A New Perspective on the Anti-Suicide Effects With Ketamine Treatment

A Procognitive Effect

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Abstract: Available evidence indicates that a single, low-dose administration of ketamine is a robust, rapid-onset intervention capable of mitigating depressive symptoms in adults with treatment-resistant mood disorders. Additional evidence also suggests that ketamine may offer antisuicide effects. Herein, we propose that the antidepressant effects reported with ketamine administration are mediated, in part, by targeting neural circuits that subserve cognitive processing relevant to executive function and cognitive emotional processing. Empirical support for the conceptual framework of the cognitive domain as a critical target of ketamine's action is the additional observation that pretreatment cognitive function predicts treatment outcomes with ketamine administration. The proposal that beneficial effects on cognitive function may be, in some individuals, the proximate mechanism mitigating symptom relief in mood disorders exists alongside the well-established deleterious effect of ketamine on cognitive function. During the past 5 years, there have been several reviews and meta-analyses concluding that ketamine has possible clinical benefits in refractory mood disorders. We introduce the conceptual framework that ketamine's salutary effects, notably in suicidality, may in part be via procognitive mechanisms.

Key Words: cognition, ketamine, suicidality, major depressive disorder, NMDA antagonist, antisuicide, procognitive

(*J Clin Psychopharmacol* 2016;36: 50–56)

Major depressive disorder (MDD) is a highly prevalent and often chronic mood disorder, affecting approximately 350 million individuals worldwide.[1] Although pharmacoepidemiological data document an inverse relationship between antidepressant prescription and completed suicide, there is a paucity of clinical trial data documenting the antisuicide effects of available antidepressants.[2,3] Currently, no Food and Drug Administration–approved agent is approved for the treatment of suicidality in adults with mood disorders. An unmet need in the treatment and management of adults with mood disorders is to specifically target dimensions of suicidality in this at-risk population.

Results from both preclinical and clinical studies indicate that disturbances in glutamatergic systems subserving emotional regulation, affective processing, and general cognitive processes are critical pathophysiological substrates in adults with mood disorders. Glutamate is the most prevalent excitatory neurotransmitter in the brain; activation of its canonical receptors (ie, postsynaptic kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] and *N*-methyl-D-aspartate [NMDA]) modulates neuroplasticity. Prolonged activation of the stress response is associated with sustained increases in extracellular glutamate as well as deficits in neurotrophic factors (e.g. brain-derived neurotrophic factor [BDNF]).[4–6] Relative and/or absolute increases in central glutamate levels is implicated in excitotoxicity, leading to neuronal atrophy in the prefrontal cortex (PFC) as well as synaptic dysconnectivity of PFC networks and their limbic targets.[5,7,8]

Ketamine has been demonstrated to act as a rapid-onset, NMDA receptor antagonist.[9,10] Ketamine is commonly used for anesthetic purposes in surgical settings at doses of 1 to 2 mg/kg; its elimination half-life is 186 minutes.[9] Temporary dissociative/psychotomimetic effects are observed with subanesthetic doses of 0.5 mg/kg between 40 and 120 minutes posttreatment and typically resolve within 240 minutes of administration.[11–15] In addition, available evidence suggests that ketamine may be capable of reducing depressive symptoms in adults with MDD or bipolar disorder (BD) who have not sufficiently responded to conventional pharmacological therapy.[11–14,16,17] Moreover, available evidence suggests that ketamine is capable of improving measures of suicidality in treatment-resistant mood populations.[16,18–21]

Herein, we propose that the antidepressant effects reported with ketamine administration are mediated, in part, by targeting neural circuits that subserve cognitive processing relevant to executive function and cognitive emotional processing (Fig. 1). Empirical support for the conceptual framework we propose (ie, cognitive domain as a critical target of ketamine) is the additional observation that pretreatment cognitive function predicts treatment outcomes with ketamine administration. The proposal that its beneficial effects on cognitive function may be, in some individuals, the proximate mechanism mitigating symptom relief in mood disorders exists alongside the well-established deleterious effect of ketamine on cognitive function. During the past 5 years, there have been several reviews and meta-analyses concluding that ketamine has possible clinical benefits in refractory mood disorders. We introduce the conceptual framework that ketamine's salutary effects, notably in suicidality, may in part be via procognitive mechanisms.

METHODS

The MEDLINE/PubMed database was searched from inception to September 1, 2015. The search was composed of randomized controlled and open-label clinical trials, as well as preclinical studies and meta-analyses investigating the use of ketamine in mood disorder populations. The search word ketamine was cross-referenced with MDD, BD, treatment-resistant depression, NMDA

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Received May 20, 2015; accepted after revision October 13, 2015.

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ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000000441

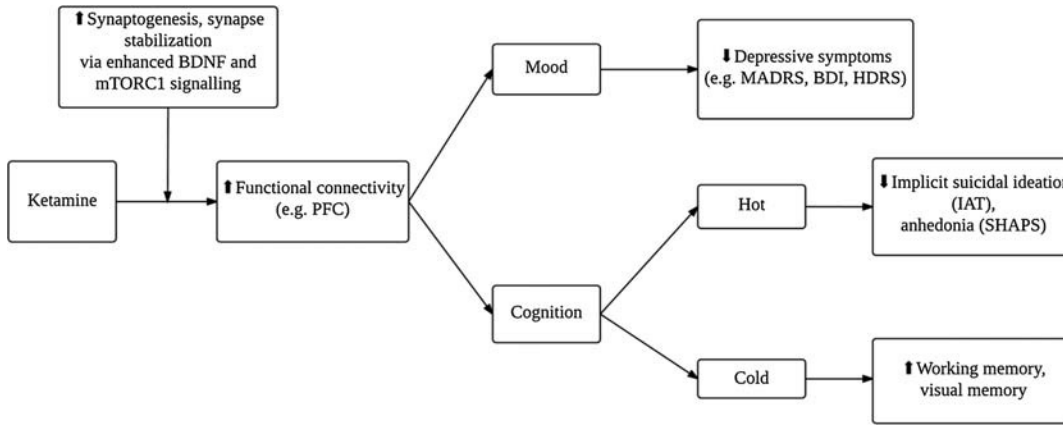

FIGURE 1. Ketamine exerts its antidepressant and antisuicidal effects via glutamatergic modulation of neural circuits subserving cognition.

antagonist, suicidality, and cognition. Reference lists from identified articles were manually searched for additional pertinent studies. Articles selected for inclusion were randomized control trials in adults with mood disorders as well as clinical and preclinical studies that were specifically reporting on the effects of ketamine on aspects of plasticity and neural structures.

RESULTS

Treatment of Depressive Symptoms and Suicidal Ideation in Treatment-Resistant MDD Populations

At subanesthetic doses, ketamine is a rapid-onset, efficacious antidepressant capable of mitigating depressive symptoms and measures of suicidality in treatment-resistant mood disorders.[16,18,19] Replicated evidence suggests that a single 0.5 mg/kg subanesthetic intravenous infusion of ketamine reduces depressive symptomatology within 40 minutes in treatment-resistant MDD (TRD) populations, as measured by the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Depression Rating Scale (HDRS), and the Beck Depression Inventory.[11–15]

Further evidence of ketamine's efficacy is instantiated by high rates of response (ie, approximately 60%–70%) and remission (ie, approximately 30%)[11–14] in TRD populations (response is defined as a 50% reduction in MADRS or HDRS score and remission is defined by MADRS score ≤10 or HDRS score ≤7). In addition to robust, reliable antidepressant efficacy, the time to onset of action with intravenous ketamine therapy in TRD is noted to be relatively brief; antidepressant effects are detected 40 minutes postinfusion, peak at 24 hours, and are sustained for up to 10 days.[12–14,22,23]

Price et al[18,19] reported that a single subanesthetic dose of ketamine (ketamine, n = 36) is capable of significantly reducing measures of implicit and explicit suicidal ideation when compared with active control (midazolam, n = 21) in TRD populations.[19] They noted that a single infusion of ketamine reduced measures of explicit suicidal ideation (ie, Beck Scale for Suicidal Ideation [BSS], MADRS suicidal item [MADRS-SI], Quick Inventory of Depressive Symptoms suicide item) in 53% of subjects, compared with 24% of midazolam-treated subjects.[19] In addition to the rapid-onset and robust antisuicide effects, a persistent antisuicide effect (ie, as measured by MADRS-SI scores) has also been reported up to 12 days following ketamine infusion.[18,19]

A separate randomized controlled trial reported significant reductions in explicit measures of suicidal ideation (BSS) 48 hours postinfusion when compared with active control (ie, midazolam, Cohen $d = 0.67$) in a TRD population enriched on the basis of elevated baseline suicidality measures (score of ≥4 on MADRS-SI, n = 24). Notwithstanding the between-group differences noted at 48 hours, no between-group differences were apparent at 72 hours or 7 days postinfusion (Table 1).[24]

Measures of suicidal ideation before treatment may have predictive validity in ketamine-treated subjects with mood disorders. For example, high composite scores of suicidal ideation at

TABLE 1. Randomized Controlled Clinical Studies of the Antisuicidal Effects of Ketamine (0.5 mg/kg Administered Intravenously for 40 Minutes)

Study	Study Characteristics	Primary Outcomes	Secondary Outcomes
Murrough et al[24]	Ketamine (n = 12) vs midazolam (n = 12)	Cohen $d = 0.34$, $P = 0.32$ at 24 h (BSS)	Cohen $d = 0.67$, $P = 0.047$ at 48 h (BSS) Cohen $d = 0.86$, $P = 0.05$ at 24 h (MADRS-SI) Cohen $d = 0.77$, $P = 0.077$ at 48 h (MADRS-SI)
Price et al[19]	Ketamine (n = 36) vs midazolam (n = 21)	Cohen $d = 0.82$, $P = 0.01$ at 24 h (explicit $SI_{composite}$)	Cohen $d = 0.25$ at 24 h (IAT: escape = Me association)
Zarate et al[13]	Crossover (n = 15); ketamine vs saline	Not suicidal ideation	Cohen $d = 0.98$, 95% CI = 0.64–1.33 at 40 min (MADRS-SI)

CI indicates confidence interval; explicit $SI_{composite}$, explicit suicidality index calculated by summing z scores on the BSS, MADRS-SI, and Quick Inventory of Depressive Symptomatology-Self Report suicidality item; IAT, Implicit Association Test.

baseline have been reported to predict better treatment response (ie, reduction in MADRS score 24-hour postinfusion compared with baseline) to ketamine when compared with those with severe baseline measures of depressive symptomatology without suicidality (ie, as measured by MADRS).[19] Reductions in composite measures of suicidal ideation were determined to be largely mediated by an improvement in depressive symptom severity (MADRS non-SI scores) and measures of hopelessness (Beck Hopelessness Scale).[19,20]

Neural Correlates of Ketamine's Mechanism of Action

A working hypothesis has been that, via glutamatergic activity, ketamine exerts a facilitative effect on neural systems (i.e., nodes, circuits, networks) subserving cognitive function.[25–29] Neural systems/circuits implicated include, but are not limited to, circuits (e.g. cognitive control networks) that proximally subserve disparate cognitive functions (e.g. executive function). For example, convergent evidence suggests that depressive symptoms represent a dysregulation of functional connectivity within PFC networks and targets in limbic regions. Alterations in neurophysiology, grey matter volume, and functional activity of the orbital and medial PFC and its connected regions seem to underlie emotional and cognitive disturbances in individuals with MDD.[30,31]

The effects of ketamine on neural circuits (e.g. PFC networks) may be different as a function of acute versus subchronic dosing. Effects on nodal regions as well as upregulation of proteins implicated in neurotrophic processes (e.g. BDNF) are observed after a single dose.[32] For example, increased regional metabolism in the right ventral striatum and decreased metabolism in the subgenual anterior and posterior cingulate cortex are observed after ketamine infusion compared with placebo in individuals with BD.[27] The foregoing changes in regional metabolism are highly correlated with improvements in depressive symptom severity (ie, reduced MADRS scores).[23] Similarly, decreased regional metabolism in the right habenula and the extended orbital and medial PFC after ketamine administration is correlated with antidepressant response in individuals with TRD.[26]

Furthermore, ketamine is observed to decrease functional connectivity between the default mode network (DMN) and the dorsal nexus (DN), pregenual anterior cingulate, and medio-PFC in individuals with mood disorders.[28] The DMN includes brain regions (ie, ventromedial PFC, anterior cingulate, lateral parietal cortex, lateral temporal cortex, amygdala, parahippocampus, and hippocampus) that are hypothesized to subserve rumination and self-referential thinking.[33] The DN is a bilateral region of the dorsal medial PFC that is overactivated in individuals with MDD; the DN has functional connectivity to the cognitive control network, the DMN, and the affective network.[28,33] Reduction in suicidal ideation (ie, HDRS-SI) in individuals with MDD 30 minutes after ketamine administration is correlated with decreased regional metabolism in the infralimbic cortex.[29]

Glutamate Modulation Leads to Synaptogenesis

Via glutamate-induced augmentation of BDNF and mammalian target of rapamycin complex 1 (mTORC1) signaling, ketamine increases synaptic formation and reverses the neuronal atrophy and PFC synaptic dysconnectivity observed in MDD pathogenesis. Preclinical evidence suggests that ketamine inhibits NMDA receptor activation of GABAergic interneurons in the PFC, resulting in the disinhibition of layer V pyramidal neurons and an increase in extracellular glutamate levels in the PFC.[25,34–36] Subsequent activation of AMPA receptors and blockade of extrasynaptic NMDA receptors lead to increased BDNF release and activation of mTORC1 signaling, promoting protein synthesis, the upregulation of AMPA receptors, the strengthening of existing synapses, and the formation of new synapses.[25,34–36]

Evidence from clinical studies support the hypothesis that ketamine exerts antidepressant effects by promoting synaptogenesis and synaptic stabilization in dysregulated PFC circuits.[32,37,38] For example, a randomized controlled trial (n = 22) reported that the presence of higher levels of plasma BDNF 240 minutes postinfusion clinically predict antidepressant response to ketamine.[32] Furthermore, plasma BDNF levels are reported to be negatively correlated with MADRS scores, whereas no association between plasma BDNF levels and depressive symptom alleviation is present with midazolam treatment.[32] Similarly, a study of an MDD population (n = 62) reported that BDNF Val66Met polymorphism accounts for 28% of variance in antidepressant response to ketamine.[38] More specifically, possession of the methionine substitution in the pro-BDNF protein, which is associated with mild cognitive deficits,[39–41] predicts low treatment response to ketamine. The foregoing findings suggest that ketamine exerts antidepressant effects by enhancing neurotrophic support and signaling pathways subserving neural plasticity.

Ketamine's Effect on Cognition

The short- and long-term neurocognitive effects of ketamine have been evaluated in populations that chronically use ketamine and in healthy populations. A 1-year longitudinal study of chronic abusers of ketamine reported that frequent and high doses of ketamine are correlated with impairments on Spatial Working Memory and Pattern Recognition Memory tasks of the Cambridge Automated Neuropsychological Test Assessment Battery (CANTAB). The deleterious effects of ketamine may, in some cases, be reversible insofar as individuals with history of ketamine misuse who abstain from using the agent exhibit no differences from healthy controls across several domains, including memory (ie, Pattern Recognition Memory of CANTAB) and executive function (ie, Spatial Working Memory and Stockings of Cambridge of CANTAB).[42]

It has also been observed that in nonclinical populations, an acute dose of ketamine (ie, 0.4–0.8 mg/kg) elicited transient impairments in episodic memory (ie, Prose Recall subtest of the Rivermead Behavioural Memory Battery, Source Memory task), semantic memory (ie, Speed of Comprehension test), and response inhibition (ie, Hayling task) immediately after infusion, although there were no residual impairments 3 days postinfusion.[43,44] It was also reported that executive function (ie, Trail Making Test B) was not adversely affected by ketamine administration.[44] Taken together, acute ketamine administration at low doses in nonclinical populations does not seem to adversely impact cognitive function according to measures employed in the conducted studies; chronic ketamine use, however, is highly associated with diminished cognitive performance, which may be, in some cases, reversible.

Preliminary evidence indicates that ketamine improves neurocognitive performance in adults with TRD. For example, Shiroma et al[45] administered 6 doses of ketamine (0.5 mg/kg) in a cohort of 15 individuals with TRD for the course of 12 days and compared neurocognitive performance from baseline to 4-week posttreatment. They reported improvements in visual memory (ie, One Card Learning Task), simple working memory (ie, One Back Test), and complex working memory (ie, Two Back Task) from baseline to endpoint. The foregoing improvements in cognitive tasks covaried with reductions in MADRS scores.

There are insufficient biomarkers/biosignatures that are predictive of response to ketamine or other antidepressant strategies. Preliminary evidence indicates that baseline interleukin-1β,

interleukin-6, and D-serine levels may identify a subset of individuals more likely to benefit with ketamine treatment.[46,47] Measures of pretreatment cognitive function have also been preliminarily evaluated to the extent to which they may be associated with/predictive of response to ketamine therapy.

Individuals with lower pretreatment attention scores (i.e., Identification Task) are more likely to respond to treatment, as measured by changes in MADRS scores.[45] Similarly, in a randomized controlled clinical trial (n = 62), Murrough et al[17] identified slower processing speed (i.e., Category Fluency, Trails A, Brief Assessment of Cognition in Schizophrenia Digit Symbol) as a significant predictor of depressive symptom reduction (i.e., reduced MADRS scores) 24 hours after infusion of ketamine. Furthermore, transient reductions in cognitive performance 40-minute postinfusion (e.g. Hopkins Verbal Learning Test and Category Fluency) are associated with treatment nonresponse.

Taken together, pretreatment deficits in discrete cognitive subdomains may predict improvement with ketamine administration in adults with mood disorders. Pretreatment and posttreatment changes in measures of cognitive function correlate (positively and negatively) with changes in depressive symptom severity. There is, however, insufficient evidence to indicate whether changes in cognitive function are independent and direct effects or pseudospecific changes largely determined by changes in depressive symptom severity.

DISCUSSION

It is hypothesized that ketamine mitigates depressive symptom severity by facilitating PFC functional connectivity, implicated as subserving mood and cognitive functions. The antisuicide effect observed with ketamine administration likely has several, nonmutually exclusive mechanisms. Herein, we posit that for some individuals, the antisuicide effect that is observed may be proximately subserved by alterations in general cognitive function.

Cognition can be broadly categorized as being emotionally or nonemotionally valenced (i.e., hot vs cold cognition, see McIntyre et al[48] for a review). Conceptualizing cognition as being with or without emotional influence is not only empirically supported but may be subserved by overlapping yet discrete substrates. For example, cold cognition represents nonemotionally valenced cognitive function and is subserved by several interacting circuits and regions including, but not limited to, the dorsolateral PFC, the dorsal anterior cingulate cortex, and the hippocampus.[49] Individuals with MDD exhibit negatively biased hot cognition and impaired cold cognition, resulting in negative affective biases and perpetuating negative schemas.[49]

Ketamine may exert benefits across both hot and cold cognitive functions. Ketamine's benefit on measures of hot cognition is instantiated by the improvement in implicit attribution style of suicidal ideation, measures of anhedonia,[50] and overall depressive symptom severity. Furthermore, ketamine reduces negative emotional perception and enhances positive bias in individuals with MDD, further supporting the favorable effect of ketamine on hot cognition.[51] The cold cognition benefit is implicated by improvements in measures of visual memory and working memory after repeat infusions. Further empirical support for the mechanistic relevance of cognitive function is the observation that measures of cognitive function pretreatment (e.g. lower attention, slower processing speed) predict antidepressant response to ketamine, suggesting that the "antidepressant effects" of ketamine may be mediated by "procognitive effects." It is conjectured that ketamine, via targeting intracellular proteins (e.g. mTORC1), facilitates neuronal integrity/plasticity with resultant recalibration of neural circuits relevant to general cognitive function (e.g. executive function).

Executive function is broadly defined as, and includes aspects of, working memory, cognitive flexibility, as well as the planning, initiating, sequencing, monitoring, and inhibition of behavior. Suicidal ideation, nonlethal self-harm, and lethal self-harm are well established in suicidology as noncontiguous, orthogonal phenomena.[52] In other words, suicidal ideation has minimal predictive validity of suicide completion. For many individuals, suicidal ideation and behavior represent impulsive, difficult-to-control cognitive, and behavioural phenomena. The foregoing observation may be understood within the conceptual framework of executive function deficits. An implication of this framework would be that an intervention capable of improving aspects of executive function (e.g. impulse control, inhibition) may be capable of reducing suicidal ideation and/or self-harm behavior.

To our knowledge, ketamine has never been demonstrated to lower suicide rates in any clinical population. Moreover, a reduction in suicidal ideation and/or nonlethal self-harm may not translate to reduced suicide completion. Nonetheless, ketamine's ability to reduce suicidal ideation as well as a compelling body of evidence that it exerts favorable effects on neural structures subserving general cognitive processes provide the basis for hypothesizing that ketamine may be procognitive in some individuals and a possible avenue for antisuicide treatment.

A limitation of extant evidence is the paucity of randomized controlled trials that are primarily evaluating ketamine's effect on measures of suicidal ideation. However, there are 15 ongoing clinical trials investigating ketamine's antisuicide effects in MDD and BD populations using diverse methods of administration (e.g. intranasal, intravenous and oral) in both inpatient and outpatient settings, as well as emergency room settings (NCT02183272, NCT02299440, NCT01700829, NCT02418702, NCT01892995, NCT02532153, NCT01944293, NCT02048423, NCT02418195, NCT02094898, NCT01667926, NCT02106325, NCT01945047, NCT02414932, NCT00088699). These additional studies in randomized controlled settings and in naturalistic settings would further characterize the potential role of ketamine in MDD treatment and suicide management.

CONCLUSIONS

Ketamine is a rapid-onset and effective pharmacological treatment for individuals with mood disorders nonresponsive to conventional multimodality approaches. It is additionally observed that ketamine reduces suicidal ideation in at-risk populations. Preclinical evidence indicates that ketamine exerts a rapid effect on molecular networks and neural structures subserving the disparate domains of psychopathology in MDD (e.g. emotional processing, cognitive function).

Ketamine has been reported to exert mixed effects on measures of cognition across nonclinical and clinical populations. In clinical populations with TRD, baseline cognitive measures may have some predictive utility. Furthermore, benefits with repeat neurocognitive measures may identify a subset of individuals who are more likely to benefit from ketamine. It is uknown, however, the extent to which improvement in cognitive function varies independently of improvement in core mood symptoms.

The antisuicide effects of ketamine are, to a large extent, mediated by the improvements observed in overall depressive symptom severity. The colinearity between suicidal ideation reduction and depressive symptom severity does not exclude the possibility that, in subsets of individuals receiving ketamine, the antisuicide effects may be independent of its effect on total depressive symptom severity. For example, it is additionally important to consider

the possible effects of ketamine on an individual's unique risk factors for suicide, independent of depressive symptoms, including but not limited to anhedonia, psychological pain, agitation, or impulsivity.[53]

Several lines of evidence suggest that in subgroups of individuals identified as at-risk for suicide, deficits in cognitive function (e.g. executive function, inhibitory/impulsivity) may be pertinent. It stands to reason that given ketamine's known effects on neural structures and possible benefits on measures of cognition, its antisuicide effects may be in part via procognitive effects. The foregoing hypothesis, augmented with neuroimaging correlates, would be important pathways for future study.

In the interim, ketamine seems to be a promising therapeutic avenue in TRD as well as in individuals with suicidality. Notwithstanding the reassuring safety profile reported to date,[54] the long-term safety and efficacy of ketamine are not established and we agree with recent recommendations to carefully characterize the safety profile of ketamine before it is embraced in routine clinical practice.[55] Other barriers to the use of ketamine in clinical care include dissociative/psychotomimetic effects, vasomotor alterations, and potential for abuse.[56]

Available evidence indicates that perhaps the stereoisomer es-ketamine may be a safer alternative to racemic ketamine.[57] Es-ketamine's effects on suicidality would further inform our conceptual framework and be of valuable assistance to regulators and clinicians. Moreover, interest in other agents that target the glutamatergic system (e.g., rapastinel, NRX-1074, nitrous oxide) in adults with mood disorders[58–60] should include measures of suicidality not only as a safety measure, but also as a primary and/or secondary outcome. For example, rapastinel (GLYX-13) is a glutamatergic modulator that has been demonstrated to exert beneficial effects on cognitive function in preclinical models[58] and antidepressant effects in clinical populations.[61] Rapastinel is currently being studied as a possible antidepressant in adults with MDD (NCT02192099, NCT01684163) and as a procognitive pharmacological agent in individuals with schizophrenia (NCT01844726); determining its potential effects on suicidality and its relationship to cognitive function would be instructive.

In summary, glutamatergic modulators are promising rapid-onset and robust treatments for adults with treatment-resistant mood disorders. The extent to which pretreatment cognitive performance identifies a subset of individuals more likely (or less likely) to benefit from and tolerate glutamatergic agents is a vista for future research. Our conceptual framework characterizing the antisuicide effects observed with ketamine as proximately mediated by, in some cases, direct and beneficial effects on general cognitive function (e.g., executive function), has both heuristic and clinical implications. From a heuristic perspective, the notion that, in some cases, aspects of suicidality may represent cognitive dysfunction has face validity in light of the role of executive function in impulse control. The clinical implications of an agent that may exert an antisuicide effect independent of its effect on core depressive symptoms is obvious insofar as suicidality is a common feature across many brain disorders in the developmental trajectory (e.g., eating disorders, substance use disorders, neurocognitive disorders). The safety, efficacy, and tolerability of other pharmaceuticals that are glutamatergic modulators are a focus of ongoing study. It would be prudent to include measures of suicidality and measures of cognitive function as dependent efficacy measures in future phase 3/4 trials.

AUTHOR DISCLOSURE INFORMATION

All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

The authors declare no conflict of interest. R.B.M. has received support from FAPESP, Brazil, and fellowship funding from Lundbeck, Canada. R.S.M. has received research/grant support and/or speaking fees from the following companies in the last 2 years: Eli Lily, AstraZeneca, Pfizer, Lundbeck, Otsuka, Sunovion, Shire, Bristol-Myers Squibb, Takeda, Forest, Merck, Takeda, Allergan, Janssen-Ortho, Stanley Medical Research Institute, National Institutes of Mental Health, National Alliance for Research on Schizophrenia and Depression, and Canadian Institutes of Health Research.

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