan and serotonin[212] and elevate the production of detrimental tryptophan catabolites, such as kynurenine and quinolinic acid (a strong agonist of the glutamatergic NMDA receptor).[213] Given the broad scope of research in this field, the interested reader is referred to several reviews detailing the mechanistic explanations of cell-mediated activation, inflammation, immune-mediated alteration of serotonin and glutamate, and other neuroprogressive processes in MDD.[211,214,215]

Subanaesthetic doses of ketamine dose-dependently suppressed TNFα and IL-6 in *in vivo* pre-clinical models.[216–218] Another study found that ketamine had hepatoprotective effects, mediated at least in part via reduced COX-2 and inducible nitric oxide synthase (iNOS) protein – both are regulated by changes in nuclear factor kappa B (NFκB) binding activity.[219] Recent data again demonstrated that ketamine inhibited transcription factor NFκB and activator protein (AP)-1, which regulate production of proinflammatory mediators.[220] These relationships are significant as prior evidence has shown that TNFα and signalling pathways that modulate NFκB activity play prominent roles in the regulation of hippocampal synaptic plasticity.[221] NFκB signalling has been implicated in regulation of neurogenesis, particularly axon initiation, elongation, guidance and branching, dendrite arbor size and complexity, and dendritic spine density in adults.[222,223]

Clinically, a single low dose of ketamine 0.25 mg/kg significantly suppressed intraoperative and postoperative increases in serum IL-6 in a randomized, double-blind study of patients undergoing coronary artery bypass surgery (CABG) with cardiopulmonary bypass. The authors note that prolonged increases in circulating IL-6 are associated with morbidity and mortality after cardiac operation and that during the first 7 days after surgery, serum IL-6 levels in the ketamine group were significantly lower than those in the control group ($p < 0.05$).[224] Another randomized, double-blind, placebo-controlled study ($n = 50$) assessing the anti-inflammatory effects of ketamine 0.5 mg/kg in cardiac surgical patients demonstrated decreased levels of increases in C-reactive protein (CRP), IL-6 and IL-10 from intensive care unit admission to post-operative day 1.[225] However, the literature is mixed,

as other studies have documented no changes in inflammatory markers in surgical settings with low-dose ketamine.[225,226] No clinical inflammatory data are currently available in trials evaluating MDD. However, continued research in this area promises to expand our understanding of ketamine's role in mediating neuroplasticity and its anti-depressant effect.

6. Conclusion

MDD is a severe medical illness that affects the lives and functioning of millions of individuals worldwide. Considerable evidence now suggests that cellular resilience and neuroplasticity contribute to the expression of affective illness.[227] This in turn provides a plausible role for implicating glutamatergic system dysregulation in the pathophysiology of mood disorders like MDD. The evidence reviewed here supports the notion that MDD is associated with abnormal functioning of the glutamatergic neurotransmitter system and continued collaboration between preclinical and clinical researchers will clarify the magnitude and extent of these abnormalities.

Given the mismatch between our ever-expanding knowledge of the glutamatergic system and the slow pace of therapeutic development, there is a clear need for improved compounds and pre-clinical models to treat MDD. For an excellent discussion of the barriers to clinical translation using glutamatergic targets and future drug development, see Javitt et al.[228] In addition, continuing proof-of-concept studies should be encouraged to identify relevant therapeutic targets. More notably for MDD, ketamine may well be the prototype for the next generation of rapid-acting novel antidepressants. In the setting of declining pharmaceutical industry involvement and the increasing cost of clinical studies, traditional clinical development should also look at implementing more adaptive design tools to maximize the use of knowledge accumulated via preclinical studies.[229] The development of innovative, safe and effective agents for the treatment of MDD will have an important impact not only on public health worldwide, but for the many individual patients and their families who struggle with this debilitating illness.

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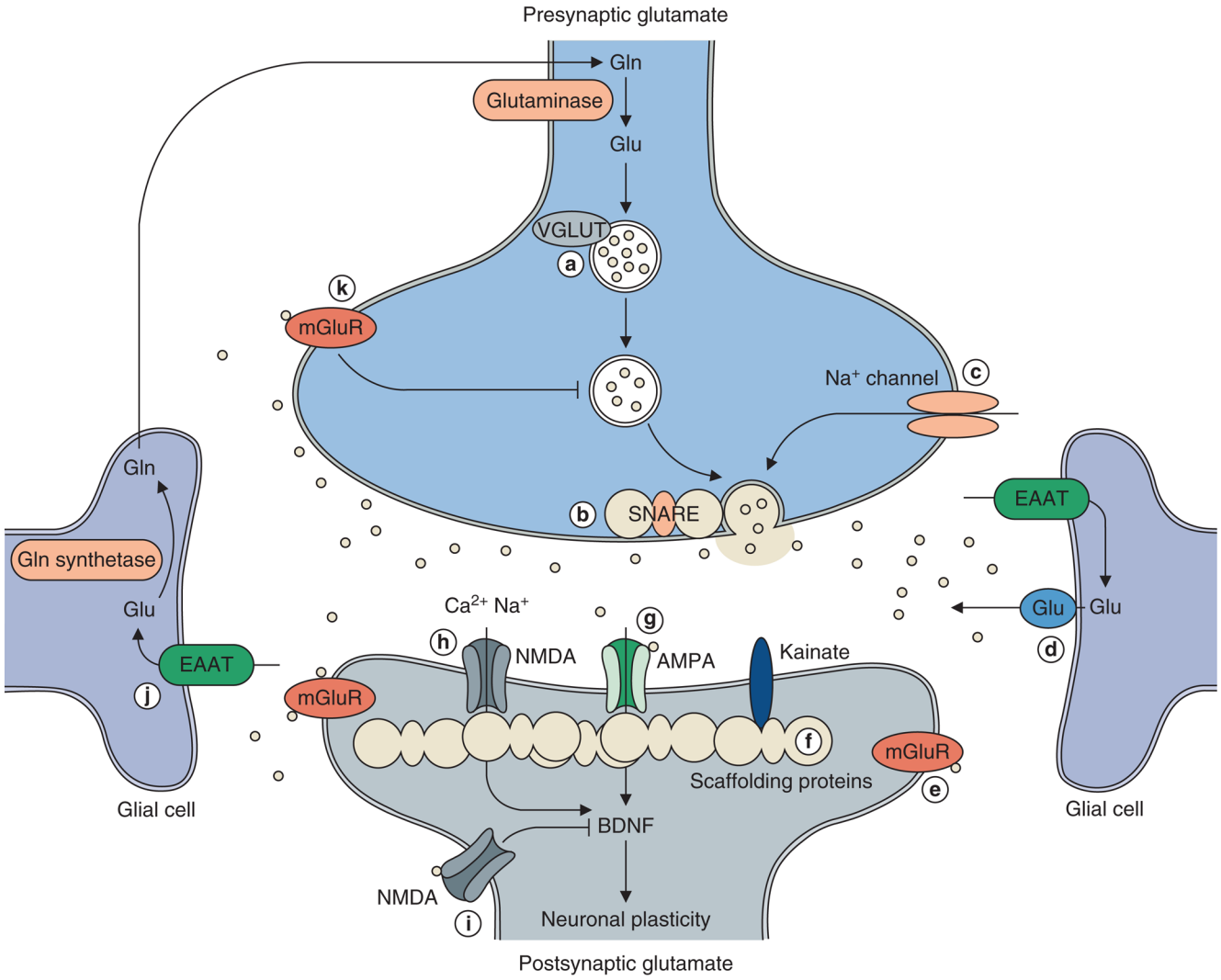

Fig. 1.

Glutamatergic neurotransmission and potential targets for drug development. Tight physiological control is maintained over glutamatergic neurotransmission. Gln is converted to Glu by glutaminase, though it can also be derived from the TCA cycle (not shown). Glu is packaged into presynaptic vesicles by VGLUT proteins and released from the neuron in an activity-dependent manner through interactions with SNARE proteins. Glu is cleared from the extracellular space by EAATs present predominantly on glia. In glial cells, Glu is converted to Gln by GS. A variety of Glu receptors are present on presynaptic and postsynaptic neurons as well as on glial cells. These include both ionotropic receptors (AMPA, NMDA and kainate), as well as mGluRs. The effect of Glu is determined by the receptor subtype, localization and interactions with various scaffolding and signalling proteins in the postsynaptic density. Activation of Glu receptors results not only in rapid ionotropic effects, but also in long-term synaptic plasticity. Potential targets for drug development numbered in the figure: (**a**) modulation of presynaptic vesicular loading of Glu; (**b**) modulation of presynaptic vesicular Glu release; (**c**) voltage-dependent Na^+ channel modulation that regulates Glu release; (**d**) modulation of extrasynaptic Glu release; (**e**) and (**k**) mGluR modulation (mGluR2/3 receptor antagonists have demonstrated antidepressant activity, mGluR2/3 agonists have demonstrated anxiolytic activity); (**f**) interactions with

scaffolding and signalling proteins; (**g**) AMPA receptor modulation; (**h**) and (**i**) NMDA receptor modulation; (**j**) facilitation of Glu clearance via EAATs. **AMPA** = α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; **BDNF** = brain-derived neurotrophic factor; **Ca** = calcium; **EAAT** = excitatory amino acid transporter; **Gln** = glutamine; **Glu** = glutamate; **GS** = glutamine synthetase; **mGluR** = metabotropic glutamate receptor; **Na**= sodium; **NMDA** = *N*-methyl-D-aspartate; **SNARE**= soluble N-ethylmaleimide sensitive factor attachment receptor complex; **TCA** = tricarboxylic acid; **VGLUT** = vesicular glutamate transporter. Reproduced from Sanacora et al.,[75] by permission from Macmillan Publishers Ltd., © 2008.

Table I

Glutamatergic targets for drug development

Glutamatergic targets	Function/role
Ionotropic receptors and subunits	
AMPA (fast) – GluR1, GluR2, GluR3, GluR4	Ligand gated ion channels; generate fast synaptic events
Kainate – GluR5, GluR6, GluR7, KA-1, KA-2	
NMDA (slow relative to AMPA) – NR1, NR2A, NR2B, NR2C, NR2D, NR3A, NR3B	
Metabotropic receptors	
Group I: mGlu1 and mGlu5	G-protein coupled receptors, mediate slower neurotransmission
Group II: mGlu2 and mGlu3	
Group III: mGlu4, mGlu6, mGlu7, mGlu8	
Transporters	
EAATs	Provide glutamate clearance from extracellular space
VGLUTs	Contribute to structural aspects of synaptic vesicle exocytosis
SNAREs	Responsible for uptake of glutamate in synaptic vesicle

AMPA = α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; **EAAT** = excitatory amino acid transporter; **GluR** = glutamate receptor; **KA** = kainate; **mGlu** = metabotropic glutamate; **NMDA** = *N*-methyl-D-aspartate; **SNARE**= soluble *N*-ethylmaleimide sensitive factor attachment receptor complex; **VGLUT** = vesicular glutamate transporter.

Table II

Glutamatergic compounds in randomized clinical controlled trials[a]

Compound (glutamatergic target/receptor)	Study design	Study population	Primary findings
Ketamine[b] (noncompetitive/high affinity NMDA receptor antagonist)			
Berman et al.[16]	pc, db, co, sd KET 0.5 mg/kg	MDD (n = 6) BPD (n = 1)	Significant improvement in depressive symptoms within 72 h after KET infusion
Zarate et al.[17]	pc, db, co, sd KET 0.5 mg/kg	TRD (n = 17)	71% met response criteria and 29% met remission criteria within 24 h of KET infusion; 35% maintained response for at least 1 wk
Diazgranados et al.[55]	pc, db, co, sd KET 0.5 mg/kg; (while on therapeutic VAL/LIT dose)	BPD (n = 17)	42% met response criteria and 31% met remission criteria within 24 h; 71% responded at some point during the trial
Zarate et al.[56]	pc, db, co, sd KET 0.5 mg/kg; (while on therapeutic VAL/LIT dose)	BPD (n = 14)	43% met response criteria and 29% met remission criteria within 24 h; 79% of subjects responded at some point during the trial
Memantine (noncompetitive/low affinity NMDA antagonist)			
Zarate et al.[57]	pc, db, 8 wk study (MEM 5–20 mg/d)	MDD (n = 32)	No difference in efficacy vs PL
Anand et al.[58]	pc, db, pg; MEM augmentation (5–20 mg/d) to LAM 100 mg or more per d, 8 wk study	BPD (n = 29)	No statistically significant benefit of MEM augmentation of LAM; p*ost hoc* antidepressant effects during initial titration (4 wk)
Lenze et al.[59]	pc, db, (MEM 10 mg bid), 12 wk study	Significant depressive/apathy symptoms by HAM-D (n = 35)	Not associated with superior affective or functional outcome vs PL in medically rehabilitating older adults with depressive and apathy symptoms
Riluzole (glutamate release inhibitor)			
Mathew et al.[60]	ran, pc, db, continuation trial of RIL 100–200 mg/d, following sd KET 0.5 mg/kg	TRD (n = 14)	No significant differences in time-to-relapse between RIL and PL groups. 65% met response with KET at 24 h
Ibrahim et al.[61]	ran, pc, db, add on RIL 100–200 mg/d after sd KET 0.5 mg/kg	TRD (n = 42)	No significant differences noted between RIL and PL treatment groups; effect size of improvement with KET was initially large and remained moderate throughout the 28 d trial
CP-101,606 (NR2B subunit-selective NMDA receptor antagonist)			
Preskorn et al.[62]	Open-label trial with PAR + db single infusion of CP-101,606 or PL	TRD (n = 30)	60% met response for CP-101,606 at d 5 primary outcome measure
MK-0657 (NR2B subunit-selective NMDA receptor antagonist [oral])			
Ibrahim et al.[63]	pc, db, co, pilot (MK-0657: 4–8 mg/d), 12 d study	TRD (n = 5)	Significant antidepressant effects were observed as early as d 5 with secondary measures (HAM-D, BDI); no effects noted with primary outcome measure (MADRS)

[a] No data from RCTs were available for amantadine (noncompetitive/low affinity NMDA antagonist).

[b] Evidence for ketamine's antidepressant effects has also been shown in several case studies and open-label investigations.

BDI = Beck Depression Inventory; **bid** = twice daily; **BPD** = bipolar depression; **co** = crossover; **db** = double blind; **HAM-D** = Hamilton Rating Scale for Depression; **KET** = ketamine; **LAM** = lamotrigine; **LIT** = lithium; **MADRS**= Montgomery–Åsberg Depression Rating Scale; **MDD** =

major depressive disorder; **MEM** = memantine; **NMDA** = *N*-methyl-D-aspartate; **PAR** = paroxetine; **pc**= PL controlled; **pg** = parallel group; **PL** = placebo; **ran** = randomized; **RCTs**= randomized controlled trials; **response** = defined as 50% reduction in symptom rating scores; **RIL** = riluzole; **sd** = single dose; **TRD** = treatment-resistant major depression; **VAL** = valproate.