Retracing our steps to understand ketamine in depression: A focused review of hypothesized mechanisms of action

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Abstract

Introduction: MDD represents a significant burden worldwide, and while a number of approved treatments exist, there are high rates of treatment resistance and refractoriness. Ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) antagonist, is a novel, rapid-acting antidepressant, however the mechanisms underlying the efficacy of ketamine are not well understood and many other mechanisms outside of NMDAR antagonism have been postulated based on preclinical data. This focused review aims to present a summary of the proposed mechanisms of action by which ketamine functions in depressive disorders supported by preclinical data and clinical studies in humans.

Methods: A literature search was completed using the PubMed and Google Scholar databases. Results were limited to clinical trials and case studies in humans that were published in English. The findings were used to compile this article.

Results: The antidepressant effects associated with ketamine are mediated via a complex interplay of mechanisms; key steps include NMDAR blockade on γ-aminobutyric acid interneurons, glutamate surge, and subsequent activation and upregulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

Discussion: Coadministration of ketamine for MDD with other psychotropic agents, for example benzodiazepines, may attenuate antidepressant effects. Limited evidence exists for these effects and should be evaluated on a case-by-case basis.

Keywords: ketamine, major depressive disorder, MDD, mechanism, drug-drug interaction

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Disclosures: The authors have nothing to disclose.

Introduction

MDD is a leading cause of disability worldwide with more than 322 million people affected.[1,2] Depressive disorders were among the top 10 conditions that contributed the largest number of additional disability-adjusted life-years globally from 1990 to 2019.[2] Approximately 20% to 30% of patients diagnosed with MDD have treatment-resistant depression (TRD), often defined as suboptimal response to at least 2 antidepressant trials of adequate dose and duration.[3] Despite the burden of MDD and availability of effective treatments, there remains a large percentage of patients who have suboptimal response. The pathophysiology of depression remains unclear, and specific biomarkers are lacking. Since the 1950s the prevailing hypotheses of MDD pathophysiology and antidepressant pharmacology have focused on monoamines.[4] Accordingly, traditional antidepressant pharmacotherapy is comprised of agents that modulate monoamine activity. In recent years, the paradigm has started to shift from the monoamine hypotheses to the neuroplasticity hypothesis, which posits that MDD results from dysregulation of

processes that allow neurons and neural systems to adapt to changes in the environment.[4]

A major disadvantage of traditional antidepressants is the 4-week to 8-week latency of onset of clinical action.[5] In addition to latency of effect, there is ongoing debate around the relationship between antidepressant use, specifically SSRIs, and suicidality.[6] All antidepressant drugs, however, carry a boxed warning for increased risk of suicidal thinking and behavior in children, adolescents, and young adults.[6] This relationship has not been observed in short-term studies in those over the age of 24 years; instead, at the population level, unchanged or decreasing risk of suicidality is observed with long-term use of antidepressants.[6] This is presumably because of improvement of depressive symptoms with long-term use. In regard to antisuicidality, there are only 2 non-antidepressant psychotropic medications, clozapine[7-9] and lithium,[10] with known antisuicidality effects outside of their impact on mood. Alternatively, ketamine, an N-methyl-D-aspartate receptor (NMDAR) antagonist originally developed for anesthetic use, exhibits antidepressant action within hours of administration in some patients.[11,12] The rapid onset of antidepressant effects associated with ketamine has led to off-label use of racemic ketamine as well as FDA approval of an intranasal formulation of the single isomer S-ketamine (esketamine) for use in TRD in combination with an oral antidepressant.[13]

Ketamine was developed in 1962 as an alternative dissociative anesthetic to phencyclidine and first administered to humans in 1964 by physicians Edward Domino and Guenter Corrsen.[14] In 1965, they published data[15] on the use of ketamine in 20 prisoners, establishing ketamine as an effective anesthetic agent. Ketamine binds at the dizocilpine site (MK-801) on the NMDAR and acts as a noncompetitive antagonist.[16,17] When administered intravenously at higher doses, ranging from 1 to 2 mg/kg, ketamine produces dissociative anesthesia.[15] In a 2010 retrospective, Domino[18] described the origins of ketamine, his early experience with it, and its current place in therapy. He wrote that, much to his surprise, a patient Domino became acquainted with in the 1980s reported that she eschewed her prescribed antidepressants in favor of illicitly obtained ketamine. The patient reported that ketamine rapidly and effectively relieved her depressive symptoms, prompting ongoing use.[18] In 2000, significant improvement in depressive symptoms was reported when patients with TRD received subanesthetic doses (0.5 mg/kg) of IV ketamine.[12] Subsequent studies[19-22] demonstrated decreased suicidality following administration, giving ketamine a rare distinction amongst psychotropic medications.

Despite its use over the last 20 years, little progress has been made in fully understanding the mechanism of ketamine in alleviating depressive symptoms. At a molecular level, ketamine antagonizes NMDAR preventing glutamate binding and the resultant influx of cations, primarily calcium.[17] However, multiple trials[23,24] employing other NMDAR antagonists have demonstrated that this alone is insufficient in generating antidepressant effects. The differing antidepressant activity between ketamine and other NMDAR antagonists suggest that ketamine possesses unique properties. There is a growing body of preclinical literature on the mechanisms underlying the antidepressant activity of ketamine.[25] The clinical significance of data generated in preclinical studies can be difficult to discern. Assessing the impact of other medications on the antidepressant effects of ketamine, while certainly a rudimentary strategy, is useful in the interpretation of preclinical data and generating clinically applicable insights. Furthermore, it helps to identify areas where further research is needed. This focused review aims to present a summary of the proposed mechanisms of action by which ketamine functions in depressive disorders supported by both preclinical and clinical studies, as well as provide insight into potential drug interactions with ketamine.

Methods

A literature search was conducted in the PubMed MEDLINE and Google Scholar databases. Results in both databases were limited to articles in English and studies in humans. All relevant literature, regardless of publication date, was included. Studies and case reports had to explicitly aim to evaluate the mechanism of ketamine in depression in humans or indirectly via reporting of potential drug interactions when ketamine was administered to humans. Preclinical data in animal studies pertinent to findings in clinical studies or case reports were then reviewed. The information from the above searches was used in compiling this article. The focus of this non-systematic review was literature providing pharmacodynamic data in humans. Keywords used were *ketamine*, *esketamine*, *depression*, *drug-drug interaction*, *pharmacodynamic interaction*, and *mechanism*.

Results

GABA Interneurons

One of the primary mechanisms that has emerged as underlying the rapid antidepressant activity of ketamine is NMDAR blockade on fast-spiking γ-aminobutyric acid (GABA) interneurons.[26,27] Fast-spiking GABA interneurons are so-named for the pattern of action potential they generate, and they play a major role in tonic inhibition of excitatory, projecting pyramidal neurons.[28] It appears that NMDAR subunit composition may be responsible for

selectivity of ketamine for NMDAR on GABA interneurons and lack of efficacy seen with other NMDAR antagonists.[29,30] This blockade on local, inhibitory GABA interneurons subsequently disinhibits excitatory pyramidal neurons resulting in a glutamate surge. Numerous preclinical studies[26-30] using rodent models of depression have demonstrated that intact GABA interneurons are required for the antidepressant effects of ketamine. Interestingly, a 2015 case report[31] described attenuated response to ketamine infusion in a woman with bipolar depression who was also taking lithium, fluoxetine, quetiapine, and lorazepam. The patient reported a "muted" response to ketamine after taking lorazepam prior to her infusion. Following discontinuation of lorazepam, the patient noted improved response and duration of effect after ketamine administration. No changes were made to any of her other medications. Subsequently 2 post-hoc analyses[32,33] evaluated the effect of concomitant benzodiazepine (BZD) administration on the antidepressant effect of ketamine. Concurrent BZD use predicted nonresponse to ketamine in a dose-dependent manner, while concurrent use of antiepileptic drugs (AED) including carbamazepine, divalproex sodium, and lamotrigine had no impact in 10 patients with TRD.[32] The mean dose in the first study,[32] reported in lorazepam equivalents, was 0.75 ± 0.29 mg for those in the responder group and 3 ± 1.4 mg in the nonresponder group. These findings were supported by reports of prolonged time to remission and shortened time to relapse in 13 patients with MDD receiving BZD compared to patients not concurrently receiving BZDs.[33] A recently published study[34] analyzing data from 2 previously conducted randomized, controlled trials reported that concurrent BZD use was a predictor of nonresponse in 47 patients with MDD to ketamine in a dose-dependent manner. Responders were receiving significantly lower doses of BZDs (7.7 ± 4.5 mg vs 32.1 ± 24.9 mg, diazepam equivalents) when compared to nonresponders.[34] Interestingly, all of these reports[31-34] describe attenuation of both acute and sustained effects of ketamine in MDD. While a recent study[35] did not replicate these findings, BZD doses were not reported. Since this may be a dose-dependent effect, it is challenging to interpret the significance of this. As of yet, no randomized controlled trials have evaluated the interaction between subanesthetic doses of ketamine for MDD and BZD. Furthermore, some clinical trials of ketamine require participants to discontinue BZDs prior to treatment,[36,37] but the above literature suggests a clinically significant interaction between the 2 and may point to the part of the underlying mechanism of ketamine.

Glutamate Surge

The glutamate surge following NMDAR blockade was initially demonstrated in preclinical animal models[38,39] and later supported by neuroimaging studies in humans.[40] Consequently, agents that block glutamate release may oppose the antidepressant effects of ketamine when administered concomitantly. Lamotrigine, an AED that exerts its action via inhibition of glutamate release, was administered prior to subanesthetic infusion of ketamine in healthy participants.[41] Compared to those who received placebo, those who received lamotrigine had significantly fewer ketamine-induced dissociative symptoms. While this study included participants without MDD or TRD, it helps illustrate the role of glutamate in mediating the effects of ketamine in vivo. It is important to note that the relationship between dissociative effects during subanesthetic infusion and antidepressant response is not well understood.[42] Recent neuroimaging data demonstrate attenuation of glutamate release following subanesthetic doses of ketamine but does not provide data on clinical outcomes associated with lamotrigine coadministration in patients with TRD.[43] A case series[44] describing 3 patients receiving repeated subanesthetic doses of ketamine while also on lamotrigine describe variable outcomes of ketamine therapy without clear evidence that coadministration of lamotrigine or other AEDs is deleterious on the antidepressant effects of ketamine.

Postsynaptic AMPAR Modulation

The NMDAR has consistently been implicated in the activity of ketamine, however another glutamate receptor, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), likely plays a central role.[45] Both AMPAR and NMDAR are ionotropic, however the synaptic currents produced by activation of each differ. NMDAR activation produces slower, longer lasting currents while AMPAR activation mediates fast synaptic transmission.[46] NMDAR are unique in that they are both ligand and voltage gated; channel opening requires ligand binding but influx of cations through the channel requires depolarization to dislodge extracellular magnesium or zinc ions that bind inside the channel at hyperpolarized membrane potentials.[47] NMDAR and AMPAR are often found together in the central nervous system as AMPAR can mediate the depolarization required for opening the NMDAR channel.[46,47] Following the glutamate surge produced by NMDAR blockade of GABA interneurons, postsynaptic AMPAR are activated and play an important role in mediating the antidepressant effects of ketamine. Preclinical studies have demonstrated increased AMPAR density following ketamine administration,[48] decreased efficacy of ketamine via AMPAR blockade,[49,50] as well as antidepressant effects of AMPAR potentiators in rodent models of depression.[51]

Two agents modulating AMPAR, riluzole and Org 26576, have been studied in patients with MDD.[52,53] Org 26576 is an AMPAR positive allosteric modulator which demon-

strated tolerability and promising antidepressant efficacy in phase I trials.[52] It failed to meet statistical significance in a phase II trial and has not been studied in MDD further. Riluzole, approved for the treatment of amyotrophic lateral sclerosis, is thought to have a net-negative effect on glutamate release.[54,55] Interestingly, it has also been shown to modulate AMPAR,[56] with 1 preclinical study[57] demonstrating enhanced AMPAR expression and AMPAR mediated membrane depolarization in a manner similar to lamotrigine and imipramine. In 2018, a clinical trial[58] demonstrated an association between lower serum brain derived neurotrophic factor (BDNF) levels at baseline in depressed patients and response to riluzole. A more recent meta-analysis[53] concluded that overall, riluzole did not demonstrate antidepressant efficacy. Alternatively, perampanel, an AED that antagonizes AMPAR, is associated with increased risk of depression in patients with and without epilepsy.[59] It should be noted that MDD is a common comorbidity of epilepsy and there is varying incidence of positive and negative antidepressant effects of different AEDs, including perampanel.[60,61]

Stronger evidence for involvement and activation of AMPAR in the antidepressant effects of ketamine comes from clinical, placebo-controlled trials[62-64] using neuroimaging techniques to explore molecular changes following ketamine administration. The time course described in the aforementioned neuroimaging studies suggests that initial AMPAR activation and ongoing modulation is implicated in both the acute and sustained antidepressant effects of ketamine. This is consistent with the proposed role of long-term potentiation mediated neural plasticity in antidepressant effects.[65] Some studies have proposed that one of the primary metabolites of ketamine, hydroxynorketamine, plays a significant role in mediating antidepressant effects independent of NMDAR antagonism via direct AMPAR activation.[66] Since the initial controversial finding, further studies[67,68] have questioned the veracity of these findings. At present, the full activity of ketamine metabolites and their clinical significance is not well understood.

mTOR Signaling

Following activation of AMPAR, intracellular signaling events including upregulation of BDNF and subsequent activation of mammalian target of rapamycin complex (mTOR) facilitates synaptogenesis.[69,70] Preclinical studies in rats and mice have demonstrated that both mTOR signaling and BDNF are required for ketamine's antidepressant effect; one preclinical study[71] found that the antidepressant response to ketamine was attenuated when study animals were pretreated with a single dose of rapamycin, an mTOR kinase inhibitor, infused directly into the medial prefrontal cortex (mPFC), one of the regions of the brain implicated in depression pathophys-

iology and the mechanism of action of ketamine. Interestingly, a number of traditional antidepressants, including fluoxetine,[72] paroxetine,[73] and fluvoxamine,[74] led to mTOR activation in a region-specific manner after chronic administration to mice in preclinical studies. In each of these studies, administration of rapamycin prevented antidepressant effects.

A 2011 case report[75] described increasing peripheral mTOR activation in correlation with improvement in depressive symptoms following ketamine administration to a patient with TRD. The purported role of mTOR was further evaluated in a human cross-over trial in which participants who had previously not responded to at least one adequate antidepressant trial received pretreatment with placebo or a single dose of rapamycin 2 hours prior to subanesthetic ketamine infusion.[76] Unexpectedly, rapamycin did not alter antidepressant efficacy of ketamine at 24 hours postinfusion, and pretreated subjects had prolonged duration of effect at the study's 2 week follow-up compared to those who had received placebo. Reasons proposed for the unexpected effect of rapamycin premedication in humans treated with ketamine are focused on the difference in concentrations when administered directly into the mPFC compared to systemic oral administration, potentially contributing to decreased central nervous system concentrations. Regarding the prolongation of antidepressant effect, the authors offered 2 possibilities: (1), that the anti-inflammatory effect of rapamycin serves to protect newly formed synapses, or (2), that rapamycin enhances autophagy essential to neuroplasticity. These possibilities are bolstered by evidence from studies of everolimus, a derivative of rapamycin that also antagonizes mTOR.[77]

Breast cancer patients treated with hormone therapy and everolimus demonstrated improved depressive symptoms compared to those treated with hormone therapy alone.[78] Another report[79] described significant improvement in mood and cognitive symptoms following a switch from calcineurin inhibitors to rapamycin in adult heart transplant patients. Calcineurin itself plays a role in mediating the effects of traditional antidepressants, and its activation is important for autophagy.[80,81] While these studies suggest that the antidepressant effect of systemically administered mTOR inhibitors is secondary to modulation of autophagy, both possibilities could simultaneously be true; regardless, this example emphasizes the importance in validating preclinical findings in humans.

Brain Derived Neurotrophic Factor

BDNF has been implicated in depressive disorders,[82] as well as other neuropsychiatric disorders including schizophrenia,[83] PTSD,[84] and Parkinson disease.[85] BDNF is increasingly recognized for the role it plays in response to

antidepressants and its potential as a biomarker for antidepressant response. This is evidenced by a meta-analysis[86] of 20 studies demonstrating increasing peripheral BDNF levels over the course of treatment with traditional antidepressants. A neuroimaging study[87] showed an association between change in resting state function connectivity, reflecting enhanced synaptic plasticity, and peripheral BDNF levels following ketamine administration in participants without MDD. Interestingly, changes in resting state function connectivity at 24 hours were only seen in participants that had increased BDNF levels at 24 hours as well. This study adds further support to the role of BDNF in ketamine response and illustrates a potential mechanism for the rapid onset of antidepressant effects seen with ketamine. A recent preclinical study[88] described differential changes in BDNF expression when mice were administered subanesthetic and anesthetic doses of ketamine. Hippocampal BDNF expression was increased at subanesthetic doses but was unchanged at higher doses, suggesting BDNF expression is, in part, responsible for the effects seen at different doses of ketamine. It could also contribute to the finding that not all patients demonstrate response to ketamine.

While a number of factors influence an individual's response to ketamine for MDD, a known polymorphism, BDNF Val66Met, that affects activity-dependent BDNF release is thought to play a role.[89] Preclinical studies using mice with this mutation demonstrated absence of antidepressant effects following ketamine administration.[90] Patients with the lower functioning polymorphism of this gene (Val/Met or Met/Met) had attenuated responses to ketamine for MDD compared to patients carrying the higher functioning polymorphism (Val/Val).[91] Subsequent work[92] did not demonstrate attenuation of antidepressant efficacy of ketamine in patients carrying the BDNF Val66Met polymorphism, but did show dose-dependent efficacy. Later reanalysis[93] demonstrated differing reduction in suicidal thoughts for Met/Met carriers compared to Val/Met and Val/Val carriers. A small cohort[94] of 6 Taiwanese patients with TRD demonstrated improved antidepressant response to a higher dose of ketamine, 0.8 mg/kg versus 0.5 mg/kg. While genotyping was not available for this cohort, a proposed reason for improved response at higher doses was the greater incidence of the Val66Met polymorphism in Asian populations.

Nonglutamatergic Signaling

Other, nonglutamatergic signaling pathways are also implicated in the antidepressant effects of ketamine. Ketamine is a weak ligand for the μ, κ, and δ opioid receptors with inhibition constant values at these sites that are more than 15 times greater than those with which it binds at the NMDAR.[95] Preclinical studies described

blocking of beneficial effects following ketamine administration when coadministered with μ-opioid antagonists,[96] findings which are supported by results of a small clinical study in which participants who received naltrexone premedication had significantly attenuated antidepressant and antisuicidality responses.[97] Two subsequent clinical studies[98,99] had discordant results. It has also been suggested that this may not be a ketamine-specific effect, rather a side effect of naltrexone.[100] The first[98] showed reduced depressive symptoms in patients receiving long-acting injectable naltrexone prior to 4 treatments with subanesthetic ketamine. Importantly, participants in this trial were receiving naltrexone for alcohol use disorder which may have introduced a confounding variable as more robust responses to ketamine are seen in patients with a first degree relative who has a history of alcohol use disorder.[101,102] A larger, retrospective study[99] (n = 40) also found no difference in antidepressant effect in participants receiving ketamine therapy and opioid ligands, either agonists (methadone, buprenorphine) or antagonists (naltrexone).

Finally, dopamine signaling likely plays a role in the antidepressant effect of ketamine and potentially mediates specific subgroups of symptoms (ie, anhedonia).[103] The role of dopaminergic signaling in depression pathophysiology has been suggested by numerous preclinical studies and supported by studies in humans as well. Pramipexole, a dopamine agonist at D_2 and D_3 receptors, has been shown to have an effect comparable to SSRIs in treating unipolar and bipolar depression.[104] Use of different atypical antipsychotics as adjunctive therapy has shown benefit in TRD.[105] Furthermore, a study[106] in patients with schizophrenia found that gene sets causing reduced NMDA and AMPA mediated synaptic currents were associated with poor antipsychotic drug response. In fact, the connection between glutamatergic signaling and antipsychotic efficacy may explain, in part, the superiority of clozapine to other antipsychotic agents. Clozapine has agonist activity at the NMDAR glycine$_B$ modulatory site causing increased glutamate and D-serine.[107]

While schizophrenia and MDD are often thought of in a dichotomous manner, neuroimaging has revealed similar brain alteration patterns in the 2 and similar patterns of normalization following treatment.[108-110] A pilot and follow-up study[111] evaluating the effects of adjunctive ketamine treatment in patients with chronic treatment-resistant schizophrenia with TRD symptoms demonstrated initial alleviation of depressive symptoms, however benefits seemed to persist for only 1 week following the first treatment and did not reappear with ongoing treatment. Interestingly, neuroimaging showed that alterations secondary to ketamine use returned to baseline at approximately 3 weeks. While there are far too many unknown variables and these findings are in

Target Site	Resulting Effects
NMDAR blockade on fast-spiking GABA interneurons	Glutamate surge due to disinhibition of glutamatergic pyramidal neurons
Propagation of postsynaptic AMPAR activation and expression	Upregulation of BDNF
Subsequent activation of mTOR signaling in addition to other downstream signaling pathways	Long-term potentiation leading to normalization of aberrant activity

FIGURE: **Summary of glutamatergic signaling implicated in the mechanism of action of ketamine in depression (AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF = brain derived neurotrophic factor; GABA = γ-aminobutyric acid; mTOR = mammalian target of rapamycin complex; NMDAR = *N*-methyl-D-aspartate receptor)**

patients with a different psychiatric disorder with differences in underlying pathology, it is possible that treatment with antipsychotics could attenuate the antidepressant effect of ketamine. Clozapine has been shown to reverse subanesthetic ketamine-induced changes in signaling in animal studies[112,113] and reduce ketamine-induced positive symptoms in humans.[114] Since a history of schizophrenia or psychosis is a relative contraindication to the use of ketamine, studies in these patient populations are few. It is unclear if coadministration of ketamine with dopamine modulating agents in patients without a history of psychosis or schizophrenia would negatively impact the antidepressant effect of ketamine.

Discussion

As ketamine use increases, it is important to identify clinically significant pharmacodynamic drug-drug interactions. BZDs have been reported[31-34] to attenuate the effect of ketamine in MDD. While not all studies have reported evidence of this interaction,[35] given the persistence of this effect in the setting of heterogeneous data and proposed mechanism of ketamine in MDD, it seems likely that BZDs pose a pharmacodynamic interaction in a dose-dependent manner. Limited data exists around ketamine and concomitant AEDs in MDD. The literature that exists suggests a potential interaction between ketamine and lamotrigine, however the use of lamotrigine should not preclude ketamine use for MDD.[41,43,44] Another small study[32] did not find AEDs to be associated with poor antidepressant response to ketamine. There are few commercially available AMPAR modulating agents, so there is a lower likelihood of coadministration of these along with ketamine in the clinical setting. Riluzole has not consistently demonstrated antidepressant effects on its own and has not provided benefit as an adjunct to ketamine.[58] Therapeutic use of perampanel while receiving ketamine for MDD has not been reported, however based on experimental neuroimaging findings in humans,

it appears to have the potential to attenuate the antidepressant effect of ketamine.[115] Agents that impact downstream signaling like rapamycin suggest potential benefit when coadministered with ketamine.[76] It is unclear how different doses and ongoing use, as opposed to a single dose given before ketamine administration, would impact the antidepressant effect of ketamine. There is significant debate as to the role opioid signaling plays in the antidepressant effect of ketamine; this is further hindered by the exclusion of patients with histories of SUD from most clinical trials. It seems likely that opioid signaling does play a role but is not sufficient for the antidepressant effect of ketamine.[95-99] Concurrent opioid ligand use should be evaluated on a case-by-case basis keeping in mind the different receptor binding properties of individual agents (ie, κ-antagonism with buprenorphine[116]). Finally, it seems likely that an interaction exists between antipsychotics and ketamine,[111-114] but this is largely theoretical at this point.

A full understanding of the mechanism and promise of ketamine as a prototypical rapid-acting antidepressant remains elusive. Despite this, a clearer picture is emerging (Figure). Data from preclinical models supported by neuroimaging studies in humans suggests that NMDAR blockade on GABA interneurons in the mPFC is the initial event that triggers the glutamate surge seen after ketamine administration. This surge is the result of disinhibition of glutamatergic pyramidal neurons and propagates post-synaptic AMPAR activation and expression. AMPAR activation and subsequent long-term potentiation is mediated by a number of downstream signaling pathways, including BDNF and mTOR. It seems that both opioid and dopamine mediated signaling are implicated and possibly responsible for specific subgroups of antidepressant effects (eg, suicidality and anhedonia). It is also possible that the antisuicidality effect associated with ketamine is separate from the antidepressant effect, even if the time course of the 2 often overlap. While

progress has been made in understanding the underlying mechanisms of the antidepressant effect of ketamine, many areas exist where further research is needed. The clinical significance of variant BDNF Val666Met polymorphisms is still being explored and has the potential to inform treatment decisions for ketamine in MDD. As described earlier, gene sets affecting NMDA and AMPA mediated synaptic currents predicted poor response to antipsychotic agents in patients with schizophrenia; while these alleles are rare, their presence may also impact the antidepressant efficacy of ketamine. Finally, potential pharmacodynamic drug-drug interactions have been explored in this review, but this is likely only the tip of the proverbial iceberg. Better delineation of concurrent psychotropic drugs in clinical studies of ketamine will aid in improving understanding of pharmacodynamic drug-drug interactions and the underlying mechanisms of ketamine.

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