Updates on Preclinical and Translational Neuroscience of Mood Disorders

A Brief Historical Focus on Ketamine for the Clinician

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Abstract:

Background: The development of new-generation antidepressants comes at a time of great clinical need when the global burden of depression, suicide, and other psychiatric conditions continues to increase. Our current treatment armamentarium is limited by the time delay needed for antidepressant effects and the significant number of patients who do not show an adequate response to antidepressants. The past 2 decades of psychiatric research has revealed that ketamine, known to be used only as an anesthetic and drug of abuse and to produce experimental models of psychosis, is effective at subanesthetic doses to ameliorate clinical depression.

Methods: We performed a systematic search of PubMed/MEDLINE indexed reports to identify clinical and translational research done with ketamine for purposes of treating depression.

Results: We will first present the rationale for investigating ketamine and other *N*-methyl-D-aspartate receptor antagonists as a novel class of glutamate system targeting antidepressants. We will summarize putative molecular pathways underlying mood disorders and outline a brief history of investigation into ketamine as a treatment for depression. Recent clinical/translational evidence of ketamine's rapid-acting antidepressant mechanism will be critically reviewed in detail.

Conclusions: At the end of this review, we will opine on the role of ketamine and derivatives in clinical practice.

Key Words: depression, ketamine, neurobiology, psychopharmacology

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Depression remains a major cause of disability and economic burden in the United States and around the world.[1–3] In addition, suicide rates continue to climb despite significant investment into treatment and prevention strategies.[4,5] Current treatment guidelines for major depressive disorder include the routine use of antidepressant medication for at least moderately disabling cases.[6] The National Institutes of Health–funded STAR*D study, the most robust set of clinical data evaluating treatment algorithms for depression, indicates that most patients will not have an adequate response to a given first-line antidepressant treatment, nor will most patients achieve remission within 2 to 3 months of treatment.[7] Many patients needed a trial of 2, 3, or more medication monotherapies or combinations before achieving an adequate response, and when successful, current antidepressants take weeks to months for full efficacy.[8] For patients who are severely depressed and suicidal, this may necessitate considerable time on a psychiatric inpatient service while waiting for a response to medications and psychotherapy. For less severely depressed outpatients, this may mean a year or more of tried and failed interventions while continuing to suffer from the burden of mental illness.

Even before the STAR*D study results were published, scientific lines of evidence began to move away from the monoamine deficiency hypotheses of depression, primarily formulated as a result of findings that antidepressants increase the functional availability of serotonin, dopamine, and norepinephrine. Newer evidence suggests that the primary excitatory neurotransmitter, glutamate, may be a final common pathway for antidepressant action. As the field produced more data linking the glutamate system to depression, agents that act on glutamate systems came under investigation as novel antidepressant treatments.[9–11]

Ketamine had been used for decades as an anesthetic, and it was generally known to psychiatrists only as a drug of abuse and to psychiatric researchers as a chemical that could replicate positive symptoms of schizophrenia. Early work had shown that ketamine was an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, along with the street drug "angel dust" or phencyclidine (PCP). When the psychotomimetic effects of these drugs were described, they were thought to relate to glutamate hypofunction as an underlying mechanism of schizophrenia.[12–14] Glutamate hyperfunction in stress-related depression also began to take hold, and there was novel interest in the use of glutamate antagonists to treat depression. Additional preclinical studies suggested that "substances capable of reducing neurotransmission at the NMDA receptor complex may represent a new class of antidepressants."[15] The first clinical studies of ketamine for depression in human subjects were reported in the 1990s.[16]

When the unexpectedly robust antidepressant action of ketamine was shown in human subjects, investigation into the underlying mechanism of this effect began in earnest. Scientific efforts have expanded greatly over the past 2 decades in government, academic, and pharmaceutical sectors. Before the first clinical trials were conducted, animal studies had shown that there was a marked difference in the biochemical effect of subanesthetic compared with anesthetic doses of ketamine,[17] which suggests that the mechanism was more complex than a simple gradual reversal of glutamate hyperactivity at the receptor level. Since then, and particularly in the past decade, research efforts have shifted into evaluating differential effects of subanesthetic doses of ketamine at glutamate receptors expressed on discrete neuronal populations. For example, subanesthetic doses of ketamine may impact cortical excitatory pyramidal neurons differently compared with cortical inhibitory interneurons that utilize GABA (γ-aminobutyric acid) as the primary inhibitory neurotransmitter. In addition, there are

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emerging data on antidepressant action related to mechanisms downstream from direct receptor effects. These may include inhibition of NMDA receptors, activation of non-NMDA receptors, activation of intracellular proteins that promote synaptic integrity, and inhibition of intracellular proteins that repress synaptic plasticity.[18,19] Interestingly, many of these separate lines of investigation converge on final common pathways controlling the structure and function of synapses and bring to attention potential pathophysiologic markers of depression. Finally, the effects of subanesthetic doses of ketamine on local neurocircuits and global brain networks are revealing specific benefits of ketamine in reversing general deleterious neurobiological features of depressive syndromes. There is no sign that momentum within the field is abating, and many NMDA receptor–modulating agents are currently also under investigation. We performed a systematic search and gathered evidence related to ketamine use for depression to describe in a historical context (Supplemental Text, Supplemental Digital Content, http://links.lww.com/JCP/A631).

THE CELLULAR PATHOPHYSIOLOGY OF DEPRESSIVE DISORDERS

It is difficult to have discussion about ketamine as a novel antidepressant without first briefly summarizing the concurrent history of investigation into the molecular pathophysiology underlying major depressive disorder and other depressive disorders. A series of experiments from 1985 to 1990 had suggested that high physiologic concentrations of glucocorticoids or prolonged stress in animal models had the potential to damage the hippocampi.[20–23] In addition, the role of excess glutamate on neuronal damage and cell death was being elucidated[20–26] (detailed review in Swann et al[27]). The link between prolonged stress, glucocorticoid excess, glutamate neurotoxicity, and the development of neuropsychiatric disorders was then posited.

The Sapolsky laboratory[28–33] suggested that prolonged stress leads to excess glucocorticoid exposure, and excess activation of glutamate receptors produces cell death and atrophy of the hippocampus. In 2002, Moghaddam's[34] laboratory from Yale University took the next logical step in suggesting the same mechanism may disrupt neurotransmission in the prefrontal cortex (PFC) and underlie stress-sensitive psychiatric disorders.

This notion was expanded on by Zarate et al[35] at the National Institutes of Health and has been extensively reviewed by Popoli et al.[10] Briefly, excess glucocorticoids may lead to glutamate-induced neurotoxicity via 1 or more of the following means: enhanced glutamate release under acute stress, which then, in PFC, becomes repressed with repeated stressors; acute stress-mediated enhancement of signaling downstream from ionotropic glutamate receptor activation, which then, in PFC, becomes repressed after repeated stressors; increased expression of synaptic machinery, including ionotropic glutamate receptors, to facilitate neurotransmission after an acute stressor, which is then reversed in medial PFC with chronic stressors. The available data suggest a link between repeated stressors and a time course of increased glutamate. A genetic predisposition to stress sensitivity may be an explanation why "usual" stressors trigger depressive episodes in some individuals but not others. This body of work is a solid foundation for subsequent thought that targeting the glutamate system may lead to novel therapies for mood disorders.[11]

HISTORY OF PSYCHIATRIC USE OF KETAMINE: PSYCHOTOMIMETIC TO ANTIDEPRESSANT

In 1959, George Crane[36] from the New Jersey State Sanatorium for Chest Diseases noticed a peculiar specific effect of one of the common antituberculous antibiotics, D-cycloserine. In his report, he detailed 27 of 37 patients treated with D-cycloserine had a "substantial improvement of a psychological nature," which was "a mental change in excess of physical improvement."[36] It so happens that D-cycloserine is a partial agonist ligand for the NMDA receptor, which prevents further activation when glutamate occupancy exceeds 40% to 45%.[37] As early as 1975, a laboratory animal screening study for novel antidepressants indicated that ketamine did "possess significant activity over a wide range of oral doses."[38] In the 1980s, ketamine and PCP were found to antagonize the NMDA receptor, blocking hippocampal neuron functions.[39–42] After the neurobehavioral effects of ketamine and PCP were characterized in humans,[12,43] a hypothesis of NMDA receptor hypofunction in schizophrenia was proposed.[14,44]

The initial hypothesis of ketamine's mechanism of action contributed in part to the clinical translation of the stress-induced glutamate neurotoxicity hypothesis.[34] As previously mentioned, this idea was borne from research on glutamate mechanisms of neurological disorders such as stroke, epilepsy, and dementia.[27,45,46] Moghaddam et al[17] used ketamine to reproduce NMDA receptor hypofunction, and it was found that subanesthetic doses resulted in increased extracellular glutamate in the PFC of animals. Later work from the same group suggested that hypofunction of NMDA receptors on GABAergic interneurons may disinhibit pyramidal cells and partly explain the mechanism of positive symptoms of schizophrenia.[47] Close in time with the 1997 study from Moghaddam et al,[17] subanesthetic doses of ketamine were given to healthy males, producing neurobehavioral and cognitive symptoms similar to those seen in schizophrenia.[48] Around this time, a separate group was investigating the effect of NMDA receptor antagonism by ketamine on depression,[16,49] citing preclinical work showing NMDA antagonists have antidepressant properties.[15,50]

OVER 2 DECADES OF RAPID-ACTING ANTIDEPRESSANT CLINICAL AND TRANSLATIONAL RESEARCH WITH KETAMINE

As understanding of the cellular pathophysiology underlying depressive disorders began to increase, theories and experimental paradigms suggested that interventions that directly or indirectly impact NMDA receptor function may be putative antidepressants.[15,50–53] One of the earliest reports, presented in 1997 at the meeting for the Society of Biological Psychiatry, hypothesized that NMDA receptor dysregulation contributes to symptoms of depression. Cappello et al[16] provided strong evidence toward this hypothesis by showing time-dependent decrease in depression symptoms that correlated to infusion with subanesthetic doses of ketamine, 0.1 mg/kg, 0.5 mg/kg, versus saline infusion. In 2000, Berman et al[49] published the first trial of ketamine as a putative rapid-acting antidepressant (RAAD) in human subjects, mentioning the earlier work of Crane[36] and Vale et al.[54] Cappello et al used the dose of 0.5 mg/kg delivered intravenously over 40 minutes based on the prior studies led by Krystal et al at Yale University,[16,43] in which the doses were selected because they seemed to produce subanesthetic behavior changes without reaching anesthesia.[55,56] Berman et al[49] completed ketamine and sham treatment in 8 patients with treatment-resistant depression, and depression symptoms returned to baseline within 1 to 2 weeks. A follow-up study by Diazgranados et al[57] in 2006 replicated this result in 18 subjects, showing a very large effect size of 1.46 after 24 hours. Similar to Cappello et al's study, depression scores returned to baseline within a week or 2. A subsequent trial by Diazgranados et al showed that ketamine is effective for bipolar treatment-resistant depression.[58] There have since been numerous trials in larger numbers of patients, and the effect of a single administration of ketamine on depression and suicidal ideation is a consistent and robust finding,[59–65] with evidence that repeated dosing produces a sustained effect.[66–68] However, ketamine's effect may not extend to patients with chronic suicidal

ideation.[69] Ketamine appears to be effective for suicidal ideation from a severe life stressor (new cancer diagnosis).[64] However, ketamine may not be effective to prevent depression, for example, in the postpartum period or after major surgery.[70,71] When used as an adjunct to electroconvulsive therapy, ketamine did not augment the antidepressant effect of electroconvulsive therapy.[72] Together, this evidence of the past decade clearly demonstrates the robust antisuicidal and RAAD action of ketamine; however, it is not a "magic bullet" that works equally well in every case of depression and may not be effective to prevent depression in those at risk.

The past decade has seen a robust increase in research interest with ketamine. Many studies have attempted to further characterize and optimize ketamine's RAAD action. A series of studies examined whether adjunctive medications might enhance or prolong the effect of ketamine. Voltage-gated sodium-channel antagonists lamotrigine and riluzole appear to decrease synaptic glutamate[73,74]; however, pretreatment with lamotrigine did not enhance the effect of ketamine; nor did addition of riluzole prolong the effect in ketamine responders.[75] Follow-up studies showed that riluzole versus placebo did not alter the course of improvement following ketamine or have any effect on ketamine nonresponders.[76,77] Although a family history of alcohol use disorder positively predicts the degree of RAAD response to ketamine,[78,79] the addition of riluzole made no difference.[80] However, the antidepressant action of traditional selective serotonin reuptake inhibitors such as escitalopram or sertraline was augmented and accelerated, respectively, by ketamine in 2 studies.[81,82]

The study by Mathew et al[75] found that lamotrigine did not alter the acute psychotomimetic effect of ketamine. It was later shown that the intensity of this acute effect is related to the degree of mood improvement.[83] It has been recently suggested that the mechanism of ketamine's RAAD and dissociative effects may have common basis.[84] However, pretreatment with the presynaptic α2 adrenergic receptor agonist clonidine seemed to mitigate psychotomimetic effects without compromising efficacy.[85] Lanicemine, an NMDA receptor antagonist like ketamine, was shown to have RAAD action without dissociative effects.[86] In addition, ketamine has now been studied against the psychoactive comparator midazolam.[60,61,65,87] It seems that ketamine's RAAD activity is not secondary to subjective effects but may be a parallel or downstream effect to RAAD action.

One interesting finding from the preclinical studies was the dose-dependent nature of the effect of ketamine needed to increase extracellular levels of glutamate and glutamate cycling.[17,88,89] This increase in glutamate cycling may be due in part to glial cell mechanisms.[90] An attempt was made to examine this effect of ketamine on glutamate in humans, but no effect was seen, possibly due to the changes occurring at levels below the detection limits of the technique used.[91] It appears that several events occur downstream from glutamate neurotransmission to produce behavioral changes in response to acute ketamine administration. Translating these animal data into humans, it has recently been shown in a dose-finding study that the effect size of subanesthetic doses of ketamine on depressive symptoms reached a maximum at the dose of 0.5 mg/kg and was lower at higher doses.[92] This animal and human work supports the notion that ketamine likely involves additional factors than gross NMDA receptor inhibition and that subanesthetic doses are functionally selective for RAAD action.

The involvement of non-NMDA receptors, specifically the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, seems to be necessary for RAAD action in animal models.[93,94] Ketamine metabolites have antidepressant action and do not seem to block the NMDA receptor.[95] It has been posited that ketamine metabolites potentiate AMPA receptors and may represent a necessary step in the pathway of RAAD action.[96] In humans, ketamine resulted in decreased frontoparietal connectivity, thought to be mediated by cortical NMDA and AMPA receptors, as measured by magnetoencephalography.[97] A separate study using magnetic resonance spectroscopy showed that ketamine may increase glutamate specifically in a region of cerebral cortex with higher AMPA/NMDA receptor ratio.[98] It is yet unclear in humans how ketamine acts via NMDA and/or AMPA receptors to exert RAAD action.

There have been several different lines of investigation into the intracellular events that occur downstream from NMDA receptor inhibition and AMPA receptor potentiation that correspond to the rapid antidepressant effect of NMDA antagonists such as ketamine. Preclinical data implicate mammalian target of rapamycin complex 1 (mTORC1) pathway activation, brain-derived neurotrophic factor (BDNF) trafficking, inhibition of glycogen synthase kinase 3, and inhibition of eukaryotic elongation factor 2,[99–104] which has been extensively reviewed. There may be a role for activation of opioidergic systems,[105] but this pathway may be irrelevant in patients with comorbid alcohol use.[106] The ultimate downstream action of ketamine and other RAADs is believed to result from transient bursts of glutamate and AMPA receptor activation, potentiation of a feed-forward biomolecular loop within dendrites and spines that involves BDNF-mediated activation of the mTORC1 pathway, and increased production of synaptic machinery, synaptogenesis, functional neuroplasticity, and amelioration of the depressive phenotype.[107] However, a recent report shed doubt on the role of mTORC1 in ketamine-mediated antidepressant effects, because an mTORC1 inhibitor, rapamycin, prolonged rather than truncated ketamine's effect.[108]

In humans, different BDNF genotypes modulated the RAAD action of ketamine in 2 studies,[103,109] but had no significant effect in 1.[110] Ketamine infusion has an unclear effect on serum BDNF, with an earlier study showing no change,[111] later studies suggesting increased peripheral BDNF with ketamine,[112,113] and a recent study showing that reduction in suicidal ideation correlated with decreased serum BDNF.[87] Other work has shown variable results when investigating peripheral biomarkers of efficacy including BDNF, other neurotrophins, and B vitamins, and it is not clear if any are useful as biomarkers.[114–119] Another potential biomarker is a protein involved in synapse formation and NMDA receptor tethering, Shank3. Higher baseline Shank3 levels predicted the antidepressant response to ketamine in patients with bipolar depression.[120] It remains to be seen whether useful biomarkers can be identified and established to predict those patients who may respond more robustly to ketamine and other RAADs.

Proposed functional changes in neurocircuits responsive to ketamine infusion have been examined. Local-level modulation in the lateral habenula, nucleus accumbens, and the PFC-hippocampal circuit, for example, with global modulation of neural connectivity makes for a compelling hypothesis of RAAD action.[121–126] Altogether, these findings suggest that ketamine, possibly by inhibiting activity of NMDA receptors and then increasing glutamatergic activation of AMPA receptors, may facilitate multiple downstream intracellular mechanisms that lead to increased BDNF mRNA, increased BDNF locally in dendrites, and ultimately to changes in neurocircuit structure and function that correlate with antidepressant behavior.

CURRENT CLINICAL USES AND PERSPECTIVES

Because racemic ketamine has no regulatory approval other than as an anesthetic and analgesic, its use in depression is considered "off-label." Indeed, when the success of intravenous ketamine was first reported, clinics that advertised off-label treatment with ketamine began to appear in communities around the United States.

Expert clinical guidance has been published in the United States and Europe for its use in this manner.[127,128]

Racemic ketamine is a 50/50 mixture of enantiomers (S)-ketamine and (R)-ketamine. (S)-ketamine is known to have higher affinity for the NMDA receptor versus (R)-ketamine, and the pure form has been studied similarly to the racemate. Intravenous esketamine was shown to be effective at doses of 0.2 and 0.4 mg/kg in an industry-sponsored study.[129] The same industry partner, Janssen Research and Development, sponsored follow-up studies of an intranasal formulation of (S)-ketamine, named "esketamine." Esketamine was found to be an effective adjunct to oral medications in patients with treatment-resistant depression and also acute depression with suicidal ideation in these studies.[130–132] Esketamine has now been approved by the US Food and Drug Administration for use in treatment-resistant depression under the brand name Spravato.

Repeated misuse/abuse of ketamine has well-known negative effects on cognition when used at relatively higher doses and for longer periods.[133] There is some concern regarding the cognitive effects of ketamine use for depression, because infusions in healthy male subjects produced acute decreases in verbal memory.[48,134] However, it may be the case that long-term alleviation of cognitive deficits from depression outweighs acute deficits induced by ketamine. In unipolar depression, cognitive predictors of mood improvement with ketamine include lower processing speed at baseline,[135] and alleviation of depression with ketamine mediates improvements in verbal memory and processing speed.[136] Improvement on cognitive tests did not correlate with improvement in depression in a small study of bipolar depressed patients, but this study was uncontrolled.[116] Esketamine affected cognition within 1 hour of intranasal dosing in phase 1 studies, but this did not last 2, 4, or 6 hours after dosing.[137] In addition, intranasal esketamine 84 mg did not affect road-driving performance 8 hours after administration, but the active comparator, mirtazapine 30 mg, did.[138] From this, it appears that racemic ketamine and pure esketamine have acute but transient negative cognitive effects related to direct pharmacologic actions, but the longer-term cognitive effects may be positive and relate to alleviation of depression.

The use of ketamine and derivatives as novel antidepressants comes in a time of great clinical need, as depression continues to be a leading cause of illness burden, and suicide rates continue to increase.[2,5] Now that the antidepressant effect of ketamine has been established, there is increasing opportunity to use ketamine as a research tool to study the neurobiology of depression. In addition, it has been neurobiologically established that the antidepressant effect of ketamine relates to subanesthetic dosing; further work is needed to determine methods to optimize ketamine treatment in individual patients. Several effects linked to ketamine use as an antidepressant may enhance the therapeutic process in patients outside its neuropharmacologic effects. With this in mind, it may be useful to attempt to augment the antidepressant effect of ketamine by harnessing these factors through combined psychotherapeutic interventions such as cognitive behavior therapy.[139]

Taken as a whole, the recent spate of research into the mechanism of action and clinical effects of ketamine has provided strong rationale for its further clinical development and basic research into molecular mechanisms of psychiatric disorders. The increasingly robust clinical data from ketamine and any other agent that similarly facilitates multimodal synaptogenesis in the PFC are stimulating a new phase of antidepressant drug development, which has been lacking since the discovery of monoaminergic agents.

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REFERENCES

1. US Burden of Disease Collaborators, Mokdad AH, Ballestros K, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319:1444–1472.
2. Greenberg PE, Fournier AA, Sisitsky T, et al. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry*. 2015;76:155–162.
3. Kessler RC. The costs of depression. *Psychiatr Clin North Am*. 2012; 35:1–14.
4. Houle JN, Light MT. The home foreclosure crisis and rising suicide rates, 2005 to 2010. *Am J Public Health*. 2014;104:1073–1079.
5. Sullivan EM, Annest JL, Simon TR, et al. Suicide trends among persons aged 10–24 years—United States, 1994–2012. *MMWR Morb Mortal Wkly Rep*. 2015;64:201–205.
6. Davidson JR. Major depressive disorder treatment guidelines in America and Europe. *J Clin Psychiatry*. 2010;71(suppl E1):e04.
7. Warden D, Rush AJ, Trivedi MH, et al. The STAR*D Project results: a comprehensive review of findings. *Curr Psychiatry Rep*. 2007;9: 449–459.
8. Machado-Vieira R, Baumann J, Wheeler-Castillo C, et al. The timing of antidepressant effects: a comparison of diverse pharmacological and somatic treatments. *Pharmaceuticals (Basel)*. 2010;3:19–41.
9. Krystal JH, Sanacora G, Blumberg H, et al. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. *Mol Psychiatry*. 2002;7(suppl 1):S71–S80.
10. Popoli M, Yan Z, McEwen BS, et al. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nat Rev Neurosci*. 2011;13:22–37.
11. Sanacora G, Zarate CA, Krystal JH, et al. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov*. 2008;7:426–437.
12. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry*. 1991;148:1301–1308.
13. Krystal JH, D'Souza DC, Mathalon D, et al. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. *Psychopharmacology (Berl)*. 2003;169:215–233.
14. Umbricht D, Schmid L, Koller R, et al. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry*. 2000;57:1139–1147.
15. Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. *Eur J Pharmacol*. 1990;185:1–10.

16. Cappello A, Charney DS, Berman RM, et al. NMDA Receptor Function in Major Depression. Abstract and poster presented at Society of Biological Psychiatry Annual Meeting at San Diego, California, May 14–18, 1997.
17. Moghaddam B, Adams B, Verma A, et al. 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.
18. Abdallah CG, Adams TG, Kelmendi B, et al. Ketamine's mechanism of action: a path to rapid-acting antidepressants. *Depress Anxiety*. 2016;33: 689–697.
19. Murrough JW, Abdallah CG, Mathew SJ. Targeting glutamate signalling in depression: progress and prospects. *Nat Rev Drug Discov*. 2017;16: 472–486.
20. Sapolsky RM. A mechanism for glucocorticoid toxicity in the hippocampus: increased neuronal vulnerability to metabolic insults. *J Neurosci*. 1985;5:1228–1232.
21. Sapolsky RM, Uno H, Rebert CS, et al. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci*. 1990;10: 2897–2902.
22. Uno H, Lohmiller L, Thieme C, et al. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques. I. Hippocampus. *Brain Res Dev Brain Res*. 1990;53:157–167.
23. Uno H, Tarara R, Else JG, et al. Hippocampal damage associated with prolonged and fatal stress in primates. *J Neurosci*. 1989;9:1705–1711.
24. Choi DW. Excitotoxic cell death. *J Neurobiol*. 1992;23:1261–1276.
25. Choi DW. Glutamate receptors and the induction of excitotoxic neuronal death. *Prog Brain Res*. 1994;100:47–51.
26. Dugan LL, Choi DW. Excitotoxicity, free radicals, and cell membrane changes. *Ann Neurol*. 1994;35(suppl):S17–S21.
27. Swann JW, Al-Noori S, Jiang M, et al. Spine loss and other dendritic abnormalities in epilepsy. *Hippocampus*. 2000;10:617–625.
28. Lee AL, Ogle WO, Sapolsky RM. Stress and depression: possible links to neuron death in the hippocampus. *Bipolar Disord*. 2002;4: 117–128.
29. Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. *Biol Psychiatry*. 2000;48: 755–765.
30. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry*. 2000;57:925–935.
31. Sapolsky RM, Alberts SC, Altmann J. Hypercortisolism associated with social subordinance or social isolation among wild baboons. *Arch Gen Psychiatry*. 1997;54:1137–1143.
32. Stein-Behrens BA, Lin WJ, Sapolsky RM. Physiological elevations of glucocorticoids potentiate glutamate accumulation in the hippocampus. *J Neurochem*. 1994;63:596–602.
33. Virgin CE Jr, Ha TP, Packan DR, et al. Glucocorticoids inhibit glucose transport and glutamate uptake in hippocampal astrocytes: implications for glucocorticoid neurotoxicity. *J Neurochem*. 1991;57:1422–1428.
34. Moghaddam B. Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. *Biol Psychiatry*. 2002;51:775–787.
35. Zarate CA Jr, Du J, Quiroz J, et al. Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: role of the glutamatergic system. *Ann N Y Acad Sci*. 2003;1003:273–291.
36. Crane GE. Cyloserine as an antidepressant agent. *Am J Psychiatry*. 1959; 115:1025–1026.
37. Hood WF, Compton RP, Monahan JB. D-Cycloserine: a ligand for the *N*-methyl-D-aspartate coupled glycine receptor has partial agonist characteristics. *Neurosci Lett*. 1989;98:91–95.
38. Sofia RD, Harakal JJ. Evaluation of ketamine HCl for anti-depressant activity. *Arch Int Pharmacodyn Ther*. 1975;214:68–74.
39. Lodge D, Anis NA. Effects of phencyclidine on excitatory amino acid activation of spinal interneurones in the cat. *Eur J Pharmacol*. 1982;77: 203–204.
40. Anis NA, Berry SC, Burton NR, et al. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by *N*-methyl-aspartate. *Br J Pharmacol*. 1983;79: 565–575.
41. Stringer JL, Guyenet PG. Elimination of long-term potentiation in the hippocampus by phencyclidine and ketamine. *Brain Res*. 1983;258: 159–164.
42. Honey CR, Miljkovic Z, MacDonald JF. Ketamine and phencyclidine cause a voltage-dependent block of responses to L-aspartic acid. *Neurosci Lett*. 1985;61:135–139.
43. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994;51:199–214.
44. Jentsch JD, Roth RH. The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology*. 1999;20:201–225.
45. Hynd MR, Scott HL, Dodd PR. Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease. *Neurochem Int*. 2004;45: 583–595.
46. Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. *Prog Neurobiol*. 2014;115:157–188.
47. Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci*. 2007;27:11496–11500.
48. Newcomer JW, Farber NB, Jevtovic-Todorovic V, et al. Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology*. 1999;20:106–118.
49. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47: 351–354.
50. Skolnick P, Layer RT, Popik P, et al. Adaptation of *N*-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. *Pharmacopsychiatry*. 1996;29: 23–26.
51. Nowak G, Trullas R, Layer RT, et al. Adaptive changes in the *N*-methyl-D-aspartate receptor complex after chronic treatment with imipramine and 1-aminocyclopropanecarboxylic acid. *J Pharmacol Exp Ther*. 1993;265:1380–1386.
52. Paul IA, Layer RT, Skolnick P, et al. Adaptation of the NMDA receptor in rat cortex following chronic electroconvulsive shock or imipramine. *Eur J Pharmacol*. 1993;247:305–311.
53. Skolnick P. Antidepressants for the new millennium. *Eur J Pharmacol*. 1999;375:31–40.
54. Vale S, Espejel MA, Dominguez JC. Amantadine in depression. *Lancet*. 1971;2:437.
55. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg*. 1966;45:29–40.
56. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of Ci-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther*. 1965;6: 279–291.
57. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006;63:856–864.
58. Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010;67:793–802.

59. Zarate CA Jr, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry*. 2012;71:939–946.
60. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry*. 2013;170:1134–1142.
61. Price RB, Iosifescu DV, Murrough JW, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depress Anxiety*. 2014;31:335–343.
62. Murrough JW, Soleimani L, DeWilde KE, et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol Med*. 2015;45:3571–3580.
63. Burger J, Capobianco M, Lovern R, et al. A double-blinded, randomized, placebo-controlled sub-dissociative dose ketamine pilot study in the treatment of acute depression and suicidality in a military emergency department setting. *Mil Med*. 2016;181:1195–1199.
64. Fan W, Yang H, Sun Y, et al. Ketamine rapidly relieves acute suicidal ideation in cancer patients: a randomized controlled clinical trial. *Oncotarget*. 2017;8:2356–2360.
65. Grunebaum MF, Galfalvy HC, Choo TH, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. *Am J Psychiatry*. 2018; 175:327–335.
66. Ghasemi M, Kazemi MH, Yoosefi A, et al. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. *Psychiatry Res*. 2014;215:355–361.
67. Lee EE, Della Selva MP, Liu A, et al. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. *Gen Hosp Psychiatry*. 2015;37:178–184.
68. Singh JB, Fedgchin M, Daly EJ, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am J Psychiatry*. 2016;173: 816–826.
69. Ionescu DF, Bentley KH, Eikermann M, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: a randomized, double blind, placebo controlled trial. *J Affect Disord*. 2019;243:516–524.
70. Xu Y, Li Y, Huang X, et al. Single bolus low-dose of ketamine does not prevent postpartum depression: a randomized, double-blind, placebo-controlled, prospective clinical trial. *Arch Gynecol Obstet*. 2017; 295:1167–1174.
71. Mashour GA, Ben Abdallah A, Pryor KO, et al. Intraoperative ketamine for prevention of depressive symptoms after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Br J Anaesth*. 2018;121:1075–1083.
72. Anderson IM, Blamire A, Branton T, et al. Ketamine augmentation of electroconvulsive therapy to improve neuropsychological and clinical outcomes in depression (ketamine-ECT): a multicentre, double-blind, randomised, parallel-group, superiority trial. *Lancet Psychiatry*. 2017;4: 365–377.
73. Ketter TA, Manji HK, Post RM. Potential mechanisms of action of lamotrigine in the treatment of bipolar disorders. *J Clin Psychopharmacol*. 2003;23:484–495.
74. Wang SJ, Wang KY, Wang WC. Mechanisms underlying the riluzole inhibition of glutamate release from rat cerebral cortex nerve terminals (synaptosomes). *Neuroscience*. 2004;125:191–201.
75. Mathew SJ, Murrough JW, aan het Rot M, et al. 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.
76. Ibrahim L, Diazgranados N, Franco-Chaves J, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology*. 2012;37: 1526–1533.
77. Niciu MJ, Luckenbaugh DA, Ionescu DF, et al. Riluzole likely lacks antidepressant efficacy in ketamine non-responders. *J Psychiatr Res*. 2014;58:197–199.
78. Phelps LE, Brutsche N, Moral JR, et al. Family history of alcohol dependence and initial antidepressant response to an *N*-methyl-D-aspartate antagonist. *Biol Psychiatry*. 2009;65:181–184.
79. Luckenbaugh DA, Ibrahim L, Brutsche N, et al. Family history of alcohol dependence and antidepressant response to an *N*-methyl-D-aspartate antagonist in bipolar depression. *Bipolar Disord*. 2012;14:880–887.
80. Niciu MJ, Luckenbaugh DA, Ionescu DF, et al. Ketamine's antidepressant efficacy is extended for at least four weeks in subjects with a family history of an alcohol use disorder. *Int J Neuropsychopharmacol*. 2014;18.
81. Hu YD, Xiang YT, Fang JX, et al. Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. *Psychol Med*. 2016;46: 623–635.
82. Arabzadeh S, Hakkikazazi E, Shahmansouri N, et al. Does oral administration of ketamine accelerate response to treatment in major depressive disorder? Results of a double-blind controlled trial. *J Affect Disord*. 2018;235:236–241.
83. Sos P, Klirova M, Novak T, et al. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. *Neuro Endocrinol Lett*. 2013;34:287–293.
84. Niciu MJ, Shovestul BJ, Jaso BA, et al. Features of dissociation differentially predict antidepressant response to ketamine in treatment-resistant depression. *J Affect Disord*. 2018;232:310–315.
85. Lenze EJ, Farber NB, Kharasch E, et al. Ninety-six hour ketamine infusion with co-administered clonidine for treatment-resistant depression: a pilot randomised controlled trial. *World J Biol Psychiatry*. 2016;17:230–238.
86. Sanacora G, Smith MA, Pathak S, et al. Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. *Mol Psychiatry*. 2014;19: 978–985.
87. Grunebaum MF, Ellis SP, Keilp JG, et al. Ketamine versus midazolam in bipolar depression with suicidal thoughts: a pilot midazolam-controlled randomized clinical trial. *Bipolar Disord*. 2017;19:176–183.
88. Chowdhury GM, Behar KL, Cho W, et al. ^{1}H-[^{13}C]-nuclear magnetic resonance spectroscopy measures of ketamine's effect on amino acid neurotransmitter metabolism. *Biol Psychiatry*. 2012;71:1022–1025.
89. Chowdhury GM, Zhang J, Thomas M, et al. Transiently increased glutamate cycling in rat PFC is associated with rapid onset of antidepressant-like effects. *Mol Psychiatry*. 2017;22:120–126.
90. Sanacora G, Banasr M. From pathophysiology to novel antidepressant drugs: glial contributions to the pathology and treatment of mood disorders. *Biol Psychiatry*. 2013;73:1172–1179.
91. Evans JW, Lally N, An L, et al. 7T (1)H-MRS in major depressive disorder: a ketamine treatment study. *Neuropsychopharmacology*. 2018; 43:1908–1914.
92. Fava M, Freeman MP, Flynn M, et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Mol Psychiatry*. 2018.
93. Koike H, Chaki S. Requirement of AMPA receptor stimulation for the sustained antidepressant activity of ketamine and LY341495 during the forced swim test in rats. *Behav Brain Res*. 2014;271:111–115.
94. Koike H, Iijima M, Chaki S. Involvement of AMPA receptor in both the rapid and sustained antidepressant-like effects of ketamine in animal models of depression. *Behav Brain Res*. 2011;224:107–111.
95. Lumsden EW, Troppoli TA, Myers SJ, et al. Antidepressant-relevant concentrations of the ketamine metabolite (2R,6R)-hydroxynorketamine

do not block NMDA receptor function. *Proc Natl Acad Sci U S A*. 2019; 116:5160–5169.

96. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition–independent antidepressant actions of ketamine metabolites. *Nature*. 2016;533: 481–486.
97. Muthukumaraswamy SD, Shaw AD, Jackson LE, et al. Evidence that subanesthetic doses of ketamine cause sustained disruptions of NMDA and AMPA-mediated frontoparietal connectivity in humans. *J Neurosci*. 2015;35:11694–11706.
98. Li M, Demenescu LR, Colic L, et al. Temporal dynamics of antidepressant ketamine effects on glutamine cycling follow regional fingerprints of AMPA and NMDA receptor densities. *Neuropsychopharmacology*. 2017; 42:1201–1209.
99. Autry AE, Adachi M, Nosyreva E, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011;475: 91–95.
100. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010;329: 959–964.
101. Li N, Liu RJ, Dwyer JM, 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.
102. Liu RJ, Fuchikami M, Dwyer JM, et al. GSK-3 inhibition potentiates the synaptogenic and antidepressant-like effects of subthreshold doses of ketamine. *Neuropsychopharmacology*. 2013;38:2268–2277.
103. Liu RJ, Lee FS, Li XY, et al. Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. *Biol Psychiatry*. 2012;71:996–1005.
104. Monteggia LM, Gideons E, Kavalali ET. The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. *Biol Psychiatry*. 2013;73:1199–1203.
105. Williams NR, Heifets BD, Blasey C, et al. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. *Am J Psychiatry*. 2018; 175:1205–1215.
106. Yoon G, Petrakis IL, Krystal JH. Association of combined naltrexone and ketamine with depressive symptoms in a case series of patients with depression and alcohol use disorder. *JAMA Psychiatry*. 2019;76:337–338.
107. Duman RS, Shinohara R, Fogaça MV, et al. Neurobiology of rapid-acting antidepressants: convergent effects on GluA1-synaptic function. *Mol Psychiatry*. 2019.
108. Abdallah CG, Averill LA, Gueorguieva R, et al. Rapamycin, an immunosuppressant and mTORC1 inhibitor, triples the antidepressant response rate of ketamine at 2 weeks following treatment: a double-blind, placebo-controlled, cross-over, randomized clinical trial (preprint). *bioRxiv*. 2018;500959.
109. Niciu MJ, Iadarola ND, Banerjee D, et al. The antidepressant efficacy of subanesthetic-dose ketamine does not correlate with baseline subcortical volumes in a replication sample with major depressive disorder. *J Psychopharmacol*. 2017;31:1570–1577.
110. Su TP, Chen MH, Li CT, et al. Dose-related effects of adjunctive ketamine in Taiwanese patients with treatment-resistant depression. *Neuropsychopharmacology*. 2017;42:2482–2492.
111. Machado-Vieira R, Yuan P, Brutsche N, et al. Brain-derived neurotrophic factor and initial antidepressant response to an *N*-methyl-D-aspartate antagonist. *J Clin Psychiatry*. 2009;70:1662–1666.
112. Duncan WC, Sarasso S, Ferrarelli F, et al. Concomitant BDNF and sleep slow wave changes indicate ketamine-induced plasticity in major depressive disorder. *Int J Neuropsychopharmacol*. 2013;16:301–311.
113. Haile CN, Murrough JW, Iosifescu DV, et al. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. *Int J Neuropsychopharmacol*. 2014;17: 331–336.
114. Lundin NB, Niciu MJ, Luckenbaugh DA, et al. Baseline vitamin B_{12} and folate levels do not predict improvement in depression after a single infusion of ketamine. *Pharmacopsychiatry*. 2014;47:141–144.
115. Permoda-Osip A, Dorszewska J, Bartkowska-Sniatkowska A, et al. Vitamin B_{12} level may be related to the efficacy of single ketamine infusion in bipolar depression. *Pharmacopsychiatry*. 2013;46:227–228.
116. Permoda-Osip A, Kisielewski J, Bartkowska-Sniatkowska A, et al. Single ketamine infusion and neurocognitive performance in bipolar depression. *Pharmacopsychiatry*. 2015;48:78–79.
117. Permoda-Osip A, Skibinska M, Bartkowska-Sniatkowska A, et al. Factors connected with efficacy of single ketamine infusion in bipolar depression. *Psychiatr Pol*. 2014;48:35–47.
118. Rybakowski JK, Permoda-Osip A, Bartkowska-Sniatkowska A. Ketamine augmentation rapidly improves depression scores in inpatients with treatment-resistant bipolar depression. *Int J Psychiatry Clin Pract*. 2017;21:99–103.
119. Rybakowski JK, Permoda-Osip A, Skibinska M, et al. Single ketamine infusion in bipolar depression resistant to antidepressants: are neurotrophins involved? *Hum Psychopharmacol*. 2013;28:87–90.
120. Ortiz R, Niciu MJ, Lukkahati N, et al. Shank3 as a potential biomarker of antidepressant response to ketamine and its neural correlates in bipolar depression. *J Affect Disord*. 2015;172:307–311.
121. Abdallah CG, Averill LA, Collins KA, et al. Ketamine treatment and global brain connectivity in major depression. *Neuropsychopharmacology*. 2017;42:1210–1219.
122. Abdallah CG, Jackowski A, Salas R, et al. The nucleus accumbens and ketamine treatment in major depressive disorder. *Neuropsychopharmacology*. 2017;42:1739–1746.
123. Abdallah CG, Salas R, Jackowski A, et al. Hippocampal volume and the rapid antidepressant effect of ketamine. *J Psychopharmacol*. 2015;29: 591–595.
124. Becker R, Braun U, Schwarz AJ, et al. Species-conserved reconfigurations of brain network topology induced by ketamine. *Transl Psychiatry*. 2016;6:e786.
125. Gass N, Schwarz AJ, Sartorius A, et al. Sub-anesthetic ketamine modulates intrinsic BOLD connectivity within the hippocampal-prefrontal circuit in the rat. *Neuropsychopharmacology*. 2014;39:895–906.
126. Yang Y, Cui Y, Sang K, et al. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. *Nature*. 2018;554:317–322.
127. Sanacora G, Frye MA, McDonald W, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. 2017;74:399–405.
128. López-Díaz Á, Murillo-Izquierdo M, Moreno-Mellado E. Off-label use of ketamine for treatment-resistant depression in clinical practice: European perspective. *Br J Psychiatry*. 2019;215:447–448.
129. Singh JB, Fedgchin M, Daly E, et al. Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. *Biol Psychiatry*. 2016;80:424–431.
130. Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry*. 2018;175:620–630.
131. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2018;75: 139–148.
132. Popova V, Daly E, Trivedi M, et al. Randomized, double-blind study of flexibly-dosed intranasal esketamine plus oral antidepressant vs. active control in treatment-resistant depression. *Biol Psychiatry*. 2018;83:S390.

133. Zhu W, Ding Z, Zhang Y, et al. Risks associated with misuse of ketamine as a rapid-acting antidepressant. *Neurosci Bull*. 2016;32:557–564.

134. Bell RF. Ketamine for chronic noncancer pain: concerns regarding toxicity. *Curr Opin Support Palliat Care*. 2012;6:183–187.

135. Murrough JW, Burdick KE, Levitch CF, et al. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. *Neuropsychopharmacology*. 2015;40:1084–1090.

136. Zheng W, Zhou YL, Liu WJ, et al. Neurocognitive performance and repeated-dose intravenous ketamine in major depressive disorder. *J Affect Disord*. 2019;246:241–247.

137. Morrison RL, Fedgchin M, Singh J, et al. Effect of intranasal esketamine on cognitive functioning in healthy participants: a randomized, double-blind, placebo-controlled study. *Psychopharmacology (Berl)*. 2018;235:1107–1119.

138. van de Loo A, Bervoets AC, Mooren L, et al. The effects of intranasal esketamine (84 mg) and oral mirtazapine (30 mg) on on-road driving performance: a double-blind, placebo-controlled study. *Psychopharmacology (Berl)*. 2017;234:3175–3183.

139. Wilkinson ST, Wright D, Fasula MK, et al. Cognitive behavior therapy may sustain antidepressant effects of intravenous ketamine in treatment-resistant depression. *Psychother Psychosom*. 2017;86:162–167.