Published in final edited form as:
Clin Pharmacol Ther. 2012 February ; 91(2): 303–309. doi:10.1038/clpt.2011.244.

Ketamine as a Novel Antidepressant: From Synapse to Behavior

James W. Murrough, M.D.[1,2,3]

[1]Mood and Anxiety Disorders Program, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

[2]Department of Neuroscience, Mount Sinai School of Medicine, New York, NY

[3]Friedman Brain Institute, Mount Sinai School of Medicine, New York, NY

Keywords

major depression; glutamate; NMDA receptor; ketamine; antidepressant

Introduction

Recent reports of a rapid antidepressant effect of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine, even in treatment-resistant populations, has spurred translational therapeutic and neuroscience research aimed at elucidating ketamine's mechanism of action. This article provides a concise overview of research findings that pertain to the effects of low-dose ketamine at the cellular, neurocircuitry and behavioral levels and describes an integrated model of the action of ketamine in depression.

Major Depression and Treatment-Resistance: The Clinical Problem

Major depressive disorder (MDD) is a common medical illness associated with enormous morbidity and public health costs (1). As defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) (2), MDD represents a heterogeneous clinical syndrome characterized by the core symptoms of pervasive, sustained low mood and/or loss of interest in the environment accompanied by a constellation of other symptoms involving alternations in sleep, appetite, energy level, psychomotor function and cognition. The devastating public health impact of MDD results in part because the illness tends to strike in young adulthood and run a chronic or recurrent course (1). Suicidal ideation and behavior is a particularly concerning component of MDD and suicide has become the third leading cause of death in individuals 15 to 24 years of age.

The advent of modern psychopharmacology for depression fundamentally transformed the practice and science of psychiatry and has relieved the suffering of untold numbers of

Correspondence: James W. Murrough, M.D., Mount Sinai School of Medicine, Department of Psychiatry, One Gustave L. Levy Place, Box 1230, New York, New York 10029, Tel: 212-241-7574, Fax: 212-241-3354, james.murrough@mssm.edu.

Support and Disclosures
Dr. Murrough is a full-time employee of Mount Sinai School of Medicine and is currently supported by NIH/NIMH (1K23MH094707-01), NARSAD (Young Investigator Award), and the American Foundation For Suicide Prevention (YIG-0-10-223). The content of this article is the responsibility of the author and does not necessarily reflect the views or opinions of the NIH or other funding agencies. Within the past two years Dr. Murrough completed a research fellowship at Mount Sinai School of Medicine that was supported in part by an educational grant from AstraZeneca to Mount Sinai.
Dr. Charney, Dean of Mount Sinai School of Medicine, has been named as an inventor on a use-patent of ketamine for the treatment of depression. If ketamine were shown to be effective in the treatment of depression and received approval from the Food and Drug Administration for this indication, Dr. Charney and Mount Sinai School of Medicine could benefit financially.

patients. Modern clinical trials research, however, indicates that current treatments for MDD are in many cases only partially effective and in some cases not at all effective. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, conducted in a large adult outpatient treatment-seeking sample with MDD (N = 3,671), found that only 36.8% of patients achieved remission following an optimized trial of the serotonin selective reuptake inhibitor (SSRI) citalopram for up to 12 weeks (3). Additional treatment steps in STAR*D yielded only modest incremental gains in remission rates and 33% of patients remained ill following up to four consecutive treatment steps involving antidepressant combination and augmentation strategies. In a second large-scale study, the Combining Medications to Enhance Depression Outcomes (CO-MED) trial compared two antidepressant combinations with SSRI monotherapy at 12 weeks and 7 months and found that remission rates for any strategy were modest (37.7% – 38.9%), similar to STAR*D, and did not differ from each other (4).

The sobering results of these large, well-designed clinical trials suggest that almost two-thirds of patients with MDD will remain ill despite an optimized trial of an antidepressant. This group of patients can be described as suffering from treatment-resistant depression (TRD), and as a group are more likely to suffer a higher symptom burden and a more chronic illness course compared to their non-TRD counterparts. For patients who eventually respond during a course of treatment, the long delay in the onset of therapeutic action (up to 12 weeks) inherent in current treatments furthers add to the illness burden and morbidity of MDD.

Ketamine as a Novel, Rapid-Acting Antidepressant

Despite the large public health burden of MDD, the pace of therapeutic discovery in this area has lagged significantly behind other areas of medicine. A major obstacle to the development of improved, more efficacious treatments is our limited understanding of the molecular mechanisms underlying the depressed state or treatment response (5). While the monoamine system has been the focus of research and treatment development in depression for more than 50 years, it is clear that novel treatment discovery in depression will require the advancement of new pathophysiological models of the disorder. Toward this end, the glutamate system and molecular mechanisms related to synaptic and neuronal plasticity are emerging as key components of a new generation of disease models of depression and antidepressant therapeutics (5,6).

In a novel proof-of-concept clinical trial targeting the glutamate system, Berman et al reported the first finding of a rapid antidepressant response to the glutamate N-methyl-D-aspartate (NMDA) receptor (NMDAR) antagonist ketamine in nine depressed patients in a randomized, saline-controlled cross-over design (7). Ketamine-related mood improvement was robust and peaked within 72 hours following a single low-dose infusion (0.5 mg/kg over 40 min). Importantly, the observed antidepressant effect was segregated in time from transient neurocognitive (including psychotomimetic and dissociative) effects, which peaked during the ketamine infusion and returned to baseline within two hours. These initial findings were then replicated and extended in a larger study of 18 inpatients with TRD utilizing a similar saline-controlled cross-over design (8). In that study, the drug-placebo effect size was very large the day following infusion and 71% of patients met response criteria at this time-point. In addition, a significant minority of patients (35%) maintained their response for at least 1 week. Following these original observations, multiple case reports, case series and several small-scale clinical trials of ketamine in depression have emerged, adding support to the hypothesis that ketamine possesses rapid-acting antidepressant properties (see Table 1).

Research has begun to investigate relapse-prevention and therapeutic maintenance strategies for patients who manifest an antidepressant response to ketamine (9,10). In a first study of 26 patients with TRD, the neuroprotective agent riluzole was tested as a relapse-prevention approach following ketamine (9). In this study, seventeen patients (65%) met response criteria and thirteen patients (50%) met remission criteria 24 hours following a single low-dose ketamine infusion. Patients who continued to maintain their response 3 days following the infusion (54%) proceeded to participate in a four-week, double blind, placebo-controlled, continuation trial of riluzole where the main outcome measure was time-to-relapse. This study did not support a specific role for riluzole for relapse prevention following ketamine, in part because both groups maintained a relatively prolonged response (> 3 weeks). In another study, repeated infusions of low-dose ketamine were administered three days a week following an electroconvulsive therapy (ECT)-like schedule (10). In this study nine patients with TRD underwent six infusions of ketamine over two weeks. The procedures were well tolerated and resulted in a sustained response during the two-week treatment period and for an average for nearly three weeks following the end of treatment. In a particularly striking case, a woman with severe and chronic TRD experienced a sustained remission from her symptoms for three months following the end of the acute treatment period in the absence of concurrent pharmacotherapy (11).

Suicidal ideation and behavior is a chief concern related to MDD and there is an urgent and unmet need for rapidly acting medical interventions for this worrisome condition. In contrast to conventional antidepressant agents that may actually worsen suicidal ideation in the short-term, preliminary evidence suggests that ketamine may possess acute anti-suicidal ideation (SI) properties (12–14). An initial study reported rapid reduction in both explicit and implicit measures of SI in response to ketamine with 81% of patients with TRD free of SI 24 hours following infusion (12). A second study reported decreases in SI as early as 40 minutes after initiation of ketamine (13) and a third study reported rapid reductions in SI following ketamine in patients presenting to the emergency department with SI and depression (14).

Ketamine is a dissociative anesthetic that causes transient altered mental function at the sub-anesthetic doses that have been studied in patients with depression, including dissociative and psychotomimetic effects. These effects are usually mild to moderate, although they can be more pronounced in a minority of cases. Ketamine is also a drug of abuse and both clinical and preclinical studies have raised concerns regarding the potential for neurotoxicity of ketamine and other NMDAR antagonists, particularly when given at high doses and over extended periods of time. Given these considerations, future clinical research with ketamine must proceed cautiously and weigh the potential risks and benefits for patients with TRD.

Molecular Mechanisms Underlying the Antidepressant Action of Ketamine

The observed antidepressant effects of ketamine in clinical populations provides compelling rationale for investigating NMDAR antagonists and other modulators of the glutamate system as novel targets for therapeutic development in MDD. In addition to NMDAR antagonism, ketamine potentiates glutamate transmission at alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPAR) and has additional inhibitory effects at muscarinic acetylcholine receptors. NMDARs, AMPARs and kainate receptors are ionotropic glutamate receptors localize throughout the central nervous system (CNS) and play a major role in signaling at excitatory synapses. Trullas and Skolnick first articulated the hypothesis that NMDAR antagonists may represent a new class of antidepressants, based in part on the observation that inescapable stress led to disruptions in hippocampal neuronal long-term potentiation (LTP) – an NMDAR-dependent process – in parallel with the observed syndrome of behavioral depression (15). This line of research

demonstrated the ability of NMDAR antagonists, including dizolcipine (also known as MK-801), to exert antidepressant effects in animal models (15) and showed that traditional monoaminergic antidepressants modified NMDARs following chronic (but not acute) treatment, suggesting that NMDAR modulation may represent a downstream effect of monoamine drugs (16). Taken together, these data suggested that targeting the NMDAR complex directly may represent a strategy leading to improved, faster-acting antidepressant agents (6).

A series of preclinical studies of ketamine in animal models of depression are beginning to yield important insights into the cellular and molecular mechanisms of ketamine's antidepressant action and the downstream consequences of NMDAR antagonism (Table 2). In particular, several recent well-designed studies have provided compelling evidence that ketamine induces rapid enhancement of synaptic structure and function in cortical regions concomitantly with antidepressant behavioral effects in rodents (17–19). Li et al reported that ketamine rapidly activated the ubiquitous mammalian target of rapamycin (mTOR) pathway, leading to increased synaptic signaling proteins as well as an increased number and function of new spine synapses in the prefrontal cortex (PFC) of rats (17). Specifically, ketamine was observed to transiently increase levels of phosphorylated eukaryotic initiation factor 4E binding protein 1 (4E-BP1), p70S6 kinase (p70S6K) and mTOR, all members of the mTOR-signaling pathway that function as key regulators of protein translation. Ketamine was also observed to increase the activation of other ubiquitous mediators of translation and synaptic plasticity, namely extracellular signal–regulated kinase (ERK) and protein kinase B (PKB/Akt). In fact, blockade of either the ERK or Atk pathway abolished the impact of ketamine on the mTOR pathway, emphasizing the interaction between plasticity-related signally pathways. Ketamine also resulted in elevate levels of several synaptic proteins (PSD95, GluR1, synapsin I), increased spine density and enhanced excitatory postsynaptic current (EPSC) frequency responses – all suggestive of a rapid enhancement of the structure and function of cortical synapses by ketamine. Blockade of mTOR signaling prevented both ketamine-induced synaptogenesis and antidepressant behavioral responses.

A second study by the same group extended these findings to a chronic mild stress (CMS) paradigm and demonstrated that ketamine was able to reverse CMS-induced deficits in behavior as well as in synaptic proteins, spine density and EPSC frequency/amplitude in PFC (19). The behavioral and molecular effects of ketamine were again blocked by inhibition of the mTOR signaling pathway. In another recent study, Autry et al reported that the antidepressant effect of ketamine was dependent on the rapid synthesis of brain-derived neurotrophic factor (BDNF) in a mouse model (18). Ketamine resulted in elevated levels of BDNF in the hippocampus (but not the nucleus accumbens) and knockouts of either BDNF and or the neurotrophic tyrosine kinase receptor (TrkB) were insensitive to the antidepressant effects of ketamine. Extending these results further, the authors found that ketamine blockade of NMDARs deactivated eukaryotic elongation factor 2 (eEF2) kinase, which resulted in reduced eEF2 phosphorylation and subsequent enhancement of BDNF translation. Several classes of antidepressants, including ECT, have also been demonstrated to increase BDNF in the hippocampus, although generally over a longer time period. A clinical study found that peripheral measures of BDNF did not increase following ketamine (20), however the significance of this finding is unclear given the potential uncoupling of peripheral and central functioning of BDNF. Finally, a study of repeated daily doses of ketamine over seven days in a CMS model found that ketamine reversed CMS-induced weight loss and normalized neuroendocrine measures but did not alter hippocampal BDNF protein levels (21).

Taken together, these studies provide compelling evidence for the involvement of synaptic plasticity and neurotrophic signaling in the mechanism of action of ketamine. The observation of mTOR pathway or BDNF pathway activation by NMDAR antagonism provides a critical link between NMDAR modulation and neurotrophic and synaptic plasticity-related theories of depression and antidepressant action (22). All three studies described above reported that the molecular and behavioral effects of ketamine were blocked by administration of the AMPAR antagonist NBQX, extending a previous report (23). Preclinical work has linked enhancement of AMPA signaling with synaptic plasticity and these findings support to a model whereby ketamine may act to both decrease NMDAR signaling and enhance AMPAR signaling with a net effect of enhancement of synaptic plasticity and neurotrophic signaling (6). Of potential therapeutic relevance, a novel class of compounds that allosterically enhances the activity of AMPARs (referred to as AMPA potentiators) has demonstrated antidepressant properties in animal models (6) and may represent a promising avenue for novel treatment development based on the glutamate system.

The Impact of Ketamine on Neurocircuitry Relevant to Depression

Current neurocircuitry models of depression posit relatively deficient dorsal and lateral PFC and anterior cingulate cortex (ACC) regulation over ventral cortical and subcortical regions that govern emotion generation and stress responses (24,25). Dorsolateral and dorsomedial regions of PFC (DLPFC and DMPFC, respectively) have been consistently found to be underactive during a major depressive episode, often in parallel with overactivity of ventral cortical structures (e.g. subgenual ACC [SGACC], orbital frontal cortex [OFC]) or subcortical limbic structures (e.g. amygdala) (24). This perturbation of neural activity results in the cognitive, emotional and behavioral manifestations of depression, while normalization of aberrant activity patterns is posited to underlie amelioration of clinical symptoms.

The question of how ketamine affects the brain at the circuit level to bring about a rapid antidepressant response remains an area of active research. A series of studies found that ketamine and other NMDAR antagonists enhance glutamateric signaling in the cortex of rodents, potentially through inhibition of GABAergic interneurons and subsequent disinhibition of cortical pyramidal neurons (26,27). Enhancement of activity at pyramidal glutamatergic synapses by ketamine would be consistent with the observations of enhanced cortical synaptic plasticity and function described above. Neuroimaging studies in humans likewise suggest that subanesthetic doses of ketamine result in elevated cortical activity, including in regions of PFC and ACC (28–31). A functional MRI (fMRI) study found that ketamine resulted in decreased activity in ventromedial PFC (VMPFC), OFC and SGACC accompanied by increased activity in posterior cingulate and other cortical regions (32). Studies utilizing proton magnetic resonance spectroscopy (^{1}H-MRS) to examine the impact of ketamine on the glutamate system *in vivo* have yielded mixed results (33,34), although the lack of robust findings may be attributed to limitations inherent in current ^{1}H-MRS methodology. It should be noted that the neuroimaging studies described above have all been conducted in healthy populations and therefore extrapolating the findings to depression remains speculative.

The molecular and neuroimaging studies summarized herein are consistent with the hypothesis that ketamine exerts its rapid antidepressant effects via rapid enhancement of PFC and ACC function (see Figure 1), although this hypothesis remains to be tested directly. Intriguingly, direct stimulation of medial PFC (MPFC) using optogenetic techniques in mice resulted in an immediate antidepressant effect in a social defeat stress paradigm (35). The same report described reduced expression of immediate early genes, reliable markers of neuronal activity, in both mouse MPFC following social defeat stress and in PFC tissue

obtained from depressed individuals postmortem, further supporting the hypothesis of reduced functioning of PFC regions in depression. A series of studies utilizing magnetoencephalographic (MEG) recordings in patients with TRD prior to infusion of a single low-dose of ketamine provide initial support for a role for the ACC in antidepressant response (36,37). In these studies, pretreatment ACC activity was associated with subsequent antidepressant response to ketamine. A significant gap in the current literature is that no study has investigated changes in neural markers following ketamine in a depressed population. Direct testing of the role of the ACC, PFC or other regions in the mechanism of action of ketamine will require optimized pre- and post-intervention imaging designs in clinical populations utilizing a placebo control condition.

Conclusions and Future Directions

Despite progress in drug discovery for MDD, there remains an unmet public health need to identify novel, rapidly acting agents for patients with treatment-resistant forms of depression. The observations of a rapid antidepressant effect of low-dose ketamine has generated considerable interest in the scientific and medical community alike, representing a proof-of-principle in targeting the NMDAR, and glutamate system more broadly, as a novel treatment approach in depression. Low-dose ketamine appears to enhance the strength of cortical synapses through NMDAR and AMPAR-dependent and neurotrophic mechanisms and may rapidly reverse prefrontal cortical deficits in depression at the neurocircuit level, leading to an amelioration of clinical symptoms. Models linking ketamine's effects at the cellular, circuit and behavioral levels in depression, however, remain to be tested directly. For example, no study to date has investigated the impact of ketamine on functional neural markers in patients with MDD.

The interpretation of the available clinical outcome data concerning the efficacy of ketamine as an antidepressant is limited by small sample sizes and the lack of an adequate control condition in some cases. To date, no large-scale study of ketamine in MDD has been completed that utilizes an "active" control condition (e.g. a different anesthetic agent) that would mimic some of ketamine's acute neuropsychiatric effects and thereby strengthen the integrity of the study blinding procedures, although these studies are underway (ClinicalTrials.gov NCT00768430). Concerns regarding potential adverse behavioral and neurotoxic effects of ketamine and its potential for abuse demand a cautious approach to treatment development. Never the less, ketamine may represent an important addition to the armamentarium of therapeutic interventions for severe and treatment refractory cases of MDD. Future research may investigate alternative dosing or delivery strategies in order to enhance the safe use of ketamine.

In parallel with clinical research designed to optimize the safety and efficacy of ketamine for TRD, translational neuroscience approaches using ketamine as a model of rapid antidepressant action hold considerable potential to advance treatment discovery for MDD. In particular, the identification of biomarkers of rapid antidepressant response using neuroimaging or other *in vivo* approaches is hoped to speed novel therapeutic discovery in depression by providing surrogate endpoints for testing novel candidate therapeutics.

References

1. Kessler RC, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289:3095–3105. [PubMed: 12813115]
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR 4th. American Psychiatric Association; Washington, DC; New York: 2000. Task Force on DSM-IV. text revision ed

3. Rush AJ, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006; 163:1905–1917. [PubMed: 17074942]
4. Rush AJ, et al. Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study. Am J Psychiatry. 2011; 168:689–701. [PubMed: 21536692]
5. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008; 455:894–902. [PubMed: 18923511]
6. Manji HK, et al. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. Biol Psychiatry. 2003; 53:707–742. [PubMed: 12706957]
7. Berman RM, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000; 47:351–354. [PubMed: 10686270]
8. Zarate CA Jr, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006; 63:856–864. [PubMed: 16894061]
9. Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. Int J Neuropsychopharmacol. 2010; 13:71–82. [PubMed: 19288975]
10. aan het Rot M, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry. 2010; 67:139–145. [PubMed: 19897179]
11. Murrough JW, Perez AM, Mathew SJ, Charney DS. A case of sustained remission following an acute course of ketamine in treatment-resistant depression. J Clin Psychiatry. 2011; 72:414–415. [PubMed: 21450159]
12. 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]
13. Diazgranados N, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry. 2010
14. Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int J Neuropsychopharmacol. 2011:1–5.
15. Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur J Pharmacol. 1990; 185:1–10. [PubMed: 2171955]
16. Skolnick P, Layer RT, Popik P, Nowak G, Paul IA, Trullas R. Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. Pharmacopsychiatry. 1996; 29:23–26. [PubMed: 8852530]
17. Li N, et al. mTOR-Dependent Synapse Formation Underlies the Rapid Antidepressant Effects of NMDA Antagonists. Science. 2010; 329:959–964. [PubMed: 20724638]
18. Autry AE, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature. 2011
19. Li N, et al. 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]
20. Machado-Vieira R, et al. Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist. J Clin Psychiatry. 2009; 70:1662–1666. [PubMed: 19744406]
21. Garcia LS, et al. Ketamine treatment reverses behavioral and physiological alterations induced by chronic mild stress in rats. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33:450–455. [PubMed: 19439250]
22. Duman RS, Monteggia LM. A Neurotrophic Model for Stress-Related Mood Disorders. Biol Psychiatry. 2006; 59:1116–1127. [PubMed: 16631126]
23. Maeng S, et al. 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]

24. Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology. 2010; 35:192–216. [PubMed: 19693001]
25. Murrough JW, Iacoviello B, Neumeister A, Charney DS, Iosifescu DV. Cognitive dysfunction in depression: Neurocircuitry and new therapeutic strategies. Neurobiol Learn Mem. 2011
26. 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]
27. Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. J Neurosci. 2007; 27:11496–11500. [PubMed: 17959792]
28. Vollenweider FX, et al. Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [18F]fluorodeoxyglucose (FDG). Eur Neuropsychopharmacol. 1997; 7:9–24. [PubMed: 9088881]
29. Langsjo JW, et al. Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology. 2003; 99:614–623. [PubMed: 12960545]
30. Langsjo JW, et al. Effects of subanesthetic ketamine on regional cerebral glucose metabolism in humans. Anesthesiology. 2004; 100:1065–1071. [PubMed: 15114201]
31. Holcomb HH, Lahti AC, Medoff DR, Cullen T, Tamminga CA. Effects of noncompetitive NMDA receptor blockade on anterior cingulate cerebral blood flow in volunteers with schizophrenia. Neuropsychopharmacology. 2005; 30:2275–2282. [PubMed: 16034443]
32. Deakin JF, Lees J, McKie S, Hallak JE, Williams SR, Dursun SM. Glutamate and the neural basis of the subjective effects of ketamine: a pharmaco-magnetic resonance imaging study. Arch Gen Psychiatry. 2008; 65:154–164. [PubMed: 18250253]
33. Rowland LM, et al. Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study. Am J Psychiatry. 2005; 162:394–396. [PubMed: 15677610]
34. Taylor MJ, Tiangga ER, Ni Mhuircheartaigh R, Cowen P. Lack of effect of ketamine on cortical glutamate and glutamine in healthy volunteers: a proton magnetic resonance spectroscopy study. J Psychopharmacol. 2011
35. Covington HE 3rd, et al. Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. J Neurosci. 2010; 30:16082–16090. [PubMed: 21123555]
36. Salvadore G, et al. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. Biol Psychiatry. 2009; 65:289–295. [PubMed: 18822408]
37. Salvadore G, et al. Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. Neuropsychopharmacology. 2010; 35:1415–1422. [PubMed: 20393460]
38. Phelps LE, Brutsche N, Moral JR, Luckenbaugh DA, Manji HK, Zarate CA Jr. Family history of alcohol dependence and initial antidepressant response to an N-methyl-D-aspartate antagonist. Biol Psychiatry. 2009; 65:181–184. [PubMed: 18996507]
39. Garcia LS, et al. 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]
40. 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

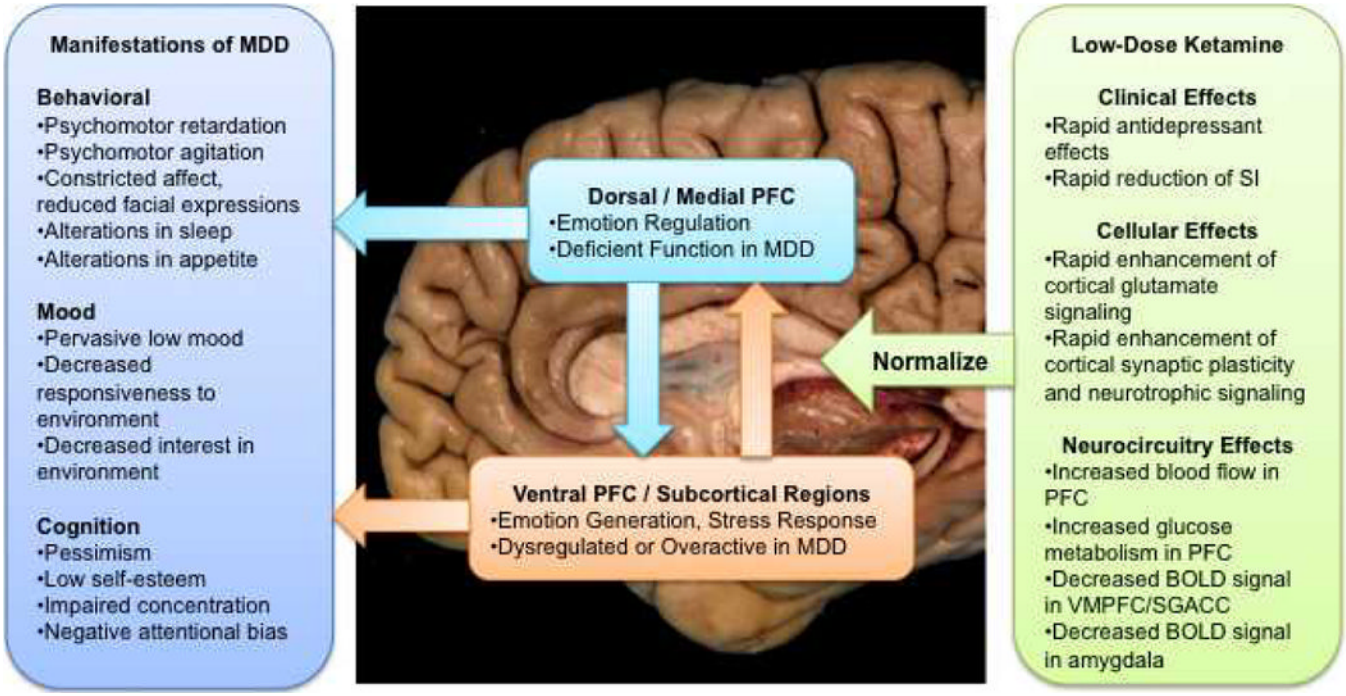

Figure 1. Clinical, Cellular and Neurocircuity Effects of Low-Dose Ketamine in Major Depression

Figure depicts schematic of cellular and neurocircuity effects of ketamine hypothesized to underlie antidepressant effects. Ketamine appears to rapidly enhance signaling at glutamatergic synapses in cortical regions important for mood regulation and induce neuroplastic changes therein, potentially accounting for both the rapid and relatively sustained clinical antidepressant effect. Clinical improvement is hypothesized to result ultimately from ketamine's ability to normalize interactions between dorsal regulation and ventral emotion generation neural systems. See text for details and references.

BOLD, blood oxygenation level-dependent; PFC, prefrontal cortex; VMPFC, ventromedial PFC, SGACC, subgenual ACC Anatomical specimen courtesy of TP Naidich, ME Fowkes and CY Tang.

Table 1

Antidepressant Effects of Ketamine in Clinical Populations

Reference	Sample	Intervention	Design	Primary Finding
aan het Rot et al 2010 (10)	TRD (N = 10)	Ketamine 0.5 mg/kg IV (six doses over 12 days)	Open-label	Well tolerated; 85% mean reduction in depressive symptoms following six infusions
Berman et al 2000 (7)	MDD (N = 6), bipolar depression (N = 1)	Ketamine 0.5 mg/kg IV (single dose)	Placebo-controlled, double-blind, crossover	Significant improvement in depressive symptoms within 72 hours
Diazgranados et al 2010 (13)	TRD (N = 33)	Ketamine 0.5 mg/kg IV (single dose)	Open-label	Significant improvement in depression and SI within four hours
Larkin et al 2011 (14)	Depressed patients presenting in the ED	Ketamine 0.2 mg/kg IV (single dose)	Open-label	Significant improvement in depressive symptoms and SI within 2 hours and up to 10 days
Machado-Vieira et al 2009 (20)	TRD (N = 23)	Ketamine 0.5 mg/kg IV (single dose)	Open-label	Significant improvement in depressive symptoms within four hours; no change in BDNF plasma levels
Mathew et al 2010 (9)	TRD (N = 23)	Ketamine 0.5 mg/kg IV (single dose); Riluzole 100–200 mg PO daily	Open-label ketamine followed by double-blind, placebo-controlled riluzole for relapse prevention	65% response at 24 hours; 54% at 72 hour; no effect of riluzole on time-to-relapse
Phelps et al 2009 (38)	TRD (N = 26)	Ketamine 0.5 mg/kg IV (single dose)	Open-label	Significant improvement in depressive symptoms within four hours; family history of alcohol dependence predicted greater improvement
Price et al 2009 (12)	TRD (N = 26)	Ketamine 0.5 mg/kg IV (single dose)	Open-label	Significant reduction in depression and SI 24 hours following ketamine
Zarate et al 2006 (8)	TRD (N = 18)	Ketamine 0.5 mg/kg IV (single dose)	Placebo-controlled, double-blind, crossover	Significant improvement in depressive symptoms up to one week; 71% response at 24 hours

Table describes clinical trials of low-dose ketamine in patients with major depression or bipolar depression (does not include case reports). ED: Emergency Department; SI: suicidal ideation; TRBD: treatment-resistant bipolar depression; TRD: treatment-resistant depression

Table 2

Behavioral and Molecular Effects of Ketamine in Animal Models of Depression

Reference	Depression Model	Intervention	Behavioral Effects	Molecular Effects
Autry et al 2011 (18)	Mice (wild-type or BDNF/Trk B-knockout); FST; NSFT; LH; CMS	Ketamine 3.0 mg/kg IP (single dose)	Acute antidepressant effects observed in non-stressed animals and CMS; antidepressant effects blocked by BDNF or TrK B knockout or NBQX	Antidepressant effects dependent on rapid (transient) synthesis of BDNF; ketamine blockade of NMDAR resulted in deactivation of eEF2 kinase, decreased eEF2 phosphorylation and de-suppression of BDNF translation
Garcia et al 2008 (39)	Rats; FST	Ketamine 5, 10 or 15 mg/kg IP (single dose)	Acute antidepressant effects observed in response to 10 and 15 (but not 5) mg/kg dose	Ketamine resulted in increased BDNF levels in hippocampus (only at higher 15 mg/kg dose)
Garcia et al 2009 (21)	Rats; CMS (40 days)	Ketamine 15 mg/kg IP (single dose or daily for 7 days)	Antidepressant effects observed in CMS model following repeated but not acute treatment	Acute and chronic treatment reversed CMS-induced weight loss and normalized corticosterone and ACTH levels; ketamine did not alter hippocampal BDNF protein levels
Koike et al 2011 (40)	Mice or rats; TST (used mice), LH (used rats)	Ketamine 10 or 30 mg/kg IP	Acute antidepressant effects observedin both LH and TST; TST effect persisted for 72h; antidepressant effects blocked by NBQX	None reported
Li et al 2010 (17)	Rats; FST; LH; NSFT	Ketamine 10 mg/kg IP (single dose)	Acute antidepressant effects observed in all three tests; effects blocked by rapamycin infusion into MPFC or administration of NBQX	Ketamine rapidly activated the mTOR signaling pathway in the PFC (increased activation/phosphorylation of 4E-BP1, p70S6K, and mTOR); ketamine increased levels of postsynaptic (PSD95, GluR1) and presynaptic (synapsin I) proteins and increased spine density and EPSC frequency and amplitude
Li et al 2011 (19)	Rats; CMS (21 days); SPT, NSFT	Ketamine 10 mg/kg IP (single dose)	Antidepressant effects observed in both tests (ketamine reversed CMS-induced behavioral abnormalities); effects lasted up to 7 days; effects blocked by ICV infusion of rapamycin	Ketamine rapidly reversed CMS-induced deficits in synaptic proteins (PSD95, GluR1, synapsin I), spine density and EPSC frequency/amplitude in PFC; molecular effects of ketamine blocked by inhibition of mTOR signaling pathway
Maeng et al 2008 (23)	Mice; FST, LH	Ketamine 0.5, 2.5 or 10 mg/kg IP (single dose)	Acute antidepressant effects observed in both tests and maintained for two weeks (in FST); effect in FST blocked by NBQX	Ketamine resulted in lower levels of phosphorylated GluR1 (S845) AMPAR subunit; effect blocked by NBQX

Table presents a selective summary of preclinical studies of ketamine in animal models of depression.

ACTH: Adrenocorticotropic hormone; AMPA: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; AMPAR: AMPA receptor; BDNF: brain-derived neurotrophic factor; CMS: chronic mild stress; CREB: cAMP response element binding protein; eEF2: eukaryotic elongation factor 2; EPSC: excitatory postsynaptic current; FST: forced swim test; GluR1: glutamate receptor 1; HPA: hypothalamic–pituitary–adrenal; ICV: intracerebroventricular; LH: learned helplessness; mTOR: mammalian target of rapamycin; MPFC: medial prefrontal cortex; NBQX: 2,3-dihydroxy-6-nitro-7-sulfoamoylbenzo(f)-quinozaline; NMDA: *N*-methyl-*D*-aspartate; NMDAR: NMDA receptor; NSFT: novelty suppressed feeding test; PAC: passive avoidance conditioning; PSD95: postsynaptic density protein 95; p70S6K: p70S6 kinase; PKA: protein kinase A; PKC: protein kinase C; SPT: sucrose preference test; TrK B: tyrosine kinase receptor B; 4E-BP1: eukaryotic initiation factor 4E binding protein 1