HHS Public Access

Author manuscript

Prog Neurobiol. Author manuscript; available in PMC 2018 May 01.

New Targets for Rapid Antidepressant Action

Rodrigo Machado-Vieira[a,*], **Ioline D Henter**[b], and **Carlos A. Zarate Jr.**[a]

[a]Experimental Therapeutics and Pathophysiology Branch, National Institute of Health, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

[b]Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

Abstract

Current therapeutic options for major depressive disorder (MDD) and bipolar disorder (BD) are associated with a lag of onset that can prolong distress and impairment for patients, and their antidepressant efficacy is often limited. All currently approved antidepressant medications for MDD act primarily through monoaminergic mechanisms. Glutamate is the major excitatory neurotransmitter in the central nervous system, and glutamate and its cognate receptors are implicated in the pathophysiology of MDD, and in the development of novel therapeutics for this disorder. The rapid and robust antidepressant effects of the N-methyl-D-aspartate (NMDA) antagonist ketamine were first observed in 2000. Since then, other NMDA receptor antagonists have been studied in MDD. Most have demonstrated relatively modest antidepressant effects compared to ketamine, but some have shown more favorable characteristics. This article reviews the clinical evidence supporting the use of novel glutamate receptor modulators with direct affinity for cognate receptors: 1) non-competitive NMDA receptor antagonists (ketamine, memantine, dextromethorphan, AZD6765); 2) subunit (GluN2B)-specific NMDA receptor antagonists (CP-101,606/traxoprodil, MK-0657); 3) NMDA receptor glycine-site partial agonists (GLYX-13); and 4) metabotropic glutamate receptor (mGluR) modulators (AZD2066, RO4917523/ basimglurant). We also briefly discuss several other theoretical glutamate receptor targets with preclinical antidepressant-like efficacy that have yet to be studied clinically; these include α-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid (AMPA) agonists and mGluR2/3 negative allosteric modulators. The review also discusses other promising, non-glutamatergic targets for potential rapid antidepressant effects, including the cholinergic system (scopolamine), the opioid system (ALKS-5461), corticotropin releasing factor (CRF) receptor antagonists (CP-316,311), and others.

Dr. Rodrigo Machado-Vieira, MD, PhD, Experimental Therapeutics and Pathophysiology Branch, 10 Center Dr, Room 7-5341, Bethesda, MD, 20892, Tel.: 301-443-3721; fax: 301-480-8792.

1. Introduction

Depression directly affects the brain and periphery and is associated with diverse other medical comorbidities due its systemic deleterious effects. The "monoamine hypothesis" of depression—which was developed after observing the pharmacological effects of early drugs for depression—is no longer the only model capable of explaining the mechanism of action of antidepressants or for studying the underlying pathophysiology of depressive episodes in mood disorders.

Currently available conventional antidepressants unfortunately have low rates of treatment response; while one-third of patients with depression will respond to their first antidepressant, approximately two-thirds will respond only after trying several classes of antidepressants (Trivedi et al., 2006). Furthermore, therapeutic approaches must be considered not only in the context of treating acute episodes, but for relapse prevention as well as intervention in the early phases of illness. With regard to conventional antidepressants, few targets besides the monoamines and the hypothalamic pituitary adrenal (HPA) stress axis have been identified as key candidates; nevertheless, the interaction between organs, proteins, hormones, and several comorbid diseases remains complex, and results of studies investigating these targets are preliminary. Thus, there is a strong need to identify and rapidly test novel antidepressants with different biological targets beyond the classic monoaminergic receptors and their downstream targets; these agents would also be expected to act faster in a larger percentage of individuals. However, in recent years the pharmaceutical industry has been investing less in psychiatry and mood disorders as a therapeutic area. This review discusses some of the striking recent advances in the development of novel, rapid-acting antidepressants as well as the potential issues and pitfalls related to research in this field. We also present an overview of the most promising targets and approaches as well as ideas for next steps for drug development.

2. Rapid Onset of Antidepressant Action

As noted above, currently available monoaminergic antidepressants are associated with a delayed onset of action of several weeks, a latency period that significantly increases risk of suicide and self-harm and is a key public health issue in psychiatric practice (Machado-Vieira et al., 2009c). This concept of a latency period before achieving antidepressant efficacy is widely accepted despite the fact that very few trials have evaluated efficacy outcomes on a daily basis during the first week of treatment with conventional antidepressants. High rate of placebo response has also been problematic when evaluating new antidepressants. As a result, much remains unknown about the actual timing of antidepressant efficacy (that is, early improvement) for any class of standard antidepressants (Katz et al., 2004; Machado-Vieira et al., 2010); most of these data come from post-hoc analyses.

Nevertheless, several clinical studies suggest that rapid antidepressant effects are achievable in humans. This lends an additional urgency to the development of new treatments for depression that target alternative neurobiological systems, particularly for those subgroups of patients who do not respond to any currently available pharmacological agents. New

therapeutics could significantly lower morbidity and mortality for both major depressive disorder (MDD) and bipolar disorder (BD) and commensurately minimize or prevent disruption to personal, family, and occupational life and functioning as well as lower risk of suicide. In addition, the neurobiological impact of cumulative exposure to depression would be minimized, which might result in less chronicity and fewer recurrences. It should also be noted that new insights into the potential association between early improvement and long-term outcomes would be helpful tools in clinical practice; knowledge gleaned from such studies could be used in the context of personalized medicine. Indeed, identifying new targets for rapid antidepressant efficacy seems to be a relevant approach not only in treatment-resistant cases but also for the initial treatment of patients who respond well to conventional monoaminergic antidepressants and are, as a result, expected to wait several weeks for therapeutic effects to manifest. Nevertheless, developing agents that exert rapid antidepressant effects remains difficult. Perhaps the most significant challenge is dealing with the gap between rapid antidepressant response, long-term treatment, and maintenance therapy after response and remission.

In the context of developing novel therapeutic targets for depression, glutamate and other ionic channel receptors seem to induce faster biological effects at intracellular downstream targets and currently represent the most promising targets for drug development. Rapid improvement is a key paradigm for achieving fast relief of symptoms and, in some cases, preventing new episodes when prodromal symptoms are observed; this paradigm is similar to that seen for other medical illnesses such as asthma, migraine, and atrial fibrillation. Below, we discuss the concept of rapid antidepressant action and present findings and perspectives related to modulation of the glutamatergic system by ketamine and other subunit-specific glutamate modulators. We also describe the molecular pathways and downstream-related targets associated with the regulation of rapid antidepressant action in diverse neurotransmitter and neuromodulatory systems.

3. Regulation of Glutamate Ionotropic Receptors (NMDA, AMPA) in the context of Rapid Antidepressant Effects: General Overview

Glutamate is the main excitatory neurotransmitter in the mammalian brain. Roughly one-third of central nervous system (CNS) neurons use glutamate and, in combination with other excitatory neurotransmitters, it plays a key role in memory, learning, and neuroplasticity (Machado-Vieira et al., 2012; Machado-Vieira et al., 2009b); broadly, the term neuroplasticity includes changes in gene regulation and intracellular signaling cascade, variations in neurotransmitter release, modifications of synaptic number and strength, modeling of dendritic and axonal architecture and, in some areas of the CNS, the generation of new neurons (Machado-Vieira et al., 2008). Glutamate is also crucial to dendritic spine formation remodeling, influencing the density and morphology of dendritic spines. Indeed, changes in glutamate levels could contribute to abnormalities in dendritic spines and may represent a therapeutic target for rapid-acting glutamate modulators.

Glutamate neurons are present in high densities in the cortex as well as in subcortical structures such as the cerebellum, hippocampus, thalamic nuclei, and caudate nucleus.

Glutamate is generated from α-ketoglutarate, an intermediate in the Krebs cycle, and is packed into secretory vesicles in the presynaptic neuron by a family vesicular glutamate transporter. Alternative sources of glutamate include enzymatic reactions regulated by glutamate dehydrogenase (GDH) and aminotransferases; in particular, alanine-aminotransferase (ALAT), aspartate aminotransferase (AAT), and the branched chain aminotransferase (BCAAT) are most likely to be involved in glutamate biosynthesis (Schousboe et al., 2013). Glutamate is subsequently released pre-synaptically into the synaptic cleft and activates both ionotropic and metabotropic glutamate receptors on astrocytes and in pre- and postsynaptic neurons. Glutamate receptor subtypes involve ligand-gated ion channels (N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors) as well as the eight G-protein coupled metabotropic receptors (mGluRs). Glutamate is not metabolized by any process; its concentrations are tightly regulated by glutamate reuptake transporters localized on neurons and glia (Danbolt, 2001).

The NMDA receptor is activated by glutamate in the presence of a co-agonist D-serine or glycine and blocked by extracellular magnesium. Only depolarization induced by AMPA receptor activation releases magnesium-induced blockade from the NMDA receptor pore, thus allowing the flow of other electrolytes (e.g., calcium) (Lai et al., 2014; Machado-Vieira et al., 2009b).

The NMDA channel includes a combination of GluN1, GluN2, GluN2B, GluN2C, GluN2D, GluN3A, and GluN3B receptor subunits. Two molecules of glycine and two of glutamate are required for ion channel activation. Other identified sites include the "s" and phencyclidine (PCP) sites. Several drugs that bind to the PCP site are defined as noncompetitive NMDA receptor antagonists. These include dizocilpine (MK-801), PCP, and ketamine. The AMPA channel is composed of the glutamate receptor GluA1, GluA2, GluA3, and GluA4 subunits, which have lower affinity for glutamate than NMDA receptors. Within the tripartite glutamate synapse and its circuitry (Machado-Vieira et al., 2009b), a complex and intricate dynamic interaction exists between ionotropic glutamate receptors and mGluRs with regard to the reuptake and transport of glutamate as well as the glutamate/glutamine recycling mechanism (Machado-Vieira et al., 2009b). Indeed, the glutamate system is far more complex than the monoaminergic system. Both ionotropic glutamate receptors and mGluRs have a wide range of effects, enzymes, downstream targets, and proposed biological models. This complexity is one of the main reasons why some glutamate modulators are so effective in treating mood disorders (eg, ketamine, lamotrigine), while others appear not to work (eg, memantine, riluzole).

4. AMPA and NMDA Receptors: Specific Findings in Mood Disorders Research

Preclinical evidence suggests that the glutamatergic system in general—and the NMDA and ionotropic receptors in the tripartite glutamatergic synapse in particular—may be central to both the pathophysiology of MDD and the mechanism of action of antidepressants (Skolnick, 1999, 2002; Skolnick et al., 1996). Most of the evidence pertaining to the

pathophysiology of mood disorders supports the presence of increased glutamate levels and activity in the brain and periphery (Zarate et al., 2010). Some researchers have hypothesized that NMDA could even represent a convergent mechanistic target for the antidepressant action of conventional antidepressants and mood stabilizers as well as novel experimental therapeutics, given that previous studies found that chronic treatment with various classes of antidepressant agents affected—predominantly by antagonizing—NMDA receptor function (Skolnick, 1999). Chronic and acute conventional antidepressants have also widely been reported to directly target NMDA receptors and dampen the presynaptic glutamate release induced by acute stress or in physiological circumstances.

In the search for novel, rapid-acting therapeutic targets, the major obstacles to success have included difficulty establishing the clinical validity of a particular target and the limited predictive value of pre-clinical models for mood disorders (Paul et al., 2010). Nevertheless, preclinical studies have noted several intriguing findings. For instance, chronic treatment with conventional antidepressants reduced the number of cortical β-adrenoreceptors (Koshikawa et al., 1989; Vetulani, 1984). In addition, the NMDA antagonists MK-801 (a non-competitive antagonist) and 1-aminocyclopropanecarboxylic acid (ACPC; a partial agonist at the glycine or co-activator site) both reduced [^{3}H] dihydroalprenolol binding to β-cortical adrenoreceptors (Klimek and Papp, 1994; Paul et al., 1992). Imipramine had similar effects (Klimek and Papp, 1994). Glutamate microinjections in the prefrontal cortex (PFC) aggravated learned helplessness in rats one and 72 hours post-administration (Petty et al., 1985). Conversely, antidepressant administration affected NMDA binding profiles and receptor function (Mjellem et al., 1993). Chronic antidepressant administration also induced adaptive changes in ligand binding at the NMDA receptor glycine site (Nowak et al., 1993). In vitro, tricyclic antidepressants (TCAs) directly interacted with the NMDA receptor complex to block NMDA's actions. One early study reported that, similar to zinc, imipramine and desipramine slowed the dissociation rate of [^{3}H] MK-801 binding; zinc is thought to act noncompetitively at a site outside the channel (Reynolds and Miller, 1988). TCAs appear to be less potent when magnesium and L-glutamate are added (Sills and Loo, 1989); they also appear to be selective for the low-affinity state of the PCP binding site. Citalopram, fluoxetine, sertraline, and TCAs such as amitriptyline and imipramine all enhanced MK-801-induced locomotor effects (Maj et al., 1991).

Research using several animal models has also demonstrated that NMDA receptor antagonists induce antidepressant-like effects (Layer et al., 1995; Meloni et al., 1993; Moryl et al., 1993; Papp and Moryl, 1994; Przegalinski et al., 1997; Trullas and Skolnick, 1990). For instance, in male Wistar rats a single dose of the NMDA antagonist ketamine interfered with induction of behavioral despair for up to 10 days post-administration (Yilmaz et al., 2002). Studies from our laboratory found that in rats, a single dose of ketamine (2.5 mg/kg) resulted in sustained antidepressant effects lasting approximately one week (Maeng et al., 2008). Another study found that a single pretreatment dose with the NMDA antagonist MK-801 induced a lasting sensitivity to the second administration of the same agent four, seven, or 14 days later (O'Neill and Sanger, 1999). Interestingly, antidepressant-like behavioral responses were observed in mice lacking interneuronal NMDA receptors, supporting the notion that NMDA antagonism is not the only mechanism involved in ketamine's rapid antidepressant effects (Pozzi et al., 2014). The role of glutamatergic

dysfunction in depression is further supported by findings that repeated antidepressant administration regionally altered mRNA expression encoding multiple NMDA receptor subunits (Boyer et al., 1998) as well as radioligand binding to these receptors within particular areas of the CNS (Skolnick, 1999). Relatedly, enhanced glutamate levels and fewer hippocampal NMDA receptors were observed in postmortem studies of individuals with mood disorders (Hashimoto et al., 2007; Scarr et al., 2003). However, it should be noted that excessive glutamate levels (caused by stress) in MDD have been associated with decreased brain volume and plasticity (Sanacora et al., 2012); glutamate antagonists, including ketamine, could reverse these deleterious effects.

In preclinical studies, the rapid antidepressant effects of ketamine appeared to involve the activation of AMPA receptors. Increased glutamatergic activity seems key to this effect, given that AMPA receptor antagonists blocked ketamine's antidepressant effects in preclinical studies (Autry et al., 2011; Duman and Aghajanian, 2012; Koike et al., 2011; Maeng et al., 2008). Specifically, pre-treatment with NBQX, an AMPA receptor antagonist, blocked ketamine's molecular and behavioral effects (Maeng et al., 2008; Zhou et al., 2014). In support of this model, increased hippocampal AMPA/NMDA receptor density ratio was observed after ketamine treatment in rodents (Tizabi et al., 2012). In the same context, low-dose ketamine enhanced glutamate activity in the PFC, activating synaptic function. This, in turn, was proposed to activate AMPA signaling (Autry et al., 2011; Maeng et al., 2008). These data support the notion that ketamine exerts rapid antidepressant-like effects by enhancing AMPA relative to NMDA throughput in critical neuronal circuits and molecular pathways and targets. Given the supported key role for AMPA in the rapid efficacy of ketamine, several new pharmacological approaches were developed and tested that target AMPA receptor function and levels. These AMPAkines, also known as AMPA positive allosteric modulators, are described in Section 8.1.

5. Ketamine as a Proof of Concept Agent in Studies of Rapid Antidepressant Action: Biological Models

Ketamine is a noncompetitive antagonist; it binds within the ion channel and blocks the influx of diverse ions. Ketamine is called a "trapping blocker" of the NMDA channel. It acts as a non-competitive NMDA receptor antagonist, which means that it only blocks the receptor when the channel is open after activation. Evidence from different models suggests that several molecular mechanisms are associated with ketamine's plasticity-inducing effects. For instance, studies of diverse proteins and intracellular signaling cascades suggest that increased neuroplasticity and synaptogenesis are key convergent downstream targets for rapid-acting agents. Links are also believed to exist between the neuroplasticity hypothesis of depression and the glutamate hypothesis of rapid antidepressant action. Improved neuronal plasticity (e.g. synaptogenesis, neurogenesis, dendritic remodeling, etc) appears to be a target for ketamine, and may reverse the deleterious effects of long-term depression such as reduced cellular resilience and stress in the hippocampus and PFC (Duman and Duman, 2015).

A full review of the evidence for ketamine's antidepressant effects is beyond the scope of this manuscript. We refer interested readers to several excellent comprehensive reviews on ketamine trials in depression (Abdallah et al., 2015; Coyle and Laws, 2015). Instead, this manuscript will focus on the neurobiological basis of rapid antidepressant action as well as alternative targets with a focus on ketamine as a proof-of-concept agent.

The hypothesis of glutamate hyperfunction for mood disorders—which differs from the hypothesis of glutamate hypofunction in schizophrenia—posits that these elevated glutamate levels may revert to normal as a result of the increased extracellular glutamate levels observed after low-dose ketamine; this effect is thought to be due to the disinhibition of pyramidal neurons mediated by the NMDA antagonism of inhibitory interneurons (Ohgi et al., 2015). Ketamine selectively induces antagonistic effects in the presence of excessive NMDA activation (Mealing et al., 1999), with a consequent increase in extrasynaptic glutamate and activation of plasticity pathways; notably, this should not be misinterpreted as glutamate hyperfunction. Indeed, transient increases in glutamate release may represent an upstream event; evidence from ^{13}C-magnetic resonance spectroscopy (MRS) (Chowdhury et al., 2012) and microdialysis (Moghaddam et al., 1997) studies support the notion that ketamine dose-dependently affects glutamate efflux. Lower Glx (a combined measure of glutamate and glutamine) levels have also been identified in imaging studies in depression (Dutta et al., 2015), and these seem to be reversed by ketamine, which prevents overstimulation of NMDA receptor or glial dysfunction.

Some investigators have suggested that ketamine's psychotomimetic effects may be related to its higher affinity for the NMDA receptor subunits GluN1 and GluN2 (Dutta et al., 2015). Interestingly, research shows that ketamine's rapid antidepressant effects are strongly predicted by its dissociative side effects (Luckenbaugh et al., 2014); both of these support the role of GluN1 and GluN2a in ketamine's rapid antidepressant efficacy. While ketamine's psychotomimetic effects could briefly mimic antidepressant effects, the fact that ketamine's antidepressant efficacy goes much beyond its short half-life suggests consistent downstream effects (beyond NMDA antagonism per se) that may explain its relatively sustained response. However, drugs with psychotomimetic side effects cannot be used in subjects with a history of psychosis (because of concerns that these may worsen or restart a psychotic state).

Although NMDA antagonism seems to mediate the antidepressants effects of ketamine, one key question remains. Why do other NMDA antagonists that also share comparable pharmacodynamics with ketamine not have similar rapid antidepressant efficacy (Emnett et al., 2013; Smith et al., 2013; Zarate et al., 2006)? Like ketamine, conventional antidepressants also reverse stress-induced reductions in dendritic arborization due to excessive glutamate levels and consequent neurotoxicity (Duman, 2009). Interestingly, early studies showed that conventional antidepressants decreased NMDA binding (Nowak et al., 1998; Paul et al., 1994; Skolnick et al., 1996). This further supports the notion that ketamine's rapid antidepressant effects are due to more than simple NMDA antagonism.

6. Ketamine's Effects on Synaptogenesis, mTOR, and Intracellular Signaling: Potential Therapeutic Implications

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that regulates cellular metabolism, growth, and survival as well as protein synthesis and transcription (Duman et al., 2012; Machado-Vieira et al., 2015). The mTOR pathway is altered in other illnesses such as obesity and diabetes, as well as in ageing and stress-related disorders (Zoncu et al., 2011). Reduced mTOR signaling has been observed in the PFC and periphery of subjects with mood disorders (Jernigan et al., 2011; Machado-Vieira et al., 2015), and ketamine has been shown to activate mTOR pathway-induced synaptogenesis, with consequent activation of other neuroprotective and neurotrophic downstream targets associated with mood disorders (eg, cyclic adenosine monophosphate response element-binding protein (CREB), brain derived neurotrophic factor (BDNF), and the Wnt pathway). Several case reports have also reported increased mTOR phosphorylation in peripheral cells after acute ketamine administration in individuals with MDD (Denk et al., 2011; Yang et al., 2013). Interestingly, mTOR inhibition by rapamycin reversed ketamine's antidepressant effects in preclinical models (Yu et al., 2013). Ketamine also stimulated mTOR signaling; the consequent rapid antidepressant action was hypothesized to depend on AMPA receptor activation (Duman et al., 2012), supporting the notion that AMPA receptors play a crucial role in ketamine's rapid antidepressant effects (see Section 4). In addition, ketamine also had antidepressant-like effects in preclinical models and increased hippocampal and prefrontal cortical mTOR levels; in contrast, pretreatment with the AMPA antagonist NBQX significantly reduced these antidepressant-like effects, and concomitantly decreased levels of mTOR and BDNF (Zhou et al., 2014).

Other researchers have proposed that increased extrasynaptic glutamate levels may activate its presynaptic receptors, thus limiting synaptic glutamate transmission. In turn, glutamate transmission may be even more disrupted by the induced loss in dendritic spines. In preclinical studies, ketamine was shown to selectively counteract these deleterious effects at the synaptosome level. Regarding the induction of synaptogenesis by ketamine, recent studies found that increased spine-remodeling and synaptic plasticity mediated the antidepressant-like effects of ketamine in preclinical models, particularly through actions at the mammalian target of rapamycin complex1 (mTORC1) signaling pathway (Li et al., 2010). However, translating these findings into potential drug development in humans is complicated because mTOR is a critical effector in cell-signaling pathways that are commonly deregulated in human cancers (Guertin and Sabatini, 2007). Thus, its activation may result in the overexpression of undesirable proteins and cascades.

Interestingly, the mTOR inhibitor rapamycin suppressed antidepressant response to ketamine. This action involved the blockade of p70S6 kinase activation and limited the expression of synaptic proteins (Chung et al., 1992; Heitman et al., 1991; Tizabi et al., 2012). In preclinical models, mTOR allowed synaptic protein translation by inhibiting the inhibitory 4E binding proteins (4E-BPs) and activating p70S6 kinase (Hoeffer and Klann, 2010; Livingstone et al., 2010). Upregulation of the synaptic plasticity markers activity-regulated cytoskeleton-associated protein (Arc), GluA1, postsynaptic density protein 95

(PSD95), and synapsin I were also observed with ketamine. Similarly, mTOR targets the suprachiasmatic nucleus (the central regulator of circadian rhythms to light in mammals) and was found to reset the circadian clock by modulating the circadian gene proteins PER1 and PER2 (Cao et al., 2010). In individuals who responded to ketamine, mTor also positively correlated with its downstream effectors, glycogen synthase kinase-3beta (GSK-3β) and dephosphorylation of eukaryotic elongation factor 2 (e-EF2) (Denk et al., 2011; Dwyer and Duman, 2013; Yang et al., 2013). This effect has been also associated with increased BDNF synthesis (Shah et al., 2014). Overall, dendritic spine growth, spine enlargement, and increased post-synaptic density protein levels have been observed after ketamine treatment (Li et al., 2010; Malenka and Bear, 2004). All three of these effects are directly modulated by mTOR pathways, suggesting that long-term potentiation as well as postsynaptic activation of neuroplasticity-related signaling pathways are involved in ketamine's rapid antidepressant effects, with consequent improvement in prefrontal synaptic connectivity.

7. Other Molecular Downstream Targets for Developing Rapid Antidepressant Treatments

As noted above, ketamine's mechanism of action goes beyond simple NMDA antagonism or even activation of the mTOR pathway (Fig. 1). It directly affects other ionic channels such as voltage-operated calcium channels (VOCC), opioid receptors, and AMPA receptors as well as monoamine and muscarinic receptors (Hirota and Lambert, 1996) and other intracellular signaling cascades associated with neuroplasticity. Other pathways associated with rapid antidepressant effects in preclinical models involve the depolarization of AMPA receptor activity to allow calcium influx and exocytosis of BDNF by activating VOCCs, thus activating downstream protein kinase B (PKB/AKT) and extracellular signal-related kinase (ERK) (Duman et al., 2012; Legutko et al., 2001). Interestingly, ketamine rapidly and transiently increased the phosphorylated and activated forms of ERK (including ERK1 and ERK2) and AKT growth factor signaling pathways (Hoeffer and Klann, 2010). Importantly, these pathways directly affect mTOR activity.

Ketamine has been also shown to regulate the neurotrophic factor BDNF (Garcia et al., 2008; Linden et al., 2000). Studies have shown that peripheral BDNF levels are increased or unaltered after ketamine treatment in patients with treatment-resistant MDD (Duncan et al., 2013; Machado-Vieira et al., 2009c). Reduced BDNF levels and expression were also found in the brain and periphery of subjects with mood disorders, and these effects seemed to be counteracted by antidepressants and mood stabilizers. One randomized trial found significantly higher plasma BDNF levels in ketamine responders than non-responders (Haile et al., 2014). Ketamine has been also shown to reduce depressive-like symptoms associated with enhanced hippocampal BDNF levels (Garcia et al., 2008). Finally, studies with knockout mice demonstrated that BDNF mediated ketamine's antidepressant-like effects (Autry et al., 2011).

Ketamine also inhibits e-EF2 kinase, a calcium-dependent protein that regulates MAP kinase and mTOR pathways. e-EF2 plays a key role in regulating synaptic plasticity in association with a concomitant increase in BDNF synthesis (Monteggia et al., 2013). The differential

clinical profile when comparing efficacy in depression among diverse NMDA antagonists has stimulated further investigation of potential alternative biological effects between different glutamatergic modulators to better understand the diverse biological actions implied by specific efficacy and clinical patterns. In this context, and in contrast to ketamine, memantine did not block e-EF2 nor alter BDNF expression. This suggests that ketamine's effects may be indirectly implicated in differential effects at neural glutamate levels as well as receptor trapping and binding (Gideons et al., 2014; Kotermanski et al., 2009). These effects seem to be related to AMPA activity and to surface expression in neurons that, in turn, stimulate quick e-EF2- and BDNF-dependent potentiation (Autry et al., 2011; Nosyreva et al., 2013).

Similarly, ketamine inhibited brain GSK-3 expression, and animals with a knock-in mutation that blocked GSK-3 phosphorylation displayed no antidepressant-like response to ketamine in the learned helplessness model (Beurel et al., 2011). Ketamine also regulates diverse genes in the circadian molecular machinery that has been shown to be disrupted in mood disorders and that is directly involved in the effects of GSK-3 (Zunszain et al., 2013). In rodent models of depression, ketamine also reversed dendritic atrophy by enhancing the number of dendritic spines and increasing hypocretin-induced post-synaptic excitatory currents (Li et al., 2011). In addition, lower spontaneous activity of gamma-aminobutyric acid (GABA)ergic interneurons and enhanced firing rate in glutamatergic pyramidal neurons in the PFC were described after ketamine use, suggesting that NMDA receptor antagonism blocks GABAergic activity with consequent increased glutamatergic transmission (Fig. 1).

Other preclinical studies using ketamine identified alternative targets (both in vitro and in vivo) that are potentially related to its efficacy. These include the opioid system (eg, sigma receptors (Robson et al., 2012)), monoamine transporters (Nishimura et al., 1998), and nucleus accumbens and ventral pallidum serotonergic 5-HT$_{1B}$ receptors in primates (Yamanaka et al., 2014). With regard to the opioid system, an interaction was observed between ketamine and μ- and κ-opioid receptors (Hirota et al., 1999; Wong et al., 1996). In addition, a preliminary PET study showed lower right habenula, insula, ventrolateral PFC, and dorsolateral PFC (dlPFC) metabolism after ketamine infusion (Carlson et al., 2013); notably, in humans, PET assessment of cerebral glucose metabolism provides a relatively specific proxy measure of glutamatergic neurotransmission. Functional neuroimaging studies also suggested that the anterior cingulate cortex (ACC) may be key to ketamine's rapid antidepressant effects (Zarate et al., 2013b), but most of these research avenues are unlikely to play a major role in target identification and drug development, in general due to the lack of receptor engagement studies and to scarce data comparing pre- vs post-treatment levels and associations with clinical outcomes.

Interestingly, preclinical studies suggest that serotonin receptors are a therapeutic target for ketamine's effects (Gigliucci et al., 2013). For instance, ketamine's antidepressant-like effects were abolished when a tryptophan hydroxylase inhibitor was used to yield serotonin-deprived rodents (Gigliucci et al., 2013).

A recent study found that higher baseline D-serine plasma levels predicted better response to ketamine in patients with treatment-resistant depression, which reinforces the potential role

of D-serine as a key regulator of response to ketamine and NMDA receptor antidepressant profile (Moaddel et al., 2015). This response seems selective to ketamine and perhaps other rapid-acting antidepressants, given that lower D- and L-serine levels were associated with reduced response to standard antidepressants (Maes et al., 1998). By reducing D-serine, ketamine decreased the activity of the NMDA receptor and, eventually, the related neuroinflammation.

8. Preclinical and Proof-of-Concept Clinical Trials with Receptor/Subunit Selective Glutamate Modulators

8.1. Ionotropic Glutamate Receptor Modulators

Early studies with ketamine (see (Niciu et al., 2014) for a recent review) inspired the pharmaceutical industry to develop similar glutamate modulators such as ketamine enantiomers. One key agent with this profile is esketamine, which acts primarily as a non-competitive NMDA receptor antagonist, but is also a dopamine reuptake inhibitor. Phase II studies of esketamine are underway using esketamine in intranasal spray form, a more feasible and rational route of administration when considering potential large-scale use (Singh et al., 2013).

Agents that target NMDA receptor subunits are also under development, and some pilot proof-of-concept trials have evaluated glutamatergic modulators (Table 1). These aim to test more specific targets within this widespread neurotransmitter system in an attempt to overcome the psychotomimetic effects associated with NMDA receptor antagonists as well as the need for IV access. Two GluN2B antagonists were tested in MDD: CP-101,606 and MK-0657. With regard to the GluN2B antagonist CP-101,606, a single infusion given as add-on therapy in individuals who did not respond to paroxetine induced an antidepressant response that lasted one week, though this response was not as robust as that of ketamine (Preskorn et al., 2008). In that study, patients were initially treated with six weeks of open-label paroxetine 40 mg/day. Non-responders (30 patients) were then randomized to IV CP-101,606 or placebo. A 60% response rate was seen for patients receiving CP-101,606 versus 20% for placebo, as assessed by the Hamilton Depression Rating Scale (HAM-D); 33% of patients met remission criteria by Day 5, and response was maintained by 78% of patients for at least one week, and by 42% of patients for 15 days after the initial dose. It should be noted that the dose was reduced to 0.5 mg/kg for 1.5 hours for half the patients because CP-101,606 caused a high number of dissociative effects at higher doses. Despite these promising preliminary findings, continued development of this compound was halted due to potential cardiovascular toxicity (specifically, QTc prolongation). Other promising subunit-specific glutamate modulators under evaluation in phase I and II trials are described in Table 1.

In monotherapy, GluN2B antagonist MK-0657 had no antidepressant efficacy in a pilot trial for individuals with treatment-resistant MDD (Ibrahim et al., 2012b). In that small, randomized, double-blind, placebo-controlled, crossover trial, oral MK-0657 was administered to individuals with treatment-resistant MDD for 12 days. Although no significant improvement was noted on the Montgomery-Asberg Depression Rating Scale

(MADRS)—the primary outcome measure—significant improvement was observed when symptoms were assessed using the HAM-D and the Beck Depression Inventory (BDI). Because only five patients were included in this analysis, additional studies with larger sample sizes are needed to definitively assess the efficacy of MK-0657. No dissociative effects were observed (Ibrahim et al., 2012b).

Another target within the NMDA receptor is the glycine site. GLYX-13 is a partial agonist at the NMDA receptor glycine binding site whose potential rapid antidepressant effects have been studied. In a phase II clinical trial (NCT01684163) as add-on treatment, a single intravenous dose of GLYX-13 had antidepressant effects within 24 hours that lasted up to seven days in MDD patients who had not responded to one or more antidepressant medications (Moskal et al., 2014). No dissociative effects were observed (Burch, 2012), suggesting that agents that target this site may induce rapid antidepressant effects without psychotomimetic effects.

AZD6765 (lanicemine) is another non-selective, non-competitive NMDA receptor antagonist with lower trapping than ketamine. Because ketamine has greater receptor affinity, AZD6765 may have reduced psychotomimetic or dissociative adverse effects while retaining antidepressant efficacy. Two small proof-of-concept studies with AZD6765 showed that a single infusion had rapid but not sustained antidepressant effects compared to placebo (Sanacora et al., 2014b; Zarate et al., 2013a); however, the antidepressant response was not as robust or sustained as that of ketamine. A subsequent, larger, six-week phase IIb trial evaluating repeated add-on AZD6765 IV infusions for three weeks (50 mg or 150 mg, 3x/week) found that it failed to separate from placebo, potentially due to the large placebo effect (Sanacora et al., 2014b). However, AZD6765 did not trigger dissociative symptoms (Sanacora et al., 2014a).

The cough suppressant dextromethorphan, a derivate of morphine with sedative and dissociative properties, is a non-selective, non-competitive NMDA receptor antagonist. It should be noted that other molecular mechanisms are also present in its mechanism of action, including sigma receptors, sigma-1, calcium channels, serotonin transporters, and muscarinic sites (Lauterbach, 2011). In animal models, dextromethorphan had antidepressant-like effects in the tail suspension test similar to those observed with both conventional and rapid-acting antidepressants such as imipramine and ketamine (Nguyen and Matsumoto, 2015). To date, no randomized controlled trials have explored dextromethorphan as monotherapy for the treatment of MDD. However, it was studied in a randomized, placebo-controlled trial as an add-on to valproic acid in BD (Lee et al., 2012); no significant group differences were seen between groups as assessed by either mean HAM-D or Young Mania Rating Scale (YMRS) scores. It has been tested in combination with quinidine (as Nuedexta) as a potential antidepressant with NMDA receptor antagonist properties. One case report found that Nuedexta had antidepressant effects in a single depressed patient with emotional lability (Messias and Everett, 2012). An open-label trial of Nuedexta in treatment-resistant MDD is ongoing (NCT01882829).

Memantine is another low-trapping NMDA receptor antagonist that showed no antidepressant response in an eight-week, placebo-controlled study in individuals with MDD

(Zarate et al., 2006). The glutamate modulator riluzole was also hypothesized to have antidepressant properties via its ability to increase glial reuptake of glutamate and AMPA receptor trafficking. While an open-label clinical trial of riluzole in MDD and bipolar depression found that riluzole had significant antidepressant effects (Zarate et al., 2005), a larger study that used riluzole as maintenance therapy for 28 days after a single IV ketamine infusion found that riluzole had no antidepressant effects (Ibrahim et al., 2012a).

Other agents currently under development that target different receptors include AMPAkines, also known as AMPA receptor positive allosteric modulators. Notably, the activation of AMPA receptor signaling plays a key role in inducing neuroplasticity and activity-dependent BDNF release (Jourdi et al., 2009). For instance, the AMPA receptor potentiator LY392098 increased BDNF expression in neuronal cultures (Legutko et al., 2001). However, at the same time, direct stimulation of AMPA receptors can be neurotoxic (O'Neill et al., 2004). To overcome this potential issue, drug development in this field has focused on the use of AMPAkines, which potentiate currents mediated by AMPA receptors. Nevertheless, success in this area has been limited by low bioavailability and potential toxicity (Menniti et al., 2013). Preclinical studies found that these agents exhibit antidepressant-like efficacy (Bleakman et al., 2007; O'Neill and Witkin, 2007), and several AMPA modulators are being developed to treat MDD, including the AMPA agonist farmampator (CX-691/ORG 2448). While older AMPAkines (e.g., levetiracetam) have shown no evidence of efficacy (Saricicek et al., 2011), several more potent compounds have been developed; these include coluracetam (BCI-540), which is in clinical trials (Dutta et al., 2015). ORG-26576, an AMPA receptor positive allosteric modulator, has also been studied. A phase Ib safety and efficacy trial found that the maximum tolerated dose (400mg po bid) of ORG-26576 demonstrated preliminary antidepressant efficacy in a small cohort (n=30) (Nations et al., 2012). Among the three doses assessed (100 mg/bid, 400 mg/bid, and placebo), however, none of the arms statistically separated over the 28-day testing period. Nevertheless, the higher dose was associated with improved speed of information processing, improved executive functioning, increased growth hormone, and decreased cortisol; no effect was seen on prolactin or BDNF levels. As is true for other glutamate modulators, replication in larger cohorts will be critical to assess the overall safety, tolerability, and antidepressant efficacy of AMPAkines.

8.2. Metabotropic Glutamate Receptors (mGluRs)

mGluRs are G protein-coupled receptors that directly affect glutamate levels and synaptic plasticity and are linked to the pathophysiology and treatment of mood disorders (Machado-Vieira et al., 2009a). They are predominantly (but not exclusively) located presynaptically at glutamatergic synapses. With the exception of mGluR1/5, their activation generally decreases neurotransmitter release, thereby limiting excitotoxic damage. To achieve efficacy, presynaptic mGluR2 agonists seem to reduce excessive glutamate release, while mGluR2/3 antagonists seem to enhance synaptic glutamate levels, commensurately boosting AMPA receptor transmission and firing rates and extracellular monoamine levels. As seen with ketamine, mGluR2/3 antagonists also directly target mTOR signaling (Dwyer et al., 2012; Koike et al., 2011).

Several mGluR2/3 antagonists, as well as the negative allosteric modulator RO4995819, were found to have antidepressant-like efficacy in rodent models of depression (reviewed in (Chaki et al., 2013)). Specifically, animal studies have noted that the increased presynaptic glutamate release induced by mGluR antagonists produced ketamine-like effects (Dwyer et al., 2012; Karasawa et al., 2005). Positive allosteric modulators do not directly activate the receptor but potentiate the response of mGluRs to glutamate. The safety and tolerability of mGluR2/3 modulators has been studied in healthy volunteers (NCT01547703 and NCT01546051) but mGluR2/3 modulators have not yet been tested in clinical trials for the treatment of MDD.

The mGluR5s are expressed pre- and post-synaptically and are involved in AMPA receptor internalization, a key mechanism for modulating synaptic plasticity (Pilc et al., 2013). mGluR5s are also physically and physiologically interconnected with NMDA receptors. Several mGluR5 antagonists were found to display antidepressant-like effects in diverse behavioral models (Chaki et al., 2013). Notably, two mGluR5 antagonists were recently tested in clinical trials for treatment-resistant MDD: AZD2066 and the mGluR5 negative allosteric modulator basimglurant (RO4917523) (Quiroz et al., 2014). Basimglurant in particular has shown promising results in two clinical trials (NCT00809562, NCT01437657) (Roche group development pipeline, http://www.roche.com/irp150128-annex.pdf). In a nine-week, double-blind, placebo-controlled study in 333 individuals with treatment-resistant MDD, basimglurant (0.5 mg or 1.5/day adjunctive to ongoing treatment with serotonin-noradrenaline reuptake inhibitors (SNRIs) or selective serotonin reuptake inhibitors (SSRIs)) (Quiroz et al., 2014) had significant antidepressant effects; further studies in depressive disorders are underway. In contrast, AZD2066 (12–18 mg/day for six weeks) as monotherapy was no more effective in patients with MDD than placebo and the SNRI duloxetine (NCT01145755).

RG1578 (an mGluR2 negative allosteric modulator) has also been tested clinically. Though preliminary results were positive, final results were disappointing (Dale et al., 2015).

9. Therapeutic Targets for Rapid Antidepressant Efficacy beyond the Glutamatergic System

9.1. Sleep Deprivation

Rapid antidepressant effects have also been observed after a night of sleep deprivation (Bunney and Bunney, 2013), but few studies have shown a potential neurobiological basis for these effects. Approximately half of patients with either MDD or bipolar depression have been found to respond positively to one night of sleep deprivation (Wu and Bunney, 1990). Although some have argued that antidepressant response to sleep deprivation is only transient and therefore not a "real" antidepressant response, evidence suggests that the antidepressant effects of sleep deprivation can be sustained with other approaches including sleep phase advancement or medications such as lithium or conventional antidepressants (Wirz-Justice and Van den Hoofdakker, 1999). One study noted that disruption in central circadian clock genes such as *BMAL1/CLOCK (NPAS2)*, which bind to enhancer boxes to

initiate the transcription of circadian genes, may be restored after a night of sleep deprivation (Bunney and Bunney, 2013).

9.2. The Cholinergic System

Another system currently under investigation as a target for rapid antidepressant effects is the cholinergic system (Drevets et al., 2013), with the underlying hypothesis being that overactive muscarinic cholinergic receptor function could lead to depression. In this context, several randomized, double-blind, placebo-controlled studies have been conducted with IV doses of the anticholinergic agent scopolamine as add-on or monotherapy in subjects with MDD or bipolar depression (Drevets et al., 2013; Jaffe et al., 2013; Khajavi et al., 2012). Scopolamine had rapid antidepressant effects equivalent to those of ketamine and, like ketamine, scopolamine's antidepressant activity is thought to be mediated by the activation of neuroplasticity (Jaffe et al., 2013). In a pilot study designed to evaluate cognitive symptoms (particularly selective attention) in depression, Furey and Drevets (2006) observed a rapid and robust antidepressant response to scopolamine, especially with a dose of 4μg/Kg (compared to 3 and 2 μg/Kg). In this pilot, double-blind, crossover placebo-controlled study of patients with MDD (n=9) and bipolar depression (n=9), scopolamine showed increased antidepressant efficacy versus placebo for depressive and anxiety symptoms (Furey and Drevets, 2006). Interestingly, the antidepressant effects of scopolamine persisted for two weeks, and repeated dosing provided additional benefit and extended response. Limitations to the use of this agent include anticholinergic side effects and the risk of psychosis at higher doses (Khajavi et al., 2012), both of which may limit its broad clinical use. Furthermore, unlike ketamine, data from scopolamine trials have not been replicated by independent laboratories or in studies with inpatients using active placebo. Assessing the effects of scopolamine in subjects with suicidal ideation, as well as the use of alternative routes of administration (e.g, intranasal, transdermal) are also necessary to confirm these preliminary results and expand the potential utility of this agent in mood disorders.

The potential mechanisms involved in scopolamine's rapid antidepressant response include modulation of the cholinergic system by blocking the hypersensitivity of muscarinic receptors, with a concomitant acute increase in acetylcholine release that affects monoamine levels (particularly serotonin and dopamine). Other potential targets for the actions of scopolamine include the modulation of NMDA receptor activity, with increased NMDA receptor gene expression associated with muscarinic receptor stimulation (Liu et al., 2004). The activation of synaptic plasticity has also been proposed as an underlying biological effect for scopolamine's rapid antidepressant activity. In this context, it was shown that scopolamine rapidly increases mTOR signaling and synaptogenesis (both number and function) in association with its rapid antidepressant-like effects (Voleti et al., 2013). Interestingly, scopolamine's antidepressant-like effects were blocked by pretreatment with mTOR and AMPA antagonists (Voleti et al., 2013). Furthermore, scopolamine—as well as systemic administration of VU0255035, a selective M1-AChR antagonist—induced antidepressant-like effects associated with the activation of prefrontal cortex mTOR1 signaling (Navarria et al., 2015). Like ketamine, scopolamine administration acutely enhances extracellular glutamate concentrations in the striatum in rodents (Rawls and

McGinty, 1998), which may activate synaptic plasticity pathways. Other cholinergic mechanisms have also been explored in the treatment of MDD. For instance, nicotinic antagonists and partial agonists have both been evaluated in proof-of-concept trials and showed limited efficacy (Vieta et al., 2014).

9.3. HPA Axis Hyperactivity

Other potential targets have been drawn from the "stress hypothesis of depression" that targets HPA axis hyperactivity. This altered pathway could be responsible for loss of synapses in the limbic system and impaired plasticity and cellular resilience (Machado-Vieira et al., 2014). In preclinical studies, stress-related dendritic remodeling was a key molecular effect of ketamine (Duman and Duman, 2015). Nevertheless, glucocorticoid mediation in the stress response may also be responsible for these key effects. Interestingly, glucocorticoids acutely increase glutamate release in the amygdala and PFC (Musazzi et al., 2013). Thus, chronic alterations in glutamate release induced by glucocorticoids/stress may dynamically affect dendritic remodeling and synaptic networks as well as extrasynaptic glutamate levels, but studies of the effects of chronic stress on glutamate levels remain limited.

In the search for effective novel antidepressants, trials have also examined corticotropin releasing factor (CRF) and glucocorticoid receptor antagonists, as well some neuropeptides such as neurokinin 1 (NK1), vasopressin, and orexin antagonists; results have been mixed and largely disappointing (Dale et al., 2015). Mifepristone, a synthetic glucocorticoid receptor antagonist, showed disappointing clinical results (http://www.in-pharmatechnologist.com/Regulatory-Safety/Sanofi-pulls-plug-on-four-Ph-III-drugs2009). An initial pilot open-label study with the CRF_1 receptor antagonist NBI-30775/R121919 showed positive results (Zobel et al., 2000), but these were not subsequently replicated in a phase II placebo-controlled, double-blind, randomized study with the CRF_1 receptor antagonist CP-316,311 (Binneman et al., 2008). NK1 and NK2 receptors are activated by substance P and neurokinin A, and their modulators have been tested for the treatment of depression. In two double-blind, placebo controlled, randomized, proof-of-concept studies, the NK1 receptor antagonists aprepitant (MK869) and L759274 reduced depressive symptoms (Kramer et al., 1998; Kramer et al., 2004); however, these results were not subsequently confirmed in five follow-up phase II studies (Keller et al., 2006) and the program was discontinued. Several other NK1 receptor antagonists have also been tested, but no positive results have yet been described (Ball et al., 2014).

9.4. The Opioid System

Another promising target for future studies is the opioid system. Stress-induced increases in dynorphin, the endogenous ligand for the kappa opioid receptor, induced dysphoria and anhedonia in both humans and rodents (Knoll and Carlezon Jr, 2010). ALKS-5461, a combination of buprenorphine (a partial μ-opioid receptor agonist and kappa opioid receptor antagonist) and samidorphan (a μ-opioid antagonist) showed positive results in phase II trials, and are currently in phase III trials as an add-on therapy for treatment-resistant MDD (http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-corporateNewsArticle&ID=18258172013). In addition to this well-designed, placebo-

controlled, double-blind, crossover study, other observational, uncontrolled studies also found a significant and generally rapid elevation in mood in treatment-resistant MDD patients treated with μ-opioid agonists (Ehrich et al., 2015). However, it is not clear if these putative therapeutic effects are broader than the potential addictive effects of this class of agents.

9.5. The Melatonergic System

The neurohormone melatonin is secreted by the pineal gland and plays a crucial role in circadian rhythms and the sleep-wake cycle. The key target for melatonin is the suprachiasmatic nucleus (SCN), which is involved in diverse biological functions including regulation of sleep and circadian rhythms (Laposky et al., 2008; Wyatt et al., 2006), mood and behavior (Srinivasan et al., 2006), and adipokine levels (Espino et al., 2011; Kozirog et al., 2011; Nduhirabandi et al., 2011). Melatonin also has immunomodulatory, neuroprotective, antioxidant, and additional chronobiological effects (Cardinali et al., 2011; Pacchierotti et al., 2001; Pandi-Perumal et al., 2006; Reiter et al., 2009). It also seems to directly target synaptic plasticity by increasing hippocampal long-term potentiation (Pandi-Perumal et al., 2006).

The two melatonin receptors (MT1 and MT2) are high affinity G_i/G_0 protein-coupled receptors with elevated expression in the brain; MT1 receptors are predominantly found in the pituitary gland and hypothalamus, and MT2 receptors are predominantly found in the retina. As noted above, the melatonergic system directly affects the circadian system and sleep-wake rhythms. Interestingly, studies have shown that during depressive and manic episodes, individuals with mood disorders have abnormal circadian rhythm and changes in sleep patterns; these abnormalities include sleep-wake irregularities (Gruber et al., 2009; Harvey, 2008; Salvatore et al., 2008), abnormal actimetric parameters (Millan et al., 2005), and circadian preference for evening (Ahn et al., 2008; Mansour et al., 2005; Wood et al., 2009). Supersensitivity to melatonin suppression by light has also been observed in BD subjects, monozygotic twins discordant for BD, and the non-affected offspring of individuals with BD, but these findings were not confirmed in a similar study evaluating euthymic BD subjects (Hallam et al., 2005c; Lewy et al., 1985; Lewy et al., 1981; Nurnberger et al., 2000). The evidence suggests that regulation of sleep homeostasis is critical to achieving and maintaining remission in subjects with mood disorders.

Interestingly, variations in the melatonin biosynthesis pathway have been shown in mood disorders. For instance, BD subjects had decreased melatonin levels in response to a light night (Nurnberger et al., 2000) as well as increased melatonin suppression to light (Nathan et al., 1999). These findings suggest a genetic trait marker in BD (Hallam et al., 2006; Hallam et al., 2005c; Kennedy et al., 1996; Lewy et al., 1985; Nurnberger et al., 1988; Whalley et al., 1991). A polymorphism in the GPR50 (H9, melatonin-related receptor) was associated with increased risk for BD, but this finding was not subsequently replicated (Alaerts et al., 2006; Thomson et al., 2005). Relatedly, abnormal melatonin secretion and biological clock setting in adapting circadian rhythms to social environment has been observed, which may induce mood episodes in individuals with BD (McClung, 2007).

Exogenous melatonin has been an effective primary therapeutic for primary insomnia and delayed sleep phase disorder. In addition, evidence suggests that treatment with melatonin agonists adjunctive to mood stabilizers may prove useful in treating sleep disorders and eventually preventing metabolic syndrome in patients with BD (Geoffrey et al., 2015; Romo-Nava et al., 2014). Lithium and valproate lowered melatonin light sensitivity in healthy volunteers (Hallam et al., 2005a; Hallam et al., 2005b). No controlled studies of melatonin in BD have been published, and mixed results were seen when melatonin was administered to BD subjects in preliminary open-label studies (Bersani and Garavani, 2000; Leibenluft et al., 1997).

With regard to specific therapeutics, the selective MT1 and MT2 receptor agonist ramelteon (8mg) (Neubauer, 2008) was approved in 2005 by the US Food and Drug Administration (FDA) to treat insomnia. One study found that in BD patients with euthymia and sleep disturbances, ramelteon adjunctive to mood stabilizers (8 mg/day, 23 weeks double-blind, n = 83) effectively maintained mood stabilization. Notably, the group taking ramelteon had half the relapse rate of those treated with placebo (Norris et al., 2013).

Agomelatine is a melatonin MT1 and MT2 receptor agonist and a 5-HT(2C) receptor antagonist (Bourin and Prica, 2009). In preclinical models of depression, agomelatine had significant antidepressant-like effects (Bertaina-Anglade et al., 2006; Millan et al., 2005; Papp et al., 2003), increased cellular proliferation, and increased synaptic levels of both norepinephrine and dopamine (Banasr et al., 2006; Van Oekelen et al., 2003).

In clinical studies, agomelatine was more effective and well-tolerated than placebo in three large, controlled, multi-centre clinical trials in MDD (Kennedy and Emsley, 2006; Loo et al., 2002; Montgomery and Kasper, 2007). In a recent six-week trial with agomelatine (25 mg/day), 81% of 21 patients with BD depression showed substantial antidepressant efficacy at study endpoint and 47% showed response during the first week of treatment (Calabrese et al., 2007). There were no dropouts secondary to adverse events, though three lithium-treated subjects had manic or hypomanic episodes during the optional extension period (Calabrese et al., 2007). In another 24-week randomized, double-blind, placebo-controlled trial for depression, agomelatine was more effective than placebo; in addition, a significantly lower relapse rate was observed with agomelatine compared to placebo during a six-month extension phase (Goodwin et al., 2009). A recent meta-analysis of 20 trials encompassing 7460 subjects in studies that used standard depression rating scales found that agomelatine was significantly more effective than placebo, with an effect size (standardized mean difference (SMD)) of 0.24 (95% confidence interval 0.12 to 0.35) and a relative risk of response of 1.25 (1.11 to 1.4). Overall, agomelatine was as effective as other antidepressants. Agomelatine also resynchronized altered circadian rhythms and had circadian phase-advancement properties (Armstrong et al., 1993; Nagayama, 1996; Redman and Francis, 1998).

Taken together, the evidence suggests that agomelatine may be an effective and safe antidepressant. Its neuroprotective and clinical effects may represent an important treatment approach for several medical conditions. However, use of melatonin in clinical practice is not as well developed as might be expected. Further studies are required to confirm these

promising findings and explore the role of melatonin agonists in the treatment of mood disorders.

9.6. Deep Brain Stimulation (DBS)

Preliminary and uncontrolled studies using deep brain stimulation (DBS) also found that it has rapid antidepressant effects in treatment-resistant MDD. The stimulation targets showing an association with rapid antidepressant effects included the subgenual cingulate gyrus, nucleus accumbens, anterior limb of the capsula interna (Bewernick et al., 2010; Lozano et al., 2008; Malone et al., 2009), and the medial forebrain bundle (Schlaepfer et al., 2013). However, it is too soon to make a definitive statement on potential targets for rapid antidepressant effects associated with this major invasive intervention

9.7. Epigenetic Mechanisms

Interestingly, epigenetic mechanisms have also been associated with the pathophysiology of mood disorders and may represent potential targets for rapid antidepressant effects. While no selective CNS-specific molecule has been developed, the most promising target seems to be histone deacetylase (HDAC) inhibition and chromatin remodeling. For instance, elevated H3 acetylation and lower nucleus accumbens HDAC2 levels were observed in a postmortem study of patients with depression (Covington et al., 2009). In addition, HDAC2 inhibitors were found to have antidepressant-like effects and improve cognition in rodents (Covington et al., 2009; Covington et al., 2010; Day and Sweatt, 2012), which suggests that HDAC inhibitors could be further investigated as potential therapeutic targets in mood disorders (Machado-Vieira et al., 2011). L-acetylcarnitine (LAC), a well-tolerated acetylating agent, also displayed rapid (as early as day three of treatment) and long-lasting antidepressant-like effects via epigenetic regulation of mGluR2s in rodents by increasing acetylated H3K27 bound to the Grm2 promoter and the NF-κB-p65 subunit. These effects increased Grm2 gene transcription encoding for mGluR2s in the hippocampus and PFC.

9.8. Neuronal Plasticity

Neuronal plasticity may also represent a promising target for identifying molecules involved in the rapid improvement of depressive symptoms. For example, positive modulators of the tropomyosin receptor kinase B (TrkB) receptor, which regulates BDNF levels, are thought to induce antidepressant activity (Castren and Rantamaki, 2010; Rantamaki and Castren, 2008), although selectivity has been an issue. mTOR modulators and related molecules involved in the rapid action of ketamine and other proof-of-concept agents may also be promising, but the limitations of using potential agonists include the risk of cell proliferation (and eventually cancer) and inflammation (Johnson et al., 2013). Nevertheless, mTOR antagonists are FDA-approved for diverse types of cancer, and more than 1,300 trials with mTOR modulators are either under way or completed. The study of mTOR subunits may thus represent a valuable alternative, especially mTORC1.

9.9. Heterodimers

The study of heterodimers is another area of interest. A heterodimer is formed by two different macromolecules; this biologically active dimer derives from two or more different

monomers. Further studies in the area may help identify compounds that modulate specific receptors that interact with others. For instance, serotonergic 5-HT$_{2A}$ receptors form heterodimers with mGluR2s (Gonzalez-Maeso et al., 2008), a combination that may represent new avenues for studying the integration between receptor activity and coupling to multiple intracellular systems.

9.10. Neurotransmitters

Finally, several types of neurotransmitters have yet to be explored in psychiatric research. For instance, most amino acids are just now being explored; promising classes include peptides (eg, substance P, NK, somatostatin, neuropeptide Y) and gasotransmitters (e.g. nitric and nitrous oxide). Notably, a recent pilot proof-of-concept study found that the inhaled anesthetic gas nitrous oxide had rapid antidepressant effects in individuals with treatment-resistant MDD (Nagele et al., 2015). In addition to being relatively safe, nitrous oxide was associated with response rates of 20% compared to 5% in the placebo group. Moving forward, the main challenge will be to translate these findings into identifying clinically relevant therapeutic targets and surrogate outcomes for these potential new, improved therapeutics for depression.

9.11. Alternative Routes of Administration

Along a somewhat different line of inquiry, alternative routes of administration have also been investigated to ascertain whether ketamine's rapid antidepressant effects could be sustained. For instance, in a double-blind, randomized, placebo-controlled trial of patients with treatment-resistant MDD, intranasal ketamine (50mg) showed similar efficacy as IV infusion 24 hours post-treatment (Lapidus et al., 2014). Interestingly, ketamine's bioavailability administered via an intranasal route has been reported to be 25%–50% (Yanagihara et al., 2003). One open-label study observed that 0.25 mg/kg IM ketamine induced similar decreases in HAM-D score as IV ketamine in subjects with MDD (Chilukuri et al., 2014). Ketamine's metabolites have also shown efficacy in preclinical models of depression, but their neurobiological basis seems to go beyond NMDA antagonism and targets the alpha-7 nicotinic receptor, a specific subtype of the nicotinic acetylcholine receptors. Hydroxynorketamine (HNK), a by-product of ketamine, also targets this receptor and may represent a relevant therapeutic target for rapid antidepressant effects (Singh et al., 2014).

10. Translating New Targets into New, Improved, Rapid-Acting Antidepressants: Perspectives and Challenges for Future Studies

As the above review has underscored, to date the most promising novel targets for achieving rapid antidepressant effects are the ionotropic glutamate receptors. However, to date, no subunit specific modulator has been shown to induce a robust and rapid antidepressant action. Moving forward, predicting response by identifying potential responders *a priori* will be key to the concept of personalized medicine. Towards this end, the search for the unique biosignatures of rapid-acting antidepressants whose validity has been tested in larger samples will require the clear evaluation of drug kinetics, ability to pass through the blood-brain barrier, and information regarding brain distribution. In the future, trials that use

enriched samples may be more efficient, as participants would be more likely to receive the potentially most effective agent available based on their biomarker signatures. A full understanding of the true clinical utility of this novel treatment approach and the key aspects of this concept for public health will be critical as we define our next steps in psychiatric research. Questions such as whether treatments should be of long or short duration, whether they should be add-on or monotherapy, what the best route of administration is, whether they should be tested in treatment-resistant cases only, and whether particular diagnostic subtypes should be emphasized will all be crucial to future investigations. The novel hypothesis that some receptor-specific antagonists could display efficacy in particular, well-defined subpopulations based on their biological profile and clinical dimensions is an important paradigm shift in the field of psychiatric research, as underscored by the new research domain criteria (RDoC) model (Cuthbert and Insel, 2013); briefly, RDoc is a research framework integrating new ways of studying mental disorders that draws from many disparate sources of information (from genomics to self-report) in order to better understand dimensions of functioning underlying the full range of human behavior. The recent shift toward RDoC symptom clusters may emphasize the potential validity of such studies and ultimately allow the identification of a subgroup of patients that may present with glutamate dysfunction-based depressive episodes.

To aid such research, one pathway of particular interest is the use of new positron emission tomography (PET) ligands that target glutamate and other systems. Given that alternative targets and approaches are particularly needed for treatment-resistant cases, and given that such cases may involve other pathways and neurotransmitter systems than in responders to monoaminergic antidepressants, it is promising to think that the field may move faster with the development of new target engagement approaches, particularly novel PET ligands. Indeed, specific PET ligands that target the glutamatergic system have recently been developed. For instance, [^{11}C]ABP688 has shown high affinity for mGluR5, which may allow the monitoring of changes in glutamate levels (DeLorenzo et al., 2015). Studies using this ligand found lower levels of regional mGluR5 binding in the prefrontal cortex, the cingulate cortex, the insula, the thalamus, and the hippocampus in subjects with MDD compared to matched healthy controls (Deschwanden et al., 2011). In addition, a pharmacological challenge in rats with ceftriaxone, which activates the GLT-1 transporter (EAAT2), was found to reduce extracellular levels of glutamate, which regulated the availability of mGluR5 allosteric sites (Zimmer et al., 2015). Relatedly, alternative imaging methods such as using ^{13}C-MRS to measure glutamate cycling (Chowdhury et al., 2012) or functional magnetic resonance imaging (fMRI) studies of brain network connectivity could also be useful to assess target engagement and key downstream mechanisms associated with antidepressant response (Dawson et al., 2014; Driesen et al., 2013).

Certainly, future proof-of-concept studies with rapid-acting agents require the use of validated measures of target engagement, which will be key to defining dose/response and receptor binding. For instance, because there are no readily available NMDA receptor ligands in PET imaging studies, alternative approaches have been used. Other studies have proposed that electroencephalography (EEG) measures could be used to detect NMDA receptor target engagement (Hong et al., 2010; Kocsis et al., 2013). Receptor occupancy studies conducted in association with plasma drug levels will also be critical for defining

dose response parameters. Use of PET ligands to conduct target engagement or drug development studies is likely to hasten drug development in the field. On a related note, the early definition of dose response curves after the serendipitous identification of potential new approaches is also critical to identifying the most suitable effective dose associated with the lowest risk of dissociative or other adverse effects. It is interesting to note that this has not yet been done with ketamine.

It should also be noted that care is needed when testing downstream targets. For instance, clinical and preclinical studies have demonstrated that GSK-3B is directly regulated by lithium, and GSK3 antagonists have shown significant antidepressant effects in animal models. However, this target is so widespread in the brain and periphery that its molecular manipulation would likely induce systemic effects and, eventually, harmful adverse effects.

Once agents with rapid antidepressant effects are identified, strategies are also needed to maintain that efficacy, either by using multiple infusions or alternate routes of administration. Relatedly, the evaluation of therapeutic steady-state drug levels is a key factor; for instance IV infusion or intranasal use hasten steady-state levels and potentiate initial exposure, which may provide faster clinical efficacy. New treatments that work synergistically may be key to the post-ketamine long-term treatment phase.

Continued exploration of new, rapid-acting antidepressant agents is key to developing new treatments for mood disorders, and few would dispute that these treatments are urgently needed. Currently available antidepressants take weeks to achieve their full effects, which leaves patients vulnerable to devastating symptoms and higher risk of self-harm. As a result, any pharmacological strategy capable of exerting rapid and sustained antidepressant effects within hours or even days could substantially improve patients' quality of life as well as public health. The evidence presented above underscores the recent developments in the search for novel therapeutics for mood disorders. These have revolutionized the field, challenged old paradigms and current limitations, and brought hope to those who must live with these devastating disorders.

Acknowledgments

Abbreviations

ACC	anterior cingulate cortex
ACPC	1-aminocyclopropanecarboxylic acid
AKT/PKB	protein kinase B
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid
Arc	activity-regulated cytoskeleton-associated protein
BD	bipolar disorder
BDI	Beck Depression Inventory
BDNF	brain-derived neurotrophic factor
CNS	central nervous system
CREB	cyclic adenosine monophosphate response element-binding protein
CRF	corticotropin releasing factor
DBS	deep brain stimulation
dlPFC	dorsolateral prefrontal cortex
EEG	electroencephalography
e-EF2	eukaryotic elongation factor 2
ERK	extracellular signal-related kinase
fMRI	functional magnetic resonance imaging
GABA	gamma aminobutyric acid
GluA1	AMPA receptor subunit 1
GSK-3B	glycogen synthase kinase 3B
HAM-D	Hamilton Depression Rating Scale
HDAC	histone deacetylase
HNK	hydroxynorketamine
HPA	hypothalamic pituitary adrenal
IRS	insulin receptor substrate
LAC	L-acetylcarnitine
MADRS	Montgomery Asberg Depression Rating Scale
MDD	major depressive disorder

mGluR	metabotropic glutamate receptor
MRS	magnetic resonance spectroscopy
mTOR	mammalian target of rapamycin
NK1	neurokinin 1
NMDA	N-methyl-D-aspartate
PCP	phencyclidine
PET	positron emission tomography
PFC	prefrontal cortex
PI3K	phosphoinositide-3 kinase
PSD95	postsynaptic density protein 95
RDoC	research domain criteria
SMD	standardized mean difference
SNRI	serotonin-noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TrkB	tropomyosin receptor kinase B
VOCC	voltage-operated calcium channels

References

Alkermes Presents Positive Results from Phase 2 Clinical Study of ALKS 5461 in Major Depressive Disorder at 53rd Annual NCDEU Meeting; http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-corporateNewsArticle&ID=18258172013

http://www.in-pharmatechnologist.com/Regulatory-Safety/Sanofi-pulls-plug-on-four-Ph-III-drugs2009. Sanofi pulls plug on four Ph III drugs, Press release 29 April 2009

Abdallah CG, Averill LA, Krystal JH. Ketamine as a promising prototype for a new generation of rapid-acting antidepressants. Ann N Y Acad Sci. 2015; 1344:66–77. [PubMed: 25727103]

Ahn YM, Chang J, Joo YH, Kim SC, Lee KY. Chronotype distribution in bipolar I disorder and schizophrenia in a Korean sample. Bipolar Disord. 2008; 10:271–275. [PubMed: 18271906]

Alaerts M, Venken T, Lenaerts AS, De Zutter S, Norrback KF, Adolfsson R, Del-Favero J. Lack of association of an insertion/deletion polymorphism in the G protein-coupled receptor 50 with bipolar disorder in a Northern Swedish population. Psychiatr Genet. 2006; 16:235–236. [PubMed: 17106423]

Armstrong SM, McNulty OM, Guardiola-Lemaitre B, Redman JR. Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome (DSPS). Pharmacol Biochem Behav. 1993; 46:45–49. [PubMed: 8255922]

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature. 2011; 475:91–95. [PubMed: 21677641]

Ball WA, Snavely D, Hargreaves RJ, Szegedi A, Lines C, Reines SA. Addition of an NK1 receptor antagonist to an SSRI did not enhance the antidepressant effects of SSRI monotherapy: results from a randomized clinical trial in patients with major depressive disorder. Hum Psychopharmacol. 2014; 29:568–577. [PubMed: 25330122]

Banasr M, Soumier A, Hery M, Mocaer E, Daszuta A. Agomelatine, a new antidepressant, induces regional changes in hippocampal neurogenesis. Biol Psychiatry. 2006; 59:1087–1096. [PubMed: 16499883]

Bersani G, Garavani A. Melatonin add-on in manic patients with treatment resistant insomnia. Biol Psychiatry. 2000; 24:185–191.

Bertaina-Anglade V, la Rochelle CD, Boyer PA, Mocaer E. Antidepressant-like effects of agomelatine (S 20098) in the learned helplessness model. Behav Pharmacol. 2006; 17:703–713. [PubMed: 17110796]

Beurel E, Song L, Jope R. Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. Mol Psychiatry. 2011; 16:1068–1070. [PubMed: 21502951]

Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, Axmacher N, Lemke M, Cooper-Mahkorn D, Cohen MX, Brockmann H, Lenartz D, Sturm V, Schlaepfer TE. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry. 2010; 67:110–116. [PubMed: 19914605]

Binneman B, Feltner D, Kolluri S, Shi Y, Qiu R, Stiger T. A 6-week randomized, placebo-controlled trial of CP-316,311 (a selective CRH1 antagonist) in the treatment of major depression. Am J Psychiatry. 2008; 165:617–620. [PubMed: 18413705]

Bleakman D, Alt A, Witkin JM. AMPA receptors in the therapeutic management of depression. CNS Neurol Disord Drug Targets. 2007; 6:117–126. [PubMed: 17430149]

Bourin M, Prica C. Melatonin receptor agonist agomelatine: a new drug for treating unipolar depression. Curr Pharm Des. 2009; 15:1675–1682. [PubMed: 19442180]

Boyer PA, Skolnick P, Fossom LH. Chronic administration of imipramine and citalopram alters the expression of NMDA receptor subunit mRNAs in mouse brain. A quantitative in situ hybridization study. J Mol Neurosci. 1998; 10:219–233. [PubMed: 9770644]

Bunney BG, Bunney WE. Mechanisms of rapid antidepressant effects of sleep deprivation therapy: clock genes and circadian rhythms. Biol Psychiatry. 2013; 15:1164–1171. [PubMed: 22906517]

Burch, RM. A phase 2, randomized, double blind, single intravenous dose study of GLYX-13, an NMDA receptor glycine site functional partial agonist, in subjects with Major Depressive Disorder with inadequate response to antidepressant medication. Presented at the Proceedings of the ACNP 51st Annual Meeting; Hollywood, FL. 2012.

Calabrese JR, Guelfi JD, Perdrizet-Chevalier C. Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. Bipolar Disord. 2007; 9:628–635. [PubMed: 17845278]

Cao R, Cho HY, Lee B, Obrietan K. Mammalian target of rapamycin signaling modulates photic entrainment of the suprachiasmatic circadian clock. J Neurosci. 2010; 30:6302–6314. [PubMed: 20445056]

Cardinali DP, Cano P, Jimenez-Ortega V, Esquifino AI. Melatonin and the metabolic syndrome: physiopathologic and therapeutical implications. Neuroendocrinology. 2011; 93:133–142. [PubMed: 21358175]

Carlson PJ, Diazgranados N, Nugent AC, Ibrahim L, Luckenbaugh D, Brutsche N, Herscovitch P, Manji HK, Zarate CAJ, Drevets WC. Neural correlates of rapid antidepressant response to ketamine in treatment-resistant unipolar depression: a preliminary positron emission tomography study. Biol Psychiatry. 2013; 73:1213–1221. [PubMed: 23540908]

Castren E, Rantamaki T. The role of BDNF and its receptors in depression and antidepressant drug action: reactivation of developmental plasticity. Dev Neurobiol. 2010; 70:289–297. [PubMed: 20186711]

Chaki S, Ago Y, Palucha-Paniewiera A, Matrisciano F, Pilc A. mGlu2/3 and mGlu5 receptors: potential targets for novel antidepressants. Neuropharmacology. 2013; 66:40–52. [PubMed: 22640631]

Chilukuri H, Reddy NP, Pathapati RM, Manu AN, Jollu S, Shaik AB. Acute antidepressant effects of intramuscular versus intravenous ketamine. Indian J Psychol Med. 2014; 36:71–76. [PubMed: 24701015]

Chowdhury GM, Behar KL, Cho W, Thomas MA, Rothman DL, Sanacora G. (1)H-[(1)(3)C]-nuclear magnetic resonance spectroscopy measures of ketamine's effect on amino acid neurotransmitter metabolism. Biol Psychiatry. 2012; 71:1022–1025. [PubMed: 22169441]

Chung J, Kuo CJ, Crabtree GR, Blenis J. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Cell. 1992; 69:1227–1236. [PubMed: 1377606]

Covington, HEr., Maze, I., LaPlant, QC., Vialou, VF., Ohnishi, YN., Berton, O., Fass, DM., Renthal, W., Rush, AJ., Wu, EY., Ghose, S., Krishnan, V., Russo, SJ., Tamminga, CA., Haggarty, SJ., Nestler, EJ. Antidepressant actions of histone deacetylase inhibitors. J Neurosci. 2009; 29:11451–11460. [PubMed: 19759294]

Covington, HEr., Vialou, VF., Nestler, EJ. From synapse to nucleus: novel targets for treating depression. Neuropharmacology. 2010; 58:683–693. [PubMed: 20018197]

Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum Psychopharmacol. 2015; 30:152–163. [PubMed: 25847818]

Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013; 11:126. [PubMed: 23672542]

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

Danbolt NC. Glutamate uptake. Prog Neurobiol. 2001; 65:1–105. [PubMed: 11369436]

Dawson N, McDonald M, Higham DJ, Morris BJ, Pratt JA. Subanesthetic ketamine treatment promotes abnormal interactions between neural subsystems and alters the properties of functional brain networks. Neuropsychopharmacology. 2014; 39:1786–1798. [PubMed: 24492765]

Day JJ, Sweatt JD. Epigenetic treatments for cognitive impairments. Neuropsychopharmacology. 2012; 37:247–260. [PubMed: 21593731]

DeLorenzo C, DellaGioia N, Bloch M, Sanacora G, Nabulsi N, Abdallah CG, Yang J, Wen R, Mann JJ, Krystal JH, Parsey RV, Carson RE, Esterlis I. Invivo ketamine-induced changes in [C]ABP688 binding to metabotropic glutamate receptor subtype 5. Biol Psychiatry. 2015; 77:266–275. [PubMed: 25156701]

Denk MC, Rewarts C, Holsboer F, Erhardt-Lehmann A, Turck CW. Monitoring ketamine treatment response in a depressed patient via peripheral mammalian target of rapamycin activation. Am J Psychiatry. 2011; 68:751–752. [PubMed: 21724677]

Deschwanden A, Karolewicz B, Feyissa AM, Treyer V, Ametamev SM, Johayem A, Burger C, Auberson YP, Sovago J, Stockmeier CA, Buck A, Hasler G. Reduced metabotropic glutamate receptor 5 density in major depression determined by [(11)C]ABP688 PET and postmortem study. Am J Psychiatry. 2011; 168:727–734. [PubMed: 21498461]

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

Driesen NR, McCarthy G, Bhagwagar Z, Bloch M, Calhoun V, D'Souza DC, Gueorguieva R, He G, Ramachandran R, Suckow RF, Anticevic A, Morgan PT, Krystal JH. Relationship of resting brain hyperconnectivity and schizophrenialike symptoms produced by the NMDA receptor antagonist ketamine in humans. Mol Psychiatry. 2013; 18:1199–1204. [PubMed: 23337947]

Duman CH, Duman RS. Spine synapse remodeling in the pathophysiology and treatment of depression. Neurosci Lett. 2015 Jan 9. epub ahead of print.

Duman RS. Neuronal damage and protection in the pathophysiology and treatment of psychiatric illness: stress and depression. Dialogues Clin Neurosci. 2009; 11:239–255. [PubMed: 19877493]

Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. Science. 2012; 338:68–72. [PubMed: 23042884]

Duman RS, Li N, Liu RJ, Duric V, Aghajanian GK. Signaling pathways underlying the rapid antidepressant actions of ketamine. Neuropharmacology. 2012; 62:35–41. [PubMed: 21907221]

Duncan WC, Sarasso S, Ferrarelli F, Selter J, Riedner BA, Hejazi NS, Yuan P, Brutsche N, Manji HK, Tononi G, Zarate CAJ. Concomitant BDNF and sleep slow wave changes indicate ketamine-

induced plasticity in major depressive disorder. Int J Neuropsychopharmacol. 2013; 16:301–311. [PubMed: 22676966]

Dutta A, McKie S, Deakin JF. Ketamine and other potential glutamate antidepressants. Psychiatry Res. 2015; 225:1–13. [PubMed: 25467702]

Dwyer JM, Duman RS. Activation of mammalian target of rapamycin and synaptogenesis: role in the actions of rapid-acting antidepressants. Biol Psychiatry. 2013; 73:1189–1198. [PubMed: 23295207]

Dwyer JM, Lepack AE, Duman RS. mTOR activation is required for the antidepressant effects of mGluR(2)/(3) blockade. Int J Neuropsychopharmacol. 2012; 15:429–434. [PubMed: 22114864]

Ehrich E, Turncliff R, Du Y, Leigh-Pemberton R, Fernandez E, Jones R, Fava M. Evaluation of opioid modulation in major depressive disorder. Neuropsychopharmacology. 2015; 40:1448–1455. [PubMed: 25518754]

Emnett CM, Eisenman LN, Taylor AM, Izumi Y, Zorumski CF, Mennerick S. Indistinguishable synaptic pharmacodynamics of the N-methyl-D-aspartate receptor channel blockers memantine and ketamine. Mol Pharmacol. 2013; 84:935–947. [PubMed: 24101301]

Espino J, Pariente JA, Rodriguez AB. Role of melatonin on diabetes-related metabolic disorders. World J Diabetes. 2011; 2:82–91. [PubMed: 21860691]

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

Garcia LS, Comim CM, Valvassori SS, Reus GZ, Barbosa LM, Andreazza AC, Stertz L, Fries GR, Gavioli EC, Kapczinski F, Quevedo J. Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32:140–144. [PubMed: 17884272]

Geoffrey PA, Etain B, Franchi JA, Bellivier F, Ritter P. Melatonin and melatonin agonists as adjunctive treatments in bipolar disorders. Curr Pharm Des. 2015; 21:3352–3358. [PubMed: 26088111]

Gideons E, Kavalali ET, Monteggia LM. Mechanisms underlying differential effectiveness of memantine and ketamine in rapid antidepressant responses. Proc Natl Acad Sci USA. 2014; 111:8649–8654. [PubMed: 24912158]

Gigliucci V, O'Dowd G, Casey S, Egan D, Gibney S, Harkin A. Ketamine elicits sustained antidepressant-like activity via a serotonin-dependent mechanism. Psychopharmacology (Berl). 2013; 228:157–166. [PubMed: 23455595]

Gonzalez-Maeso J, Ang RL, Yuen T, Chan P, Weisstaub NV, Lopez-Gimenez JF, Zhou M, Okawa Y, Callado LF, Milligan G, Gingrich JA, Filizola M, Meana JJ, Sealfon SC. Identification of a serotonin/glutamate receptor complex implicated in psychosis. Nature. 2008; 452:93–97. [PubMed: 18297054]

Goodsaid FM, Mendrick DL. Translational medicine and the value of biomarker qualification. Sci Transl Med. 2010; 2:47ps44.

Goodwin GM, Emsley R, Rembry S, Rouillon F. Agomelatine Study Group. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2009; 70:1128–1137. [PubMed: 19689920]

Gruber J, Harvey AG, Wang PW, Brooks JOr, Thase ME, Sachs GS, Ketter TA. Sleep functioning in relation to mood, function, and quality of life at entry to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Affect Disord. 2009; 114:41–49. [PubMed: 18707765]

Guertin DA, Sabatini DM. Defining the role of mTOR in cancer. Cancer Cell. 2007; 12:9–22. [PubMed: 17613433]

Haile CN, Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Foulkes A, Iqbal S, Mahoney J Jr, De La Garza Rn, Charney DS, Newton TF, Mathew SJ. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatmentresistant depression. Int J Neuropsychopharmacol. 2014; 17:331–336. [PubMed: 24103211]

Hallam KT, Olver JS, Chambers V, Begg DP, McGrath C, Norman TR. The heritability of melatonin secretion and sensitivity to bright nocturnal light in twins. Psychoneuroendocrinology. 2006; 31:867–875. [PubMed: 16769177]

Hallam KT, Olver JS, Horgan JE, McGrath C, Norman TR. Low doses of lithium carbonate reduce melatonin light sensitivity in healthy volunteers. Int J Neuropsychopharmacol. 2005a; 8:255–259. [PubMed: 15850501]

Hallam KT, Olver JS, Norman TR. Effect of sodium valproate on nocturnal melatonin sensitivity to light in healthy volunteers. Neuropsychopharmacology. 2005b; 30:1400–1404. [PubMed: 15841104]

Hallam KT, Olver JS, Norman TR. Melatonin sensitivity to light in monozygotic twins discordant for bipolar I disorder. Aust N Z J Psychiatry. 2005c; 39:947. [PubMed: 16168024]

Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am J Psychiatry. 2008; 165:820–829. [PubMed: 18519522]

Hashimoto K, Sawa A, Iyo M. Increased levels of glutamate in brains from patients with mood disorders. Biol Psychiatry. 2007; 62:1310–1316. [PubMed: 17574216]

Heitman J, Movva N, Hall MN. Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast. Science. 1991; 253:905–909. [PubMed: 1715094]

Hirota K, Lambert DJ. Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth. 1996; 77:441–444. [PubMed: 8942324]

Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG. Stereoselective interaction of ketamine with recombinant μ, κ and δ opiod receptors expressed in chinese hamster ovary cells. Anesthesiology. 1999; 90:174–182. [PubMed: 9915326]

Hoeffer CA, Klann E. mTOR signaling: at the crossroads of plasticity, memory and disease. Trends Neurosci. 2010; 33:67–75. [PubMed: 19963289]

Hong LE, Summerfelt A, Buchanan RW, O'Donnell P, Thaker GK, Weiler MA, Lahti AC. Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine. Neuropsychopharmacology. 2010; 35:632–640. [PubMed: 19890262]

Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, Moaddel R, Wainer I, Luckenbaugh DA, Manji HK, Zarate CA. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology. 2012a; 37:1526–1533. [PubMed: 22298121]

Ibrahim L, Diazgranados N, Jolkovsky L, Brutsche N, Luckenbaugh D, Herring WJ, Potter WZ, Zarate CAJ. A randomized, placebo-controlled, crossover pilot trial of the oral selective NR2B antagonist MK-0657 in patients with treatment-resistant major depressive disorder. J Clin Psychopharmacol. 2012b; 32:551–557. [PubMed: 22722512]

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

Jernigan CS, Goswami DB, Austin MC, Iyo AH, Chandran A, Stockmeier CA, Karolewicz B. The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35:1774–1779. [PubMed: 21635931]

Johnson SC, Rabinovitch PS, Kaeberlein M. mTOR is a key modulator of ageing and age-related disease. Nature. 2013; 493:338–345. [PubMed: 23325216]

Jourdi H, Hsu YT, Zhou M, Qin Q, Bi X, Baudry M. Positive AMPA receptor modulation rapidly stimulates BDNF release and increases dendritic mRNA translation. J Neurosci. 2009; 29:8688–8697. [PubMed: 19587275]

Karasawa J, Shimazaki T, Kawashima N, Chaki S. AMPA receptor stimulation mediates the antidepressant-like effect of a group II metabotropic glutamate receptor antagonist. Brain Res. 2005; 1042:92–98. [PubMed: 15823257]

Katz MM, Tekell JL, Bowden CL, Brannan S, Houston JP, Berman N, Frazer A. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. Neuropsychopharmacology. 2004; 29:566–579. [PubMed: 14627997]

Keller M, Montgomery S, Ball WA, Morrison M, Snavely D, Liu G, Hargreaves RJ, Hietala J, Lines C, Beebe K, Reines SA. Lack of efficacy of the substance p (neurokinin1 receptor) antagonist

aprepitant in the treatment of major depressive disorder. Biol Psychiatry. 2006; 59:216–223. [PubMed: 16248986]

Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. Eur Neuropsychopharmacol. 2006; 16:93–100. [PubMed: 16249073]

Kennedy SH, Kutcher SP, Ralveski E, Brown GM. Nocturnal melatonin and 24-hour 6-sulphatoxymelatonin levels in various phases of bipolar affective disorder. Psychiatry Res. 1996; 63:219–222. [PubMed: 8878318]

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

Klimek V, Papp M. The effect of MK-801 and imipramine on beta-adrenergic and 5-HT2 receptors in the chronic mild stress model of depression in rats. Pol J Pharmacol. 1994; 46:67–69. [PubMed: 7981774]

Knoll AT, Carlezon WA Jr. Dynorphin, stress, and depression. Brain Res. 2010; 1314:56–73. [PubMed: 19782055]

Kocsis B, Brown RE, McCarley RW, Hajos M. Impact of ketamine on neuronal network dynamics: translational modeling of schizophrenia-relevant deficits. CNS Neurosci Ther. 2013; 19:437–447. [PubMed: 23611295]

Koike H, Iijima M, Chaki S. Involvement of AMPA receptor in both the rapid and sustained antidepressant-like effects of ketamine in animal models of depression. Behav Brain Res. 2011; 224:107–111. [PubMed: 21669235]

Koshikawa N, Maruyama Y, Kobayashi M, Campbell IC. Rapid development of brain beta-adrenoceptor down-regulation induced by phenelzine: subcellular studies. Eur J Pharmacol. 1989; 170:101–104. [PubMed: 2558891]

Kotermanski SE, Wood JT, Johnson JW. Memantine binding to a superficial site on NMDA receptors contributes to partial trapping. J Physiol. 2009; 587:4589–4604. [PubMed: 19687120]

Kozirog M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res. 2011; 50:261–266. [PubMed: 21138476]

Kramer MS, Cutler N, Feighner J, Shrivastava R, Carman J, Sramek JJ, Reines SA, Liu G, Snavely D, Wyatt-Knowles E, Hale JJ, Mills SG, MacCoss M, Swain CJ, Harrison T, Hill RG, Hefti F, Scolnick EM, Cascieri MA, Chicchi GG, Sadowski S, Williams AR, Hewson L, Smith D, Carlson EJ, Hargreaves RJ, Rupniak NM. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science. 1998; 281:1640–1645. [PubMed: 9733503]

Kramer MS, Winokur A, Kelsey J, Preskorn SH, Rothschild AJ, Snavely D, Ghosh K, Ball WA, Reines SA, Munjack D, Apter JT, Cunningham L, Kling M, Bari M, Getson A, Lee Y. Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. Neuropsychopharmacology. 2004; 29:385–392. [PubMed: 14666114]

Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. Prog Neurobiol. 2014; 115:157–188. [PubMed: 24361499]

Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, Feder A, Iosifescu DV, Charney DS, Murrough JW. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry. 2014

Laposky AD, Bass J, Kohsaka A, Turek FW. Sleep and circadian rhythms: key components in the regulation of energy metabolism. FEBS Lett. 2008; 582:142–151. [PubMed: 17707819]

Lauterbach EC. Dextromethorphan as a potential rapid-acting antidepressant. Medical Hypotheses. 2011; 76:717–719. [PubMed: 21367535]

Layer RT, Popik P, Olds T, Skolnick P. Antidepressant-like actions of the polyamine site NMDA antagonist, eliprodil (SL-82.0715). Pharmacol Biochem Behav. 1995; 52:621–627. [PubMed: 8545484]

Lee SY, Chen SL, Chang YH, Chen SH, Chu CH, Huang SY, Tzeng NS, Wang CL, Lee IH, Yeh TL, Yang YK, Lu RB. The DRD2/ANKK1 gene is associated with response to add-on dextromethorphan treatment in bipolar disorder. J Affect Disord. 2012; 138:295–300. [PubMed: 22326841]

Legutko B, Li X, Skolnick P. Regulation of BDNF expression in primary neuron culture by LY392098, a novel AMPA receptor potentiator. Neuropharmacology. 2001; 40:1019–1027. [PubMed: 11406193]

Leibenluft E, Feldman-Naim S, Turner EH, Wehr TA, Rosenthal NE. Effects of exogenous melatonin administration and withdrawal in five patients with rapid-cycling bipolar disorder. J Clin Psychiatry. 1997; 58:383–388. [PubMed: 9378688]

Lewy AJ, Nurnberger JI Jr, Wehr TA, Pack D, Becker LE, Powell RL, Newsome DA. Supersensitivity to light: possible trait marker for manic-depressive illness. Am J Psychiatry. 1985; 142:725–727. [PubMed: 4003592]

Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Rosenthal NE. Manicdepressive patients may be supersensitive to light. Lancet. 1981; 1:383–384. [PubMed: 6110011]

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian GK, Duman RS. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010; 329:959–964. [PubMed: 20724638]

Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, Li XY, Aghajanian G, Duman RS. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol Psychiatry. 2011; 69:754–761. [PubMed: 21292242]

Linden AM, Valsanen J, Lakso M, Nawa H, Wong G, Castren E. Expression of neurotrophins BDNF and NT-3, and their receptors in rat brain after administration of antipsychotic and psychotropic agents. J Mol Neurosci. 2000; 14:27–37. [PubMed: 10854034]

Liu HF, Zhou WH, Xie XH, Cao JL, Gu J, Yang GD. Muscarinic receptors modulate the mRNA expression of NMDA receptors in brainstem and the release of glutamate in periaqueductal grey during morphine withdrawal in rats. Sheng Li Xue Bao. 2004; 56:95–100. [PubMed: 14985837]

Livingstone M, Atas E, Meller A, Sonenberg N. Mechanisms governing the control of mRNA translation. Phys Biol. 2010; 7:021001. [PubMed: 20463379]

Loo H, Hale A, D'Haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. Int Clin Psychopharmacol. 2002; 17:239–247. [PubMed: 12177586]

Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Effects of subcallosal cingulate deep brain stimulation on negative self-bias in patients with treatment-resistant depression. Biol Psychiatry. 2008; 64:461–467. [PubMed: 18639234]

Luckenbaugh D, Niciu MJ, Ionescu DF, Nolan NM, Richards EM, Brutsche N, Guevara S, Zarate CAJ. Do the dissociative side effects of ketamine mediate its antidepressant effects. J Affect Disord. 2014; 159:56–61. [PubMed: 24679390]

Machado-Vieira R, Baumann J, Wheeler-Castillo C, Latov D, Henter ID, Salvadore G, Zarate CAJ. The timing of antidepressant effects: a comparison of diverse pharmacological and somatic treatments. Pharmaceuticals. 2010; 3:19–41. [PubMed: 27713241]

Machado-Vieira R, Ibrahim L, Henter ID, Zarate CA Jr. Novel glutamatergic agents for major depressive disorder and bipolar disorder. Pharmacol Biochem Behav. 2012; 100:678–687. [PubMed: 21971560]

Machado-Vieira R, Ibrahim L, Zarate CAJ. Histone deacetylases and mood disorders: epigenetic programming in gene-environment interactions. CNS Neurosci Ther. 2011; 17:699–704. [PubMed: 20961400]

Machado-Vieira R, Manji HK, Zarate CA. The role of the tripartite glutamatergic synapse in the pathophysiology and therapeutics of mood disorders. Neuroscientist. 2009a; 15:525–539. [PubMed: 19471044]

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

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

Machado-Vieira R, Soeiro-de-Souza MG, Richards EM, Teixeira AL, Zarate CAJ. Multiple levels of impaired neural plasticity and cellular resilience in bipolar disorder: developing treatments using

an integrated translational approach. World J Biol Psychiatry. 2014; 15:84–95. [PubMed: 23998912]

Machado-Vieira R, Yuan P, Brutsche N, DiazGranados N, Luckenbaugh D, Manji HK, Zarate CA Jr. Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist. J Clin Psychiatry. 2009c; 70:1662–1666. [PubMed: 19744406]

Machado-Vieira R, Zanetti MV, Teixeira AL, Uno M, Valiengo LL, Soeiro-de-Souza MG, Oba-Shinjo SM, de Sousa RT, Zarate CAJ, Gattaz WF, Marie SK. Decreased AKT1/mTOR pathway mRNA expression in short-term bipolar disorder. Eur Neuropsychopharmacol. 2015; 25:468–473. [PubMed: 25726893]

Maeng S, Zarate CA Jr, Du J, Schloesser RJ, McCammon J, Chen G, Manji HK. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. Biol Psychiatry. 2008; 63:349–352. [PubMed: 17643398]

Maes M, Verkerk R, Vandoolaeghe E, Lin A, Scharpe S. Serum levels of excitatory amino acids, serine, glycine, histidine, threonine, taurine, alanine and arginine in treatment-resistant depression: modulation by treatment with antidepressants and prediction of clinical responsivity. Acta Psychiatr Scand. 1998; 97:302–308. [PubMed: 9570492]

Maj J, Rogoz Z, Skuza G. Antidepressant drugs increase the locomotor hyperactivity induced by MK-801 in rats. J Neural Transm Gen Sect. 1991; 85:169–179. [PubMed: 1930880]

Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron. 2004; 44:5–21. [PubMed: 15450156]

Malone DAJ, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, Rauch SL, Rasmussen SA, Machado AG, Kubu CS, Tyrka AR, Price LH, Stypulkowski PH, Giftakis JE, Rise MT, Malloy PF, Salloway SP, Greenberg BD. Deep brain stimulation of the ventral capsule/ventral striatum for treatmentresistant depression. Biol Psychiatry. 2009; 65:267–275. [PubMed: 18842257]

Mansour HA, Wood J, Chowdari KV, Dayal M, Thase ME, Kupfer DJ, Monk TH, Devlin B, Nimgainkar VL. Circadian phase variation in bipolar I disorder. Chronobiol Int. 2005; 22:571–584. [PubMed: 16076655]

McClung CA. Circadian genes, rhythms and the biology of mood disorders. Pharmacol Ther. 2007; 114:222–232. [PubMed: 17395264]

Mealing GA, Lanthorn TH, Murray CL, Small DL, Morley P. Differences in degree of trapping of low-affinity uncompetitive N-methyl-d-aspartic acid receptor antagonists with similar kinetics of block. J Pharmacol Exp Ther. 1999; 288:204–210. [PubMed: 9862772]

Meloni D, Gambarana C, De Montis MG, Dal Pra P, Taddei I, Tagliamonte A. Dizocilpine antagonizes the effect of chronic imipramine on learned helplessness in rats. Pharmacol Biochem Behav. 1993; 46:423–426. [PubMed: 7903459]

Menniti FS, Lindsley CW, Conn PJ, Pandit J, Zagouras P, Volkmann RA. Allosteric modulators for the treatment of schizophrenia: targeting glutamatergic networks. Curr Top Med Chem. 2013; 13:26–54. [PubMed: 23409764]

Messias E, Everett B. Dextromethorphan and quinidine combination in emotional lability associated with depression: a case report. Prim Care Companion CNS Disord. 2012; 14 PCC.12l01400.

Millan MJ, Brocco M, Gobert A, Dekeyne A. Anxiolytic properties of agomelatine, an antidepressant with melatoninergic and serotonergic properties: role of 5-HT2C receptor blockade. Psychopharmacology (Berl). 2005; 177:448–458. [PubMed: 15289999]

Mjellem N, Lund A, Hole K. Reduction of NMDA-induced behaviour after acute and chronic administration of desipramine in mice. Neuropharmacology. 1993; 32:591–595. [PubMed: 8336822]

Moaddel R, Luckenbaugh D, Xie Y, Villasenor A, Brutsche NE, Machado-Vieira R, Ramamoorthy A, Lorenzo MP, Garcia A, Bernier M, Torjman MC, Barbas C, Zarate CAJ, Wainer IW. D-serine plasma concentration is a potential biomarker of (R,S)-ketamine antidepressant response in subjects with treatment-resistant depression. Psychopharmacology (Berl). 2015; 232:399–409. [PubMed: 25056852]

Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci. 1997; 17:2921–2927. [PubMed: 9092613]

Monteggia LM, Gideons E, Kavalali ET. The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. Biol Psychiatry. 2013; 73:1199–1203. [PubMed: 23062356]

Montgomery SA, Kasper S. Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. Int Clin Psychopharmacol. 2007; 22:283–291. [PubMed: 17690597]

Moryl E, Danysz W, Quack G. Potential antidepressive properties of amantadine, memantine and bifemelane. Pharmacol Toxicol. 1993; 72:394–397. [PubMed: 8361950]

Moskal JR, Burch R, Burgdorf JS, Kroes RA, Stanton PK, Disterhoft JF, Leander JD. GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. Expert Opin Investig Drugs. 2014; 23:243–254.

Musazzi L, Treccani G, Mallei A, Popoli M. The action of antidepressants on the glutamate system: regulation of glutamate release and glutamate receptors. Biol Psychiatry. 2013; 73:1180–1188. [PubMed: 23273725]

Nagayama H. Chronic administration of imipramine and lithium changes the phase-angle relationship between the activity and core body temperature circadian rhythms in rats. Chronobiol Int. 1996; 13:251–259. [PubMed: 8889249]

Nagele P, Duma A, Kopec M, Gebara MA, Parsoei A, Walker M, Janski A, Panagopoulos VN, Cristancho P, Miller JP, Zorumski CF, Conway CR. Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. Biol Psychiatry. 2015; 78:10–18. [PubMed: 25577164]

Nathan PJ, Burrows GD, Norman TR. Melatonin sensitivity to dim white light in affective disorders. Neuropsychopharmacology. 1999; 21:408–413. [PubMed: 10457538]

Nations KR, Dogterom P, Bursi R, Schipper J, Greenwald S, Zraket D, Gertsik L, Johnstone J, Lee A, Pande Y, Ruigt G, Ereshefsky L. Examination of Org 26576, an AMPA receptor positive allosteric modulator, in patients diagnosed with major depressive disorder: an exploratory, randomized, double-blind, placebo-controlled trial. J Psychopharmacol. 2012; 26:1525–1539. [PubMed: 22954616]

Navarria A, Wohleb ES, Voleti B, Ota KT, Dutheil S, Lepack AE, Dwyer JM, Fuchikami M, Becker A, Drago F, Duman RS. Rapid antidepressant actions of scopolamine: Role of medial prefrontal cortex and M1-subtype muscarinic acetylcholine receptors. Neurobiol Dis. 2015; 82:254–261. [PubMed: 26102021]

Nduhirabandi F, Du Toit EF, Blackhurst D, Marais D, Lochner A. Chronic melatonin consumption prevents obesity-related metabolic abnormalities and protects the heart against myocardial ischemia and reperfusion injury in a prediabetic model of dietinduced obesity. J Pineal Res. 2011; 50:171–182. [PubMed: 21073520]

Neubauer DN. A review of ramelteon in the treatment of sleep disorders. Neuropsychiatr Dis Treat. 2008; 4:69–79. [PubMed: 18728808]

Nguyen L, Matsumoto RR. Involvement of AMPA receptors in the antidepressant-like effects of dextromethorphan in mice. Behav Brain Res. 2015 Mar 21. epub ahead of print.

Niciu MJ, Henter ID, Luckenbaugh DA, Zarate CAJ, Charney DS. Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. Annu Rev Pharmacol Toxicol. 2014; 54:119–139. [PubMed: 24392693]

Nishimura M, Sato K, Okada T, Yoshiya I, Schloss P, Shimada S, Tohyama M. Ketamine inhibits monoamine transporters expressed in human embryonic kidney 293 cells. Anesthesiology. 1998; 88:768–774. [PubMed: 9523822]

Norris ER, Burke K, Correll JR, Zemanek KJ, Lerman J, Primelo RA, Kaufmann MW. A double-blind, randomized, placebo-controlled trial of adjunctive ramelteon for the treatment of insomnia and mood stability in patients with euthymic bipolar disorder. J Affect Disord. 2013; 144:141–147. [PubMed: 22963894]

Nosyreva E, Szabla K, Autry AE, Ryazanov AG, Monteggia LM, Kavalali ET. Acute suppression of spontaneous neurotransmission drives synaptic potentiation. J Neurosci. 2013; 33:6990–7002. [PubMed: 23595756]

Nowak G, Legutko B, Skolnick P, Popik P. Adaptation of cortical NMDA receptors by chronic treatment with specific serotonin reuptake inhibitors. Eur J Pharmacol. 1998; 342:367–370. [PubMed: 9548410]

Nowak G, Trullas R, Layer RT, Skolnick P, Paul IA. Adaptive changes in the Nmethyl- D-aspartate receptor complex after chronic treatment with imipramine and 1-aminocyclopropanecarboxylic acid. J Pharmacol Exp Ther. 1993; 265:1380–1386. [PubMed: 8099620]

Nurnberger JI Jr, Adkins S, Lahiri DK, Mayeda A, Hu K, Lewy A, Miller A, Bowman ES, Miller MJ, Rau L, Smiley C, Davis-Singh D. Melatonin suppression by light in euthymic bipolar and unipolar patients. Arch Gen Psychiatry. 2000; 57:572–579. [PubMed: 10839335]

Nurnberger JI Jr, Berrettini W, Tamarkin L, Hamovit J, Norton J, Gershon E. Supersensitivity to melatonin suppression by light in young people at high risk for affective disorder. A preliminary report. Neuropsychopharmacology. 1988; 1:217–223. [PubMed: 3251502]

O'Neill MF, Sanger GJ. A single pretreatment with MK-801 or cocaine enhances their locomotor stimulant effects in rats. Brain Res. 1999; 834:103–111. [PubMed: 10407098]

O'Neill MJ, Bleakman D, Zimmerman DM, Nisenbaum ES. AMPA receptor potentiators for the treatment of CNS disorders. Curr Drug Targets CNS Neurol Disord. 2004; 3:181–194. [PubMed: 15180479]

O'Neill MJ, Witkin JM. AMPA receptor potentiators: application for depression and Parkinson's disease. Curr Drug Targets. 2007; 8:603–620. [PubMed: 17504104]

Ohgi Y, Futamura T, Hashimoto K. Glutamate signaling in synaptogenesis and NMDA receptors as potential therapeutic targets for psychiatric disorders. Curr Mol Med. 2015; 15:206–221. [PubMed: 25817855]

Pacchierotti C, Iapichino S, Bossini L, Pieraccini F, Castrogiovanni P. Melatonin in psychiatric disorders: a review on the melatonin involvement in psychiatry. Front Neuroendocrinol. 2001; 22:18–32. [PubMed: 11141317]

Pandi-Perumal SR, Srinivasan V, Maestroni GJ, Cardinali DP, Poeggeler B, Hardeland R. Melatonin: nature's most versatile biological signal? FEBS J. 2006; 273:2813–2838. [PubMed: 16817850]

Papp M, Gruca P, Boyer PA, Mocaer E. Effect of agomelatine in the chronic mild stress model of depression in the rat. Neuropsychopharmacology. 2003; 28:694–703. [PubMed: 12655314]

Papp M, Moryl E. Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. Eur J Pharmacol. 1994; 263:1–7. [PubMed: 7821340]

Paul IA, Nowak G, Layer RT, Popik P, Skolnick P. Adaptation of the N-methyl-Daspartate receptor complex following chronic antidepressant treatments. J Pharmacol Exp Ther. 1994; 269:95–102. [PubMed: 8169857]

Paul IA, Trullas R, Skolnick P, Nowak G. Down-regulation of cortical betaadrenoceptors by chronic treatment with functional NMDA antagonists. Psychopharmacology (Berl). 1992; 106:285–287. [PubMed: 1312732]

Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010; 9:203–214. [PubMed: 20168317]

Petty F, McChesney C, Kramer G. Intracortical glutamate injection produces helplesslike behavior in the rat. Pharmacol Biochem Behav. 1985; 22:531–533. [PubMed: 2859611]

Pilc A, Wieronska JM, Skolnick P. Glutamate-based antidepressants: preclinical psychopharmacology. Biol Psychiatry. 2013; 73:1125–1132. [PubMed: 23453290]

Pozzi L, Dorocic IP, Wang X, Carlen M, Meletis K. Mice lacking NMDA receptors in parvalbumin neurons display normal depression-related behavior and response to antidepressant action of NMDAR antagonists. PLoS One. 2014; 9:e83879. [PubMed: 24454710]

Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-

aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. J Clin Psychopharmacol. 2008; 28:631–637. [PubMed: 19011431]

Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry. 2009; 66:522–526. [PubMed: 19545857]

Przegalinski E, Tatarczynska E, Deren-Wesolek A, Chojnacka-Wojcik E. Antidepressant-like effects of a partial agonist at strychnine-insensitive glycine receptors and a competitive NMDA receptor antagonist. Neuropharmacology. 1997; 36:31–37. [PubMed: 9144639]

Quiroz JA, Tamburri P, Deptula D, Banken L, Beyer U, Fontoura P, Santarelli L. The efficacy and safety of basimglurant as adjunctive therapy in major depression; a randomized, double-blind, placebo controlled study. Neuropsychopharmacology. 2014; 39:S376–S377.

Rantamaki T, Castren E. Targeting TrkB neurotrophin receptor to treat depression. Expert Opin Ther Targets. 2008; 12:705–715. [PubMed: 18479217]

Rawls SM, McGinty JF. Muscarinic receptors regulate extracellular glutamate levels in the rat striatum: An in vivo microdialysis study. J Pharmacol Exp Ther. 1998; 286:91–98. [PubMed: 9655846]

Redman JR, Francis AJ. Entrainment of rat circadian rhythms by the melatonin agonist S-20098 requires intact suprachiasmatic nuclei but not the pineal. J Biol Rhythms. 1998; 13:39–51. [PubMed: 9486842]

Reiter RJ, Paredes SD, Manchester LC, Tan DX. Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. Crit Rev Biochem Mol Biol. 2009; 44:175–200. [PubMed: 19635037]

Reynolds IJ, Miller RJ. [3H]MK801 binding to the N-methyl-D-aspartate receptor reveals drug interactions with the zinc and magnesium binding sites. J Pharmacol Exp Ther. 1988; 247:1025–1031. [PubMed: 2849655]

Robson MJ, Elliott M, Seminerio MJ, Matsumoto RR. Evaluation of sigma (sigma) receptors in the antidepressant-like effects of ketamine in vitro and in vivo. Eur Neuropsychopharmacol. 2012; 22:308–317. [PubMed: 21911285]

Romo-Nava F, Alvarez-Icaza Gonzalez D, Fresan-Orellana A, Saracco Alvarez R, Becerra-Palars C, Moreno J, Ontiveros Uribe MP, Berlanga C, Heinze G, Buijs RM. Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. Bipolar Disord. 2014; 16:410–421. [PubMed: 24636483]

Salvatore P, Ghidini S, Zita G, DePanfilis C, Lambertino S, Maggini C, Baldessarini RJ. Circadian activity rhythm abnormalities in ill and recovered bipolar I disorder patients. Bipolar Disord. 2008; 10:256–265. [PubMed: 18271904]

Sanacora, G., Johnson, M., Khan, A., Atkinson, S., Riesenberg, R., Schronen, J. Adjunctive lanicemine (AZD6765) in patients with major depressive disorder and a history of inadequate response to antidepressants: primary results from a randomized, placebocontrolled study (PURSUIT). Presented at the 53rd Meeting of the ACNP; Hollywood, FL, USA. 2014a.

Sanacora G, Smith MA, Pathak S, Su HL, Boeijinga PH, McCarthy DJ, Quirk MC. Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. Mol Psychiatry. 2014b; 19:978–985. [PubMed: 24126931]

Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression. An emerging fronteir of neuropsychopharmacology for mood disorders. Neuropharmacology. 2012; 62:63–77. [PubMed: 21827775]

Saricicek A, Maloney K, Muralidharan A, Ruf B, Blumberg HP, Sanacora G, Lorberg B, Pittman B, Bhagwagar Z. Levetiracetam in the management of bipolar depression: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011; 72:744–750. [PubMed: 21034692]

Scarr E, Pavey G, Sundram S, MacKinnon A, Dean B. Decreased hippocampal NMDA, but not kainate or AMPA receptors in bipolar disorder. Bipolar Disord. 2003; 5:257–264. [PubMed: 12895203]

Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry. 2013; 73:1204–1212. [PubMed: 23562618]

Schousboe A, Bak LK, Waagepetersen HS. Astrocytic control of biosynthesis and turnover of the neurotransmitters glutamate and GABA. Front Endocrinol (Lausanne). 2013; 4:102. [PubMed: 23966981]

Shah A, Carreno FR, Frazer A. Therapeutic modalities for treatment resistant depression: focus on vagal nerve stimulation and ketamine. Clin Psychopharmacol Neurosci. 2014; 12:83–93. [PubMed: 25191499]

Sills MA, Loo PS. Tricyclic antidepressants and dextromethorphan bind with higher affinity to the phencyclidine receptor in the absence of magnesium and L-glutamate. Mol Pharmacol. 1989; 36:160–165. [PubMed: 2568580]

Singh, JB., Fedgchin, M., Daly, E., Xi, L., Melman, C., De Bruecker, G., Tadic, A., Sienaert, P., Wiegand, F., Manji, HK., Drevets, WC., Van Neuten, L. Efficacy and safety of intravenous esketamine in patients with treatment-resistant depression: a double-blind, double-randomization, placebo-controlled phase 2a study. Presented at the ACNP 52nd Annual Meeting; Hollywood, FL. 2013.

Singh NS, Zarate CAJ, Moaddel R, Bernier M, Wainer IW. What is hydroxynorketamine and what can it bring to neurotherapeutics? Expert Rev Neurother. 2014; 14:1239–1242. [PubMed: 25331415]

Skolnick P. Antidepressants for the new millennium. Eur J Pharmacol. 1999; 375:31–40. [PubMed: 10443562]

Skolnick P. Modulation of glutamate receptors: strategies for the development of novel antidepressants. Amino Acids. 2002; 23:153–159. [PubMed: 12373530]

Skolnick P, Layer RT, Popik P, Nowak G, Paul IA, Trullas R. Adaptation of Nmethyl- D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. Pharmacopsychiatry. 1996; 29:23–26. [PubMed: 8852530]

Smith EG, Deligiannidis KM, Ulbricht CM, Landolin CS, Patel JK, Rothschild AJ. Antidepressant augmentation using the N-methyl-D-aspartate antagonist memantine: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2013; 74:966–973. [PubMed: 24229746]

Srinivasan V, Smits M, Spence W, Lowe AD, Kayumov L, Pandi-Perumal SR, Parry B, Cardinali DP. Melatonin in mood disorders. World J Biol Psychiatry. 2006; 7:138–151. [PubMed: 16861139]

Thomson PA, Wray NR, Thomson AM, Dunbar DR, Grassie MA, Condie A, Walker MT, Smith DJ, Pulford DJ, Muir W, Blackwood DH, Porteous DJ. Sexspecific association between bipolar affective disorder in women and GPR50, an Xlinked orphan G protein-coupled receptor. Mol Psychiatry. 2005; 10:470–478. [PubMed: 15452587]

Tizabi Y, Bhatti BH, Manaye KF, Das JR, Akinfiresoye L. Antidepressant-like effects of low ketamine dose is associated with increased hippocampal AMPA/NMDA receptor density ratio in female Wistar-Kyoto rats. Neuroscience. 2012; 213:72–80. [PubMed: 22521815]

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006; 163:28–40. [PubMed: 16390886]

Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur J Pharmacol. 1990; 185:1–10. [PubMed: 2171955]

Van Oekelen D, Luyten WH, Leysen JE. 5-HT2A and 5-HT2C receptors and their atypical regulation properties. Life Sci. 2003; 72:2429–2449. [PubMed: 12650852]

Vetulani J. Complex action of antidepressant treatment on central adrenergic system: possible relevance to clinical effects. Pharmacopsychiatry. 1984; 17:16–21. [PubMed: 6324248]

Vieta E, Thase ME, Naber D, D'Souza B, Rancans E, Lepola U, Olausson B, Szamosi J, Wilson E, Hosford D, Dunbar G, Tummala R, Eriksson H. Efficacy and tolerability of flexibly-dosed adjunct TC-5214 (dexmecamylamine) in patients with major depressive disorder and inadequate response to prior antidepressant. Eur Neuropsychopharmacol. 2014; 24:564–574. [PubMed: 24507016]

Voleti B, Navarria A, Liu RJ, Banasr M, Li N, Terwilliger R, Sanacora G, Eid T, Aghajanian G, Duman RS. Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. Biol Psychiatry. 2013; 74:742–749. [PubMed: 23751205]

Whalley LJ, Perini T, Shering A, Bennie J. Melatonin response to bright light in recovered, drug-free, bipolar patients. Psychiatry Res. 1991; 38:13–19. [PubMed: 1658841]

Wirz-Justice A, Van den Hoofdakker RH. Sleep deprivation in depression: what do we know, where do we go? Biol Psychiatry. 1999; 46:445–453. [PubMed: 10459393]

Wong CS, Cherng CH, Luk HN, Ho ST, Tung CS. Effects of NMDA receptor antagonists on inhibition of morphine tolerance in rats: binding at μ-opioid receptors. Eur J Pharmacol. 1996; 297:27–33. [PubMed: 8851162]

Wood J, Birmaher B, Axelson D, Ehmann M, Kalas C, Monk K, Turkin S, Kupfer DJ, Brent D, Monk TH, Nimgainkar VL. Replicable differences in preferred circadian phase between bipolar disorder patients and control individuals. Psychiatry Res. 2009; 166:201–209. [PubMed: 19278733]

Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. Am J Psychiatry. 1990; 147:14–21. [PubMed: 2403471]

Wyatt JK, Dijk DJ, Ritz-de Cecco A, Czeisler CA. Sleep-facilitating effect of exogenous melatonin in healthy young men and women is circadian-phase dependent. Sleep. 2006; 29:609–618. [PubMed: 16774150]

Yamanaka H, Yokoyama C, Mizuma H, Kurai S, Finnema SJ, Halldin C, Doi H, Onoe H. A possible mechanism of the nucleus accumbens and ventral pallidum 5-HT1B receptors underlying the antidepressant action of ketamine: a PET study with macaques. Transl Psychiatry. 2014; 4:e342. [PubMed: 24399045]

Yanagihara Y, Ohtani M, Kariya S, Uchino K, Hiraishi T, Ashizawa N, Aoyama T, Yamamura Y, Yamada Y, Iga T. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers Biopharm. Drug Dispos. 2003; 24:37–43.

Yang C, Zhou ZQ, Gao ZQ, Shi JY, Yang JJ. Acute increases in plasma Mammalian target of rapamycin, glycogen synthase kinase-3b, and eukaryotic elongation factor 2 phosphorylation after ketamine treatment in three depressed patients. Biol Psychiatry. 2013; 73:e35–e36. [PubMed: 22884969]

Yilmaz A, Schulz D, Aksoy A, Canbeyli R. Prolonged effect of an anesthetic dose of ketamine on behavioral despair. Pharmacol Biochem Behav. 2002; 71:341–344. [PubMed: 11812542]

Yu JJ, Zhang Y, Wang Y, Wen ZY, Liu XH, Qin J, Yang JL. Inhibition of calcineurin in the prefrontal cortex induced depressive-like behavior through mTOR signaling pathway. Psychopharmacology (Berl). 2013; 225:361–372. [PubMed: 22875481]

Zarate C Jr, Machado-Vieira R, Henter I, Ibrahim L, Diazgranados N, Salvadore G. Glutamatergic modulators: the future of treating mood disorders? Harv Rev Psychiatry. 2010; 18:293–303. [PubMed: 20825266]

Zarate CA Jr, Singh JB, Quiroz JA, De Jesus G, Denicoff KK, Luckenbaugh DA, Manji HK, Charney DS. A double-blind, placebo-controlled study of memantine in the treatment of major depression. Am J Psychiatry. 2006; 163:153–155. [PubMed: 16390905]

Zarate CA, Mathews D, Ibrahim L, Chaves JF, Marquardt C, Ukoh I, Jolkovsky L, Brutsche N, Smith MA, Luckenbaugh D. A randomized trial of a lowtrapping nonselective N-methyl-D-aspartate channel blocker in major depression. Biol Psychiatry. 2013a; 74:257–264. [PubMed: 23206319]

Zarate CA, Mathews DC, Furey ML. Human biomarkers of rapid antidepressant effects. Biol Psychiatry. 2013b; 73:1142–1155. [PubMed: 23374639]

Zarate CA, Quiroz JA, Singh JB, Denicoff KD, De Jesus G, Luckenbaugh DA, Charney DS, Manji HK. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. Biol Psychiatry. 2005; 57:430–432. [PubMed: 15705360]

Zhou W, Wang N, Yang C, Li XM, Zhou ZQ, Yang JJ. Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. Eur Psychiatry. 2014; 29:419–423. [PubMed: 24321772]

Zimmer ER, Parent MJ, Leuzy A, Aliaga A, Aliaga A, Moquin L, Schirrmacher ES, Soucy JP, Skelin I, Gratton A, Gauthier S, Rosa-Neto P. Imaging in vivo glutamate fluctuations with [(11)C]ABP688: a GLT-1 challenge with ceftriaxone. J Cereb Blood Flow Metab. 2015; 35:1169–1174. [PubMed: 25806702]

Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, Holsboer F. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J Psychiatr Res. 2000; 34:171–181. [PubMed: 10867111]

Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol. 2011; 12:21–35. [PubMed: 21157483]

Zunszain PA, Horowitz MA, Cattaneo A, Lupi MM, Pariante CM. Ketamine: synaptogenesis, immunomodulation and glycogen synthase kinase-3 as underlying mechanisms of its antidepressant properties. Mol Psychiatry. 2013; 18:1236–1241. [PubMed: 23877835]
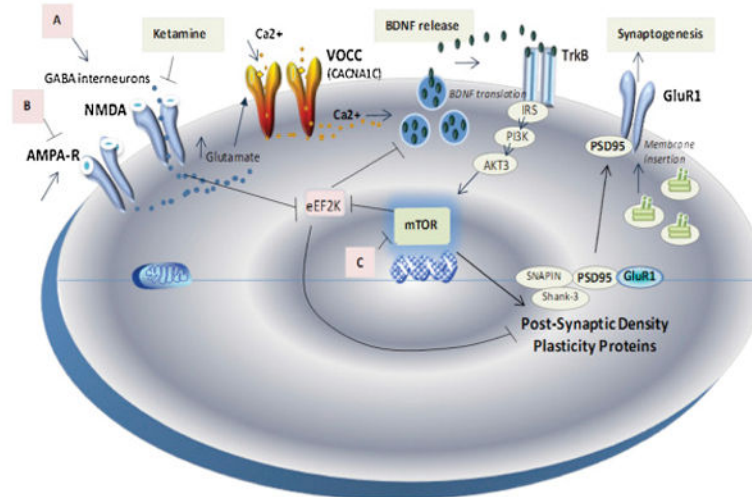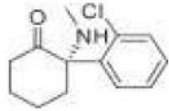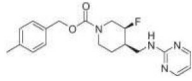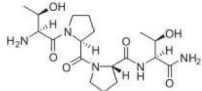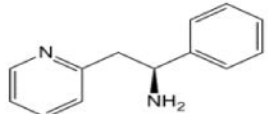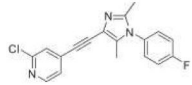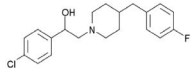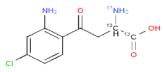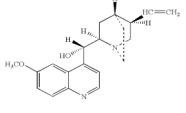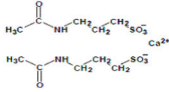
Fig. 1.
Schematic representation of postulated targets implicated in ketamine's mechanism of rapid antidepressant action that are amenable to pharmacological manipulation: A) GABA interneuron inhibition that leads to increased glutamate transmission, B) enhanced AMPA throughput, and C) mTOR activation.

AKT3: protein kinase B3; AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF: brain-derived neurotrophic factor; GABA: gamma aminobutyric acid; GluA1: AMPA receptor subunit 1; IRS: insulin receptor substrate; mTOR: mammalian target of rapamycin; NMDA: N-methyl-D-aspartate; PI3K: phosphoinositide-3 kinase; PSD95: postsynaptic density protein 95; TrkB: tropomyosin receptor kinase B; VOCC: voltage-operated calcium channel.

Table 1

The "Glutamate Storm" in Mood Disorders: Perspectives for the Development of New Glutamate Modulators for Depression

Glutamate modulator	Mechanism of action	Development status	Structure
Esketamine	Non-competitive NMDA channel blocker	Positive results in phase II for depression	
MK-0657 (CERC-301)	GluN2B antagonist	Concluded phase II for MDD	
GLYX-13 (rapastinel)	Glycine site partial agonist	Starting phase III for treatment-resistant MDD	
Org 26576	AMPA potentiator	Development halted after failed phase II in MDD	Not available
AZD6765 (Lanicemine)	Low-trapping NMDA antagonist	Positive results in phase II A/B for treatment-resistant MDD	
Basimglurant (RG-7090)	mGluR5 negative allosteric modulator	Under phase II for treatment-resistant MDD	
NRX-1074	NMDA glycine site partial agonist	Under phase II for MDD	Not available
(Eliprodil) EVT-101	Selective GluN2B antagonist	Completed phase I, no data available	
AV-101	Glycine receptor antagonist	Starting phase I B	
Dextro-methorphan and quinidine (Nuedexta)	Non-competitive NMDA antagonist	FDA approved for PBA. Case reports in MDD	
Acamprosate	NMDA and mGluR5 antagonist	Initial studies in MDD	

NMDAR: N-methyl-D-aspartate receptor; GluN2B: NMDA receptor subunit, glutamate-binding site; mGluR5: metabotropic glutamate receptor 5; MDD: major depressive disorder; PBA: pseudobulbar affect.