Ketamine as a Novel Antidepressant: From Synapse to Behavior

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Recent reports of a rapid antidepressant effect of the glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine, even in treatment-resistant populations, have 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 the treatment of depression.

MAJOR DEPRESSION AND RESISTANCE TO TREATMENT: 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 fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV),[2] MDD is 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 partly from the fact that the illness tends to strike in young adulthood and runs a chronic or recurrent course.[1] Suicidal ideation (SI) 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 has transformed the practice and science of psychiatry fundamentally and has relieved the suffering of untold numbers of patients. Modern research based on clinical trials, however, indicates that current treatments for MDD are only partially effective in many cases 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 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 serotonin selective reuptake inhibitor 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 significantly 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, they 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 further adds to the burden of illness 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 mechanisms and neurocircuitry underlying the depressed state or treatment response.[5] Although the monoamine system has been the focus of research and treatment development for depression over a period of more than 50 years, discovery of a novel treatment for depression will clearly require the advancement of new pathophysiological models of the disorder. Toward this end, the glutamate system and the

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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 NMDA receptor (NMDAR) antagonist ketamine in nine depressed patients in a randomized, saline-controlled crossover design.[7] Ketamine-related mood improvement was robust and peaked within 72 h following a single low-dose infusion (0.5 mg/kg over 40 min). Importantly, the observed antidepressant effect was segregated in time from the transient neurocognitive (including psychotomimetic and dissociative) effects, which peaked during ketamine infusion and returned to baseline within 2 h. These initial findings were then replicated and extended in a larger study of 18 inpatients with TRD by using a similar saline-controlled crossover design.[8] In that study, the size of the drug–placebo effect was very large the day following infusion, and 71% of patients met the 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 (**Table 1**).

Research has begun into the prevention of relapse and development of therapeutic maintenance strategies for patients who show an antidepressant response to ketamine.[9,10] In an initial study of 26 patients with TRD, the neuroprotective agent riluzole was tested as a relapse-prevention approach following ketamine administration.[9] In this study, 17 patients (65%) met the response criteria and 13 patients (50%) met the remission criteria 24 h following a single ketamine infusion. Patients who continued to maintain their response 3 days after the infusion (54%) proceeded to participate in a 4-week, double-blind, placebo-controlled, continuation trial of riluzole, in which the main outcome measure was time to relapse. This study did not support a specific role for riluzole in relapse prevention following ketamine, in part because both groups maintained a relatively prolonged response. In another study, repeated infusions of low-dose ketamine were administered 3 days a week following a schedule similar to that of electroconvulsive therapy.[10] In this study, nine patients with TRD underwent six infusions of ketamine over 2 weeks. The procedures were well tolerated and resulted in a sustained response during the 2-week treatment period and, on average, for nearly 3 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 3 months following the end of the acute treatment period in the absence of concurrent pharmacotherapy.[11]

Table 1 Antidepressant effects of ketamine in clinical populations

Reference	Sample	Intervention	Design	Primary finding
aan het Rot *et al.*[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.*[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 h
Diazgranados *et al.*[13]	TRD (*N* = 33)	Ketamine 0.5 mg/kg IV (single dose)	Open-label	Significant improvement in depression and SI within 4 h
Diazgranados *et al.*[41]	TRD (*N* = 18)	Ketamine 0.5 mg/kg IV (single dose)	Placebo-controlled, double-blind, crossover, add-on study	Significant improvement in depressive symptoms within 40 min up to three days; overall 71% response
Larkin *et al.*[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 h and up to 10 days
Machado-Vieira *et al.*[20]	TRD (*N* = 23)	Ketamine 0.5 mg/kg IV (single dose)	Open-label	Significant improvement in depressive symptoms within 4 h; no change in BDNF plasma levels
Mathew *et al.*[9]	TRD (*N* = 26)	Ketamine 0.5 mg/kg IV (single dose); riluzole 100–200 mg p.o. daily	Open-label ketamine followed by double-blind, placebo-controlled riluzole for relapse prevention	65% Response at 24 h; 54% at 72 h; no effect of riluzole on time to relapse
Phelps *et al.*[38]	TRD (*N* = 26)	Ketamine 0.5 mg/kg IV (single dose)	Open-label	Significant improvement in depressive symptoms within 4 h; family history of alcohol dependence predicted greater improvement
Price *et al.*[12]	TRD (*N* = 26)	Ketamine 0.5 mg/kg IV (single dose)	Open-label	Significant reduction in depression and SI 24 h following ketamine
Zarate *et al.*[8]	TRD (*N* = 18)	Ketamine 0.5 mg/kg IV (single dose)	Placebo-controlled, double-blind, crossover	Significant improvement in depressive symptoms up to 1 week; 71% response at 24 h

Table describes clinical trials of low-dose ketamine in patients with major depression or bipolar depression (does not include case reports). ED, emergency department; MDD, major depressive disorder; p.o., oral; SI, suicidal ideation; TRD, treatment-resistant depression.

SI and suicidal behavior are chief concerns related to MDD, and there is an urgent and unmet need for rapid-acting medical interventions for this worrisome condition. In contrast to conventional antidepressant agents, which may actually worsen SI in the short term, preliminary evidence suggests that ketamine may possess acute anti-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 becoming free of SI 24 h following infusion.[12] A second study reported decreases in SI as early as 40 min after initiation of ketamine administration,[13] and a third study reported rapid reduction in SI following ketamine administration in patients admitted to the emergency department with SI and depression.[14]

Ketamine is a dissociative anesthetic, which causes transient altered mental function at subanesthetic doses, including dissociative and psychotomimetic effects. These effects are usually mild to moderate at the doses used in the clinical antidepressant studies, 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 it is administered at high doses and over extended periods. 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 a 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 α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs) and has additional inhibitory effects at muscarinic acetylcholine receptors. NMDARs, AMPARs, and kainate receptors are ionotropic glutamate receptors that localize throughout the central nervous system and play a major role in the signaling process at excitatory synapses. Trullas and Skolnick first articulated the hypothesis that NMDAR antagonists may represent a new class of antidepressants, partly on the basis of the observation that inescapable stress leads to disruptions in hippocampal neuronal long-term potentiation—an NMDAR-dependent process—in parallel with the observed syndrome of behavioral depression.[15] This line of research showed 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, thereby suggesting that NMDAR modulation may represent a downstream effect of monoamine drugs.[16] Overall, 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 levels of synaptic signaling proteins along with an increased number and elevated function of new spine synapses in the prefrontal cortex (PFC) of rats.[17] Specifically, ketamine was observed to transiently increase the 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 synaptic plasticity, namely, extracellular signal–regulated kinase (ERK) and protein kinase B (PKB/Akt). In fact, blockade of either the extracellular signal–regulated kinase or Akt pathway abolished the impact of ketamine on the mTOR pathway, emphasizing the interaction between plasticity-related signaling pathways. Ketamine also resulted in elevated levels of several synaptic proteins (postsynaptic density 95 or PSD95, glutamate receptor 1, and synapsin I), increased spine density, and enhanced excitatory postsynaptic current (EPSC) 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 paradigm involving chronic mild stress and demonstrated that ketamine was able to reverse chronic mild stress–induced deficits in behavior as well as in synaptic proteins, spine density, and EPSC frequency/amplitude in the 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 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 the subsequent enhancement of BDNF translation. Several classes of antidepressants and techniques, including electroconvulsive therapy, have also been shown to increase BDNF in the hippocampus, although generally over a longer period. A clinical study found that peripheral measures of BDNF did not increase following ketamine administration;[20] however, the significance of this finding is unclear considering the potential uncoupling of peripheral and central

Table 2 Behavioral and molecular effects of ketamine in animal models of depression

Reference	Depression model	Intervention	Behavioral effects	Molecular effects
Autry *et al.*[18]	Mice (wild-type or BDNF/Trk B-knockout); FST; NSFT; LH; CMS	Ketamine 3.0 mg/kg i.p. (single dose)	Acute antidepressant effects observed in nonstressed 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.*[39]	Rats; FST	Ketamine 5, 10 or 15 mg/kg i.p. (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.*[21]	Rats; CMS (40 days)	Ketamine 15 mg/kg i.p. (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 levels
Koike *et al.*[40]	Mice or rats; TST (used mice), LH (used rats)	Ketamine 10 or 30 mg/kg i.p.	Acute antidepressant effects observed in both LH and TST; TST effect persisted for 72 h; antidepressant effects blocked by NBQX	None reported
Li *et al.*[17]	Rats; FST; LH; NSFT	Ketamine 10 mg/kg i.p. (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.*[19]	Rats; CMS (21 days); SPT, NSFT	Ketamine 10 mg/kg i.p. (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.*[23]	Mice; FST, LH	Ketamine 0.5, 2.5, or 10 mg/kg i.p. (single dose)	Acute antidepressant effects observed in both tests and maintained for 2 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.

4E-BP1, eukaryotic initiation factor 4E-binding protein 1; 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; i.p., intraperitoneal; LH, learned helplessness; MPFC, medial prefrontal cortex; mTOR, mammalian target of rapamycin; 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; PFC, prefrontal cortex; 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.

functioning by BDNF. Finally, a study of repeated daily doses of ketamine over 7 days in a model of chronic mild stress found that ketamine reversed chronic mild stress–induced weight loss and normalized neuroendocrine measures but did not alter hippocampal BDNF 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 and BDNF-pathway activation by NMDAR antagonism provides a critical link between NMDAR modulation and the 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 2,3-dihydroxy-6-nitro-7-sulfoamoylbenzo(f)-quinozaline, extending the findings of a previous report.[23] Preclinical work has linked enhancement of AMPA signaling with synaptic plasticity, and these findings support a model in which 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 enhance the activity of AMPARs (referred to as AMPA potentiators) has shown antidepressant properties in animal models[6] and may represent a promising avenue for novel treatment development based on the glutamate system.

IMPACT OF KETAMINE ON NEUROCIRCUITRY RELEVANT TO DEPRESSION

Current neurocircuitry models of depression posit relatively deficient functioning of the dorsal and lateral PFC and anterior cingulate cortex (ACC) and relative overactivity of ventral cortical and subcortical regions that govern emotion generation and

stress responses.[24,25] The 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) and orbital frontal cortex) or the subcortical limbic structures (e.g., amygdala).[24] This perturbation of neural activity results in the cognitive, emotional, and behavioral manifestations of depression, whereas normalization of aberrant activity patterns is posited to underlie the 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 glutamatergic signaling in the cortex of rodents, potentially through inhibition of γ-amino butyric acid-based (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 study found that ketamine resulted in decreased activity in the ventromedial PFC, orbital frontal cortex, and SGACC, accompanied by increased activity in the posterior cingulate and other cortical regions.[32] Studies using 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. All the neuroimaging studies described above were conducted in healthy populations; 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 (**Figure 1**), although this hypothesis remains to be tested directly. Intriguingly, direct stimulation of the medial PFC using optogenetic techniques in mice resulted in an immediate antidepressant effect in a social-defeat-stress paradigm.[35] The same report described the reduced expression of immediate early genes, reliable markers of neuronal activity, in both mouse medial PFC following social defeat stress and PFC tissue obtained from the postmortem examination of depressed individuals, further supporting the hypothesis of reduced functioning of PFC regions in depression. A series of studies using magnetoencephalographic recordings in patients with TRD before infusion of a single low dose of ketamine provides initial support for a significant role by the ACC/medial PFC in antidepressant response.[36,37] In these studies, the ACC activity before treatment was associated with the subsequent antidepressant response to ketamine. A significant gap in the current literature is that no study has investigated changes in neural markers following ketamine administration in a depressed population. Direct testing of the role of the ACC, PFC, or other regions of the brain in the mechanism of action of ketamine in clinical populations will require optimized pre- and postintervention imaging designs that use a placebo control.

CONCLUSIONS AND FUTURE DIRECTIONS

Despite the 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 ketamine has generated considerable interest in the scientific and medical community alike, representing a proof of principle in targeting the NMDAR, and the glutamate system more broadly, as a

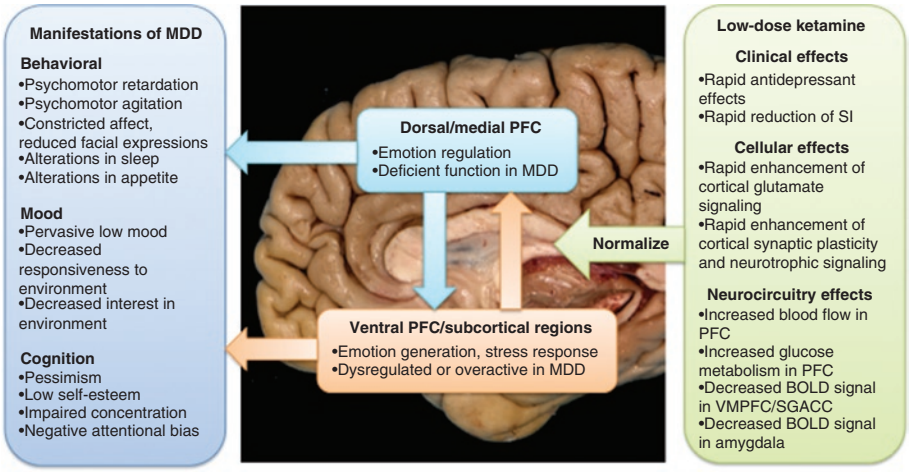

Figure 1 Clinical, cellular, and neurocircuitry effects of low-dose ketamine in major depression. Figure depicts schematic of cellular and neurocircuitry effects of ketamine hypothesized to underlie antidepressant effects. Ketamine appears to rapidly enhance signaling at glutamatergic synapses in cortical 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; MDD, major depressive disorder; PFC, prefrontal cortex; SGACC, subgenual ACC; VMPFC, ventromedial PFC. Anatomical specimen courtesy of AP Naidich, ME Fowkes, and CY Tang.

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 PFC-based deficits in depression at the neurocircuitry level, leading to an amelioration of clinical symptoms. Models linking ketamine's effects at the cellular, circuitry, and behavioral levels in depression, however, remain to be tested directly. For example, no study thus far 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 the 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 using an "active" control condition (e.g., a different anesthetic agent) that would mimic some of ketamine's acute neurocognitive effects and thereby strengthen the integrity of the study's blinding procedures, although these studies are currently under way (ClinicalTrials.gov NCT00768430). Concerns regarding the potential adverse behavioral and neurotoxic effects of ketamine and its potential for abuse necessitate a cautious approach to treatment development. Nonetheless, 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 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 for 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 the discovery of a novel therapy for depression by providing surrogate end points for testing novel candidate therapeutic agents.

CONFLICT OF INTEREST

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