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Ketamine and the neurobiology of depression: Toward next-generation rapid-acting antidepressant treatments

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Ketamine has emerged as a transformative and mechanistically novel pharmacotherapy for depression. Its rapid onset of action, efficacy for treatment-resistant symptoms, and protection against relapse distinguish it from prior antidepressants. Its discovery emerged from a reconceptualization of the neurobiology of depression and, in turn, insights from the elaboration of its mechanisms of action inform studies of the pathophysiology of depression and related disorders. It has been 25 y since we first presented our ketamine findings in depression. Thus, it is timely for this review to consider what we have learned from studies of ketamine and to suggest future directions for the optimization of rapid-acting antidepressant treatment.

depression | stress | antidepressant | ketamine | neuroplasticity

The discovery of the rapid antidepressant effects of R,S-ketamine (ketamine) was hailed simultaneously as the most improbable and transformative advance in depression pharmacotherapy in many decades. In the 1990 s, ketamine was known as a dissociative anesthetic (1) with nociceptive efficacy (2, 3) and uses in veterinary medicine (4). Ketamine misuse was a public health concern (5–7). Nicknamed "Special K," its profound effects on consciousness were called the "K hole" (8). The initiation of schizophrenia-related studies with ketamine in humans in the 1990s (9–11) stimulated controversy because of its psychoactive effects (12). Keatmine targeted glutamate receptors and produced response within hours of administration of a single dose. From the start, there were concerns as to whether its risks outweighed its benefits (13). The risks associated with ketamine treatment are real, and they have informed optimal clinical practice. However, when used appropriately, the remarkable efficacy of intermittent subanesthetic ketamine or the more potent of its two isomers at N-methyl-D-aspartate glutamate receptors (NMDAR), S-ketamine (Esketamine) can have a transformative positive impact on the lives of people suffering from depression, and potentially, the public health burden associated with treatment-resistant symptoms of depression. This review begins by characterizing advances in the conceptual framework for the biology of depression that set the stage for the discovery of the antidepressant effects of ketamine. It then describes the therapeutic impact of ketamine and considers mechanisms underlying its efficacy. Lastly, it addresses progress made in enhancing ketamine efficacy and safety.

The Neurobiology of Depression: Beyond the Monoamine Hypothesis

Historically, psychiatric psychopharmacology progressed more rapidly than pathophysiology. By 1957, pioneers identified the principal medication classes used currently to treat depression, the monoamine oxidase inhibitors, monoamine transporter antagonists, lithium, and the antipsychotics (14–17). These medications provided clues to the biology of depression, leading to monoamine-centric hypotheses (18, 19). Monoamine depletion studies led by Charney and colleagues at Yale (20) clearly implicated ongoing monoamine availability in the sustained efficacy of monoamine transporter antagonist antidepressants. However, the failure of monoamine depletion to produce depression in healthy individuals (21) challenged the notion that depression was simply a deficit in monoamine signaling.

At that point, Charney and Krystal broadened their focus to encompass the intrinsic signaling mechanisms of the cortex and limbic system. We now know that depression is associated with altered cortico-limbic structure (22), functional connectivity (23, 24), and functional regulation of circuits regulating mood (25, 26). These insights are driving circuit-based interventions for depression (27, 28). The molecular

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and cellular underpinnings of these alterations are emerging from postmortem studies characterizing the transcriptomic, epigenomic, and proteomic landscape of depression (29–33). A complete assessment of the biology of depression, however, is beyond the scope of this review. Here, we highlight three relevant recently characterized depression-related alterations in glutamate synaptic signaling [see for review: (34, 35)]:

The first characteristic is reduced glutamate synaptic efficacy as reflected in reduced amplitude of sensory evoked potentials (36) and in reduced cortical functional connectivity (23). Also, a recent study in PTSD with or without comorbid major depression (37) reported reduced synaptic strength as reflected by reduced "energy per cycle," i.e., decreased metabolic activity (tricarboxylic acid cycle activity) per each molecule of glutamate released by neurons.

The second characteristic is reduced synaptic density. Preclinical studies described reductions in synaptic density and dendritic retraction in chronically stressed animals (38, 39). Human postmortem findings also report reduced synaptic density and reductions in genes coding for synaptic proteins (40, 41). Lower synaptic density in depression is also evident in vivo where it is associated with cortical circuit dysregulation (42).

A third characteristic is disrupted synaptic glutamate homeostasis. Preclinical research (43, 44) suggests that stress-related disruption of glial function, particularly glutamate transport, elevates extracellular glutamate levels, overstimulates extrasynaptic N-methyl-D-aspartate (NMDA) receptors (NMDAR), downregulates glutamate synaptic function, contributes to synaptic pruning, and produces depression-like behavior in animals. Analyses of postmortem tissue from depressed patients also reveal reductions in glial integrity (45) and downregulation of membrane glutamate transporters (46).

Ketamine: Clinical Efficacy Tied to Restoration of Synaptic Efficacy and Synaptic Density

Clinical Efficacy. Ketamine and Esketamine efficacy contrasts with traditional antidepressant treatments. The first trial of subanesthetic ketamine (0.5 mg/kg, administered intravenously over 40 min) revealed antidepressant effects from a single dose that emerged over a few hours and became more pronounced over the following days (47). The first replication of this study mirrored these findings in patients with treatment-resistant depression symptoms (48). Subsequent clinical trials of ketamine and Esketamine replicated and extended these findings (49, 50). Ketamine and Esketamine produce response rates over 50% and remission rates between 30% and 50%, much higher than one would expect for a traditional antidepressant prescribed for treatment-resistant symptoms, i.e., response rates of <20% and remission rates of <15% (51) and comparable to electroconvulsive therapy (52). With ongoing treatment, the frequency of ketamine dosing can be reduced without loss of efficacy (53, 54). The durability of ketamine efficacy during long-term treatment is impressive. In a randomized Esketamine discontinuation study, only approximately 25% of patients relapsed during Esketamine treatment in the year following responding to Esketamine plus a new antidepressant. Responders who stopped Esketamine but continued their antidepressant had a relapse rate of over 57% (55). In other words, Esketamine shows signs of superior protection against depression relapse in comparison to a newly initiated antidepressant (55) than traditional antidepressants in comparison to placebo (56). Overall, there is no clear evidence that tolerance develops to its therapeutic effects during long-term treatment (57).

Safety concerns limit Esketamine to clinic settings and efforts to develop strategies for in-home ketamine treatment have raised clinical concerns. The principal medical side effects of ketamine and Esketamine are elevated blood pressure, nausea and vomiting, and dissociation (57). These effects are generally managed by pretreatment optimization of hypertension management and a serotonin-3 receptor antagonist for nausea. Preparing patients for the dissociative effects prior to treatment, supporting them during drug administration, and debriefing patients following treatment are usually sufficient to manage these symptoms. Rarely, patients benefit from additional supportive care or benzodiazepine administration. When ketamine is administered outside of clinic settings, there is an additional risk of misuse of the prescribed ketamine. This concern is amplified by evidence that rates of ketamine recreational use increased significantly in the United States since the Food and Drug Administration (FDA) approval of Esketamine (7).

Reversing Stress and Depression Effects on Glutamate Synaptic Signaling through Restoration of Synaptic Efficacy and Synaptic Density. Preclinical studies provide foundational insights into mechanisms underlying the efficacy of ketamine in patients (Fig. 1). The antidepressant effects of ketamine share features with other forms of neuroplasticity whereby transient circuit activation produces long-lasting potentiation of synaptic signaling, sometimes referred to as Hebbian plasticity (58). The first step in the processes leading to antidepressant efficacy of ketamine is inhibition of interneuron activity (59), resulting in disinhibition of glutamate release. The importance of this step is supported by evidence that chemogenic inhibition of prefrontal cortex interneurons (60) or knockdown of GluN2B NMDAR subunits on somatostatin (SST) and parvalbumin (PV) interneurons but not glutamatergic neurons (61) prevents or occludes the antidepressant efficacy of ketamine. The importance of the resulting glutamate neuronal activation is supported by the convergent antidepressant effects of local infralimbic cortex ketamine administration and pharmacological (62) and optogenetic (63) activation of the same brain region. In stressed animals, activation of NMDAR (64) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR) (65) restore synaptic efficacy, elevate brain-derived neurotrophic factor (BDNF) levels, trigger local release of BDNF, and activate signaling cascades downstream from the receptor for BDNF, tropomyosin receptor kinase B (Trk B) receptors, including the mammalian target for rapamycin (mTOR). mTOR activation, in turn, drives restoration of dendritic spines pruned by stress-related processes (65, 66). The onset of antidepressant behavioral effects produced by ketamine precedes the emergence of regrown spines (66), suggesting that restoration of synaptic efficacy and other processes initiate antidepressant effects. However, antidepressant behavioral effects persist with the same timescale as the newly regrown

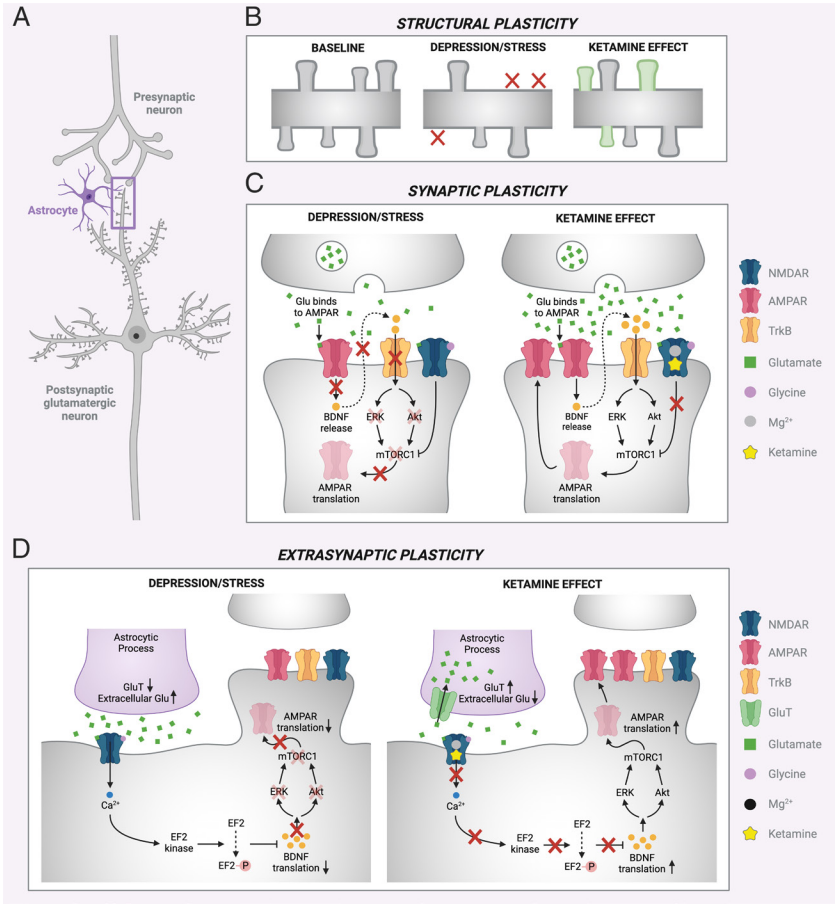

Fig. 1. Schematic of proposed mechanisms of ketamine's antidepressant effect (*A*): (*B*) structural plasticity is induced leading to growth of dendritic spines in the prefrontal cortex, (*C*) enhanced synaptic efficacy, (*D*) extrasynaptic NMDA receptors' role in homeostatic plasticity.

spines (67) and interference with spine restoration shortens the duration of ketamine's antidepressant effects (66). Thus, mTOR-dependent spine restoration appears to be related directly to the duration of ketamine efficacy.

Translational research studies now provide evidence in healthy humans and depressed patients that support aspects of the models for ketamine efficacy outlined in the prior two paragraphs:

Support for a link between ketamine-related glutamate release and antidepressant response. The ability of ketamine to stimulate human cortical glutamate release was demonstrated using a direct ^{13}C-magnetic resonance spectroscopy (MRS) technique (68) and an indirect positron emission tomography (PET) method (69, 70). Using the latter approach, the magnitude of glutamate release correlated with the magnitude of depression improvement (71).

Support for an association between ketamine-related enhancement of synaptic efficacy and antidepressant response. Preliminary studies suggest that antidepressant response is associated with an increase in the amplitude of sensory evoked potentials and stimulus-induced high-frequency cortical activity, as changes were observed in ketamine responders but not in ketamine nonresponders or healthy individuals (72, 73). Effective ketamine treatment also may ameliorate deficits in resting cortical functional connectivity (74).

Support for a role for synaptic regrowth in ketamine-related antidepressant response. A pilot PET study of synaptic density provided evidence for the existence of at least two mechanisms contributing to ketamine efficacy (75). Ketamine did not affect synaptic density 24 h after a single dose in healthy individuals (n = 9) or depressed individuals without synaptic deficits (n = 6). While the depressed individuals without synaptic deficits improved after ketamine, their improvement was unrelated to changes in synaptic density and not associated with the degree of dissociative symptoms, i.e., a behavioral marker of the degree of NMDAR target engagement. However, in patients with depression with synaptic deficits (n = 6), ketamine increased synaptic density in a manner that was correlated with both clinical improvement and degree of dissociative symptoms.

Ketamine and Restoration of Homeostatic Plasticity within the Microcircuit

Ketamine effects on stress-related homeostatic plasticity also may contribute to its antidepressant effects (58, 76). By homeostatic plasticity, we refer to synaptic neuroadaptations to changes in neural activity that restore the balance between excitation and inhibition within microcircuits (77) and that complement input-specific synaptic plasticity (78). Depression produces synaptic downscaling as a response to impaired glutamate homeostasis as a consequence of astroglial dysfunction (43, 79) or enhanced tonic glutamate release (58). In both cases, NMDAR blockade by ketamine alleviates a homeostatic "break" on synaptic efficacy and neurotrophic signaling, in part, by reducing the phosphorylation of eukaryotic translation elongation factor-2 (eEF2) and activation of eEF2 kinase. These effects complement the ability of ketamine-induced glutamate release to drive restorative plasticity.

Homeostatic plasticity also may contribute to the ability to progressively reduce the frequency of ketamine dosing over time during long-term treatment. Treatments typically begin with twice-weekly ketamine infusions and then gradually decrease this frequency over time. It is not yet clear why the duration of ketamine's therapeutic effects increases over time. One wonders if the increased duration of efficacy is related to increasing persistence of dendritic spines. If so, then steps that protect these spines might extend the duration of ketamine efficacy. Ketamine's enhancement of AMPAR activation and raising of BDNF levels produces phosphorylation of methyl CpG binding protein 2 (MeCP2) Ser421, a protein implicated in ketamine's effects on homeostatic plasticity (58) contributing to the prolongation but not the initiation of its antidepressant effects (80, 81). MeCP2, in turn, regulates mTOR signaling (82, 83) and, downstream, dysbindin (84). Dysbindin, in turn, is implicated in homeostatic regulation of glutamate release (85) as well as the outgrowth, maturation, and maintenance of dendritic spines (86, 87). Thus, the extended duration of ketamine efficacy with repeated dosing may engage specific proteins that might be targeted by novel treatments to extend the duration of ketamine efficacy.

Glutamatergic alterations in major depression are paralleled by disturbances in gamma-aminobutyric acid (GABA) signaling, reflected in lower cortical GABA levels in vivo (88, 89). These reductions are prominent in severely ill patients with psychosis or with prominent blunting of mood reactivity and vegetative signs of depression (90). Postmortem studies also describe compromised GABA neuronal integrity, particularly for SST GABA interneurons. In patients with treatment-resistant symptoms and GABA deficits, serotonin transporter antagonist (91), transcranial magnetic stimulation (92), and electroconvulsive therapy (93) treatments restored cortical GABA levels. One pilot study reported ketamine-related restoration of cortical GABA levels (94), a finding that was not replicated (95).

In animal studies, ketamine corrects stress-related reductions in GABA neuronal markers and GABA physiologic signals (inhibitory postsynaptic potentials) within cortico-limbic microcircuits (96, 97). Its induction of Hebbian and homeostatic synaptic plasticity is likely to occur in synapses between glutamate and GABA neurons (35), as well as between glutamate neurons. In animals, stress produces significant changes in GABA neurons, particularly in SST interneurons (35, 98). SST neurons modulate cortical functional connectivity by gating the efficacy of inputs to distal dendrites (99, 100). In stressed animals, SST neurons show reduced expression of molecular markers of functional integrity (101). GABA deficits in mice hemizygous for knockout of the γ_2 subunit of the $GABA_A$ receptor exhibit homeostatic adaptations including downregulation of glutamate receptors and glutamate synapses (97). Thus, chronic GABA deficits associated with stress appear to produce allostatic adaptations that maladaptively restore excitation/inhibition balance but at a reduced setpoint for both GABA and glutamate synaptic connectivity. Ketamine also reverses the stress-related changes in glutamate and GABA signaling, maintaining excitation/inhibition balance but at normal levels (96, 97). α_5-preferring $GABA_A$ receptor agonism may produce similar effects (102).

From Ketamine to Next-Generation Rapid-Acting Antidepressant Treatment

In the space below, we identify key questions related to ketamine efficacy that point to strategies optimizing NMDAR antagonist antidepressant treatments.

Protect the Integrity of the Restored Synaptic Connectivity Produced by Ketamine. We (J.H.K., S.T.W., G.S., S.J., and A.P.K.) have treated patients who seem to have a complete therapeutic response to a single dose of ketamine only to see this improvement fade unless another dose of ketamine is administered. Clearly, restoration of an optimistic, positive psychological attitude in these cases is not sufficient on its own to prevent relapse. As the maintenance of ketamine's antidepressant effects depends directly on restoration of lost spines (66), relapse may reflect the impermanence of regrown spines (67) or post-ketamine increases in spine elimination (Fig. 2). Thus, strategies that might prolong the persistence of the regrown spines might also extend ketamine efficacy. Two types of interventions are already shedding light on paths to extend ketamine efficacy: behavioral interventions and mTOR inhibition.

Psychotherapy may augment and prolong the antidepressant efficacy of ketamine, as suggested by a pilot study of cognitive behavioral therapy delivered on the days following a ketamine infusion (103). Neural mechanisms underlying this effect are not well understood. Ketamine affects memory reconsolidation as well as the subsequent separation of memory engrams in the hippocampus. Experiences, such as fear extinction, can by themselves engender the kind of dendritic spine growth in the frontal cortex that is characteristic of ketamine's effects (104). Also, there may be nonspecific immunological and neurotrophic effects of psychotherapy similar to another behavioral intervention, exercise. Exercise has robust antidepressant effects in humans (105) and animals (106). In animals, exercise raises brain BDNF levels, activates mTOR, promotes neurogenesis, and increases spinogenesis. It also protects newly created spines by reducing microglial inflammatory functions and

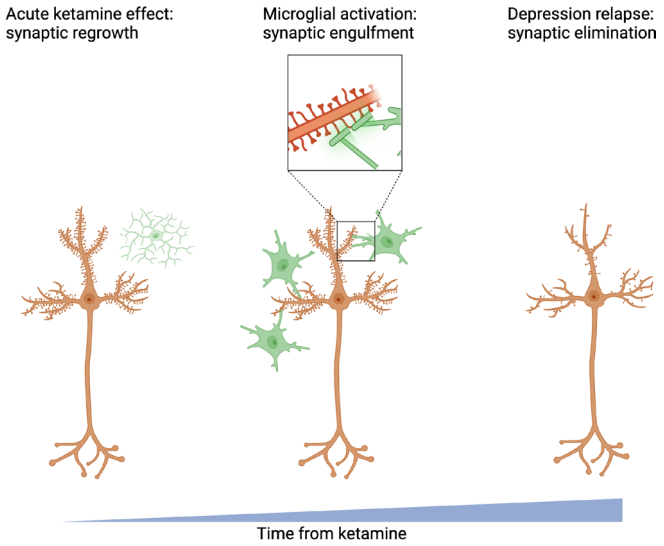

Fig. 2. Potential mechanism limiting ketamine's duration of action.

promoting their neurotrophic functions (104, 107). Psychotherapy is a form of enrichment of the social environment. In animals, environmental enrichment raises BDNF levels, activates Akt/mTOR signaling, promotes synaptic growth, and protects dendritic integrity (108–113). Thus, it is possible that psychotherapies enhance and sustain ketamine efficacy through synergistic activity-dependent forms of neuroplasticity.

Another potential strategy for maintenance of ketamine-induced synapses is engagement of perineuronal nets (PNNs), which stabilize synapses and regulate synaptic plasticity. This extracellular matrix compartment coats PV interneurons (114), a potential initial target for ketamine's antidepressant effects. The integrity of PNNs in the ventral hippocampus may be required for sustained antidepressant effects of ketamine (115), while repeated ketamine doses cause degradation of PNNs elsewhere (116–118).

Low-dose mTOR inhibition may extend the duration of ketamine efficacy. In a within-subject study of 20 depressed patients, pretreatment with the mTOR inhibitor, rapamycin, increased ketamine response rates at 2 wk from 13 to 41% (119). This finding contrasted with the blockade of ketamine's antidepressant effects by intracortical rapamycin, which produced much higher brain exposure to rapamycin (65). The extension of ketamine antidepressant effects by rapamycin might reflect the protection of regrown synapses from elimination by microglia (Fig. 3). Rapamycin may accomplish this by inhibiting mTOR, enhancing autophagy, and promoting the repolarization of microglia, i.e., inhibiting the inflammatory functions of microglia (120–122) and promoting their neurotrophic activity (123–126). Rapamycin also may paradoxically enhance ketamine activation of mTOR through negative feedback loops induced by mTORC1 inhibition, such as phosphatidylinositol-3 kinase (PI3K), AKT serine-threonine protein kinase (AKT), and extracellular signal-regulated kinase (ERK) activation (127, 128).

Neuroinflammation appears to be an important contributor to treatment resistance of depression symptoms (129). The synergy of rapamycin, an immunosuppressant, and ketamine highlights the importance of antiinflammatory effects of ketamine to its clinical efficacy. The antiinflammatory effects of ketamine include reductions in proinflammatory cytokine release, inhibition of the proinflammatory kinase, glycogen synthase kinase 3β (GSK3β) (130), effects on the kynurenine pathway, interference with interferon signaling, reduction of microglial inflammatory polarization, and enhancement of microglial autophagic activity (129, 131–133).

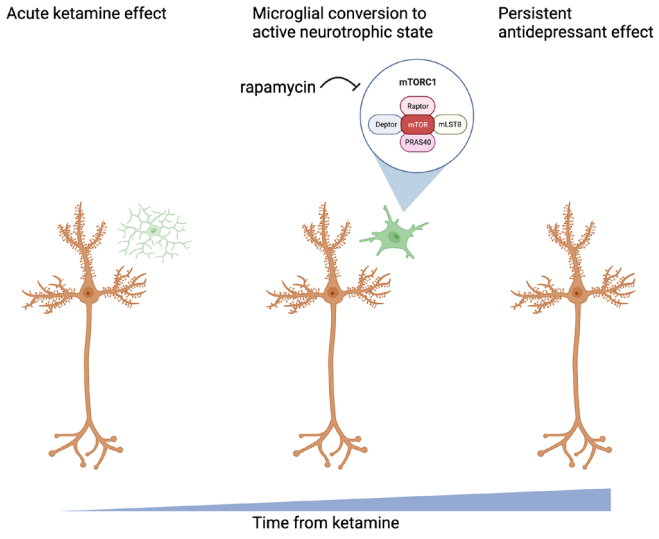

Fig. 3. Potential avenue of extension of ketamine effect by mTOR inhibition.

Enhancing Ketamine Effects on Neuroplasticity via NMDAR Subtype Selectivity. In randomized trials, ketamine is effective in a narrow dose range centered on 0.5 mg/kg administered intravenously over 40 min (47), but not at 0.2 mg/kg (134–136). At 1.0 mg/kg, ketamine has greater dissociative effects but not greater efficacy (135), while at anesthetic doses, ketamine is not antidepressant (137).

The narrow therapeutic dose range for ketamine limits its candidate primary brain targets to just a few including NMDARs and perhaps hyperpolarization-activated cyclic nucleotide-gated potassium channel 1 (HCN1) and TrkB receptors (138). The optimal ketamine dose for raising extracellular glutamate levels coincides with the typical antidepressant dose (139). Ketamine loses efficacy at anesthetic doses where it suppresses glutamate release (140). At these doses, ketamine blocks presynaptic NMDARs and HCN1 channels that promote glutamate release (141). Knockout of HCN1 channels prevents the emergence of ketamine's antidepressant and neuroplastic effects (141). Thus, blockade of presynaptic NMDARs and HCN1 channels may limit ketamine efficacy.

Optimizing subunit selectivity might improve NMDAR antagonist tolerability or efficacy, although the path forward is not clear. Ketamine produces a higher affinity use-dependent blockade of the NMDAR cation channel and a lower affinity allosteric inhibition of channel opening, associated with anesthetic doses (142). Ketamine competes with magnesium for binding to the cation channel. This competition conveys greater ketamine potency at NMDARs with lower magnesium affinity, receptors bearing GluN2C and GluN2D subunits, relative to receptors bearing GluN2A or GluN2B subunits (143–145), although some studies challenge this view (146). Subunit selectivity may create a path to focus NMDAR antagonism on targets that promote efficacy and avoid those that may impede its effectiveness. Psychedelics, for example, enhance glutamate release and activate mTOR without blocking synaptic NMDARs or HCN1 channels (147–149) and single doses of psychedelic drugs appear to produce longer-duration antidepressant effects (150–152) than single doses of ketamine.

GluN2B-selective NMDAR antagonists appear to produce antidepressant effects in patients at doses that also evoke dissociative symptoms (153). In animals, GluN2B subunit-selective antagonists produce antidepressant effects via Hebbian plasticity (65, 154) and normalization of homeostatic adaptations (155–157). Knockdown of GluN2B subunits prevents or occludes the expression of ketamine's antidepressant effects (80, 158). There may be drawbacks of blocking GluN2B-containing receptors. GluN2Bs figure prominently among postsynaptic NMDARs and blockade may reduce Hebbian plasticity (64). Also, GluN2B receptors contribute to presynaptic glutamate release (159) and blockade of these receptors reduces glutamate release that might underlie

therapeutic neuroplasticity. One might infer that low doses of GluN2B-preferring NMDAR antagonists would produce restorative neuroplasticity without interfering with efficacy. However, low doses of the GluN2B-preferring NMDAR antagonist, memantine, were ineffective (160).

Selective blockers of the highest affinity targets for ketamine, GluN2C- and GluN2D-containing NMDARs, also might be considered. These NMDAR subtypes are well-represented in interneuron populations (161–165), although they are present in fewer excitatory synapses than GluN2B or GluN2A. GluN2D knockout mice do not exhibit glutamatergic neuronal activation in response to ketamine (166). The GluN2D-prefering NMDAR antagonist, S-methadone (146), showed efficacy in a preclinical study (167), where it activated mTOR and induced synaptic regrowth. Despite an encouraging preliminary report (168), press releases suggest that S-methadone failed in Phase III clinical trials. Questions related to the optimal dosing of GluN2D-selective antagonists remain. Selective antagonism of GluN2D-containing NMDARs has yet to be tested. Although GluN2C-containing NMDARs are the highest affinity target for ketamine (169), they appear to contribute to dissociative but not antidepressant effects. GluN2C knockout animals show attenuated behavioral abnormalities but not reduced antidepressant efficacy (170).

Optimize Ketamine Effects on Synaptic and Downstream Signaling. Proteins in the signaling cascades activated by ketamine might be targeted as 1) alternative monotherapies for depression, 2) as adjunctive strategies to augment ketamine efficacy, or 3) as a strategy for creating a "nondissociative" ketamine via synergy, i.e., combination of a subdissociative dose of ketamine with an agent that conveys full efficacy. Drugs targeting proteins in ketamine-activated signaling cascades have shown promise in preclinical antidepressant studies (76). Because ketamine inhibits GABA neuronal activation and increases glutamate release, drugs that inhibit $GABA_A$ receptor signaling (171, 172) or block glutamate release-inhibiting metabotropic glutamate receptor-2 (173, 174) would be expected to reproduce or augment ketamine's antidepressant effects. As activation of NMDA and AMPA glutamate receptors mediates a component of ketamine efficacy, drugs that facilitate activation of NMDARs (62, 175–177) or AMPARs (AMPAkines) (178–181) might also augment ketamine efficacy. In addition, drugs that raise BDNF levels, enhance TrkB receptor activation, or directly augment the activation of key steps in Akt/GSK-3/mTOR signaling (182–184) might similarly enhance ketamine's efficacy. As has been suggested for GSK-3 inhibition, this strategy for combination treatment may enable a subdissociative dose of ketamine to achieve full efficacy (184).

Improve Ketamine Safety by Reducing the Dissociative Effects and Abuse Liability. The primary strategy employed to date to develop a nondissociative NMDAR antagonist antidepressant has been to simply test subdissociative doses. To date, this strategy has not yielded a treatment with superior efficacy to ketamine. One might argue that the combination of buproprion and dextromethorphan is an effective antidepressant (185), but this medication has yet to show a ketamine-like clinical profile of rapid benefits and efficacy for treatment-resistant symptoms.

To date, tests of pharmacologic combination strategies to attenuate ketamine-induced dissociation have not yet yielded viable treatment approaches. Lamotrigine (186), lorazepam (187), and nimodipine (188) attenuate ketamine-induced dissociative symptoms in humans. Pretreatment with an mGluR2 agonist (189) also attenuated ketamine-related working memory impairment in healthy subjects. However, lamotrigine, lorazepam, and mGluR2 agonism reduce ketamine increases in cortical excitability (190–193) and thereby may interfere with ketamine efficacy. While nimodipine also reduces cortical excitability (194) and protects against NMDAR antagonist toxicity (195), it has yet to be tested in combination with ketamine during depression treatment. Clozapine (196), but not haloperidol (197, 198), attenuates ketamine-induced psychosis in people with schizophrenia or healthy subjects. Glycine transporter-1 (GlyT1) antagonists also reduced ketamine-induced psychosis in one study (199), but this finding was not replicated with another GlyT1 inhibitor (200).

Ketamine misuse may be the greatest risk associated with ketamine treatment. This risk is well-managed when ketamine or Esketamine are administered solely within clinics and patients do not have ketamine access at home. However, growing anecdotal reports of misuse of ketamine prescribed for home use are a concern (201, 202). We (J.H.K. and G.S.) have seen cases of individuals prescribed "take home" ketamine who subsequently developed compulsive ketamine use. Many NMDAR antagonists have abuse liability including ketamine (203), nitrous oxide (204, 205), dextromethorphan (206), phencyclidine (207), and ethanol (208). R-ketamine, the ketamine enantiomer of ketamine with reduced potency at NMDA and opioid receptors, also appears to have reduced abuse liability than S-ketamine in animals (209). Pharmacologic strategies for reducing the abuse liability of ketamine while preserving efficacy have yet to bear fruit. The euphoric effects of ketamine are not attenuated by pretreatment with the dopamine D_2 receptor antagonist, haloperidol (198), or the opioid receptor antagonist, naltrexone (210). While we could not replicate the blockade of antidepressant effects of ketamine by naltrexone (211, 212), ketamine's indirect facilitation of endogenous opioid signaling may contribute to its antidepressant effects (213). In contrast, in recovering ethanol-dependent patients, nimodipine reduced ketamine-induced euphoria (188). Thus, combining ketamine with a blockade of voltage-dependent calcium channels may reduce both dissociation risks and abuse liability.

Conclusions

Ketamine and Esketamine, with brexanolone, MDMA, and the psychedelics, have ushered in a first generation of rapid-acting antidepressants. Ketamine targets aspects of the neurobiology of depression that had not been linked so directly to prior treatments and it has led to the characterization of novel forms of antidepressant-related neuroplasticity. Twenty-five years have passed since we (J.H.K.) first presented the ketamine findings in depression. Thus, it is timely to work toward a next era of rapidly acting antidepressants that complement or even supersede ketamine and Esketamine in safety and efficacy. This review highlighted both general and specific strategies that might be pursued:

- Protecting the integrity of regrown synapses through exercise, psychotherapy, and medications, like mTORC1 inhibitors, that promote repolarization of microglia, shifting them from proinflammatory to neurotrophic functional states.
- Enhancing ketamine's ability to engage synaptic plasticity through avoiding HCN1 antagonism and optimizing NMDAR subtype selectivity.
- Targeting the downstream signaling mechanisms induced by ketamine as alternative monotherapies, combination treatments that augment ketamine efficacy, or that yield a nondissociative rapid-acting antidepressant, i.e., combination of a subdissociative dose of ketamine with another agent that augments its efficacy.
- Development of combination treatments or new chemical entities that preserve efficacy but reduce the dissociative symptoms and abuse liability of ketamine.

These strategies also have implications for the optimization of psychedelic treatments for depression. Psychedelics increase glutamate release and activate mTOR (214), but they do not block NMDARs. It is not clear whether this difference contributes to the long-lasting antidepressant effects of psychedelics (151). However, psychedelics may not block maladaptive homeostatic plasticity as they do not block NMDARs, raising the possibility that ketamine and psychedelics have differing profiles of clinical efficacy. Nevertheless, the convergent effects of ketamine and psychedelics upon many downstream signaling mechanisms (147, 149, 215) may suggest that strategies outlined above for augmenting ketamine efficacy and safety might apply to psychedelics. In turn, efforts to create "nonhallucinogenic" psychedelics via biased 5-HT_{2A} receptor agonism, partial 5-HT_{2A} receptor agonism, combinations of 5-HT_{2A} receptor agonists and antagonists, and other strategies (216–222) may suggest strategies for improving upon ketamine.

This is an opportune moment to press forward toward safer and more effective treatments for depression. Prior to the approval of Esketamine, psychiatry seemed to be backing away from its most effective treatments, perhaps as an expression of therapeutic nihilism. For example, the number of sites delivering electroconvulsive therapy has declined (223). Yet, the need is high. Depression is a leading contributor to the global burden of disease (224), in part due to ineffectively treated depression. The STAR*D study suggested that approximately one-third of patients do not achieve remission over 1 y despite multiple treatment attempts (225). An earlier study suggested that if patients do not attain clinical response over 1 y, only 20% of these patients will respond over the subsequent 4 y (226).

Psychiatry is increasingly interventional in addressing the treatment-resistant symptoms of depression, highlighted by the recent revisiting of deep brain stimulation as a depression treatment (28). As psychotherapists, psychiatrists engage in one of the most intense, invasive, and prolonged interventions in all of medicine. Ketamine, Esketamine, brexanolone, psychedelics, and MDMA are all intensive psychopharmacologic interventions that powerfully modulate consciousness, carry medical risks, but also offer paths to address the nihilism arising from the limited efficacy of standard treatment options. This is a very hopeful moment for psychiatric psychopharmacology and one that may profoundly impact the global burden of depression.

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