Ketamine for Depression: An Update

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A decade has now passed since research into the antidepressant effects of ketamine began in earnest, after the clinical trial reported by Zarate *et al.* in 2006 (1). In that proof-of-concept study, 18 medication-free patients with treatment-resistant major depressive disorder (TRD) showed a large reduction in core depressive symptoms within hours of receiving a single low-dose 0.5 mg/kg intravenous infusion of ketamine as measured by the 21-item Hamilton Depression Rating Scale compared with saline placebo. Perhaps most strikingly, the antidepressant effects persisted without additional dosing of ketamine for days or up to several weeks in some cases. While these unexpected findings have been met with justifiable skepticism, replication from independent research programs is now fostering a degree of consensus in the field that ketamine is in fact associated with a true rapid-onset and persistent antidepressant effect, even in patients with TRD (2,3). If the observed effect is true, what are the implications and what are the critical research questions to now be asked?

The current issue of *Biological Psychiatry* contains three articles on the topic of ketamine and depression that show both the progress that has been made in this area and the notable limitations in our current understanding. Two preclinical reports—one from Sarkar and Kabbaj (4) and one from Ren *et al.* (5)—examine sexual dimorphism and the role of gamma-aminobutyric acid (GABA) signaling in the antidepressant response to ketamine, respectively. The third article by Singh *et al.* reports on a phase II clinical trial of S-ketamine (also referred to as "esketamine") in patients with TRD (6). I will consider each report briefly below.

Women on average are reported to experience higher rates of major depression compared to men, although the biological underpinnings accounting for this discrepancy remain poorly understood. Contributing to this lack of knowledge is the exclusive use of male rodents in many preclinical studies of depression and antidepressant response. Making progress in this area, Sarkar and Kabbaj investigated sex differences in behavioral and synaptic responses to ketamine in a chronic social isolation stress paradigm in male and female Sprague Dawley rats (4). The authors found that male rats were more sensitive to the prodepressant effects of social isolation than female rats, perhaps contrary to expectations based on the higher incidence of depression in women. Ketamine reversed increases in immobility time in both male and female rats in the forced swim test after social isolation, but the two sexes diverged on their synaptic response to ketamine: only male rats showed the predicted increase in synaptic proteins within the medial prefrontal cortex (mPFC), including synapsin-1, postsynaptic density protein 95, and the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) subunit glutamate receptor 1. Therefore, while ketamine exerted the predicted antidepressant-like behavioral response in female

rats, this effect appeared to be independent of enhanced availability of synaptic proteins within the PFC. Although this result may seem surprising, the effect of ketamine on cortical protein levels in preclinical models is in fact rather variable (7–9). For example, while Li *et al.* found that the antidepressant-like effect of ketamine in male rats was associated with enhanced synaptic protein levels within the mPFC that was dependent on the activation of mammalian target of rapamycin (mTOR) signaling pathways (7), Autry *et al.* did not find evidence of mTOR regulation by ketamine within the cortex of male mice (8). A separate recent study found that ketamine triggered a stronger antidepressant-like effect in female compared with male mice, which was associated with a higher level of the ketamine metabolite (2S,6S;2R,6R)-hydroxynorketamine; regulation of cortical or hippocampal mTOR was not observed in this study in either male or female mice (10). It should be noted that the dose ranges of ketamine tested in these studies differed from one another, making comparisons between studies more difficult. In a recent example of open science, four pharmaceutical research laboratories pooled previously unpublished data showing no consistent effect of ketamine on phosphorylated mTOR or synaptic protein levels in male Sprague Dawley rats (9). The data summarized here underscore the complexity of these experimental procedures and the caution required in interpreting the yielded results.

Ren *et al.* (5) investigated the role of the GABA system in the antidepressant action ketamine using GABA$_A$ receptor γ2 subunit heterozygous mice (only female mice were used in the behavioral experiments). Previous studies characterizing in vivo brain GABA levels using proton magnetic resonance spectroscopy suggest reduced GABA levels in male and female adults with major depression, which may be particularly pronounced in patients with TRD. Consistent with these human data, the GABA-deficient γ2 subunit heterozygous mice showed a prodepressive phenotype. Interestingly, these mice also showed a reduction in the availability of both N-methyl-D-aspartate receptors (NMDARs) and AMPARs and displayed reduced functioning of glutamatergic synapses within the mPFC and hippocampus. Remarkably, treatment with ketamine rapidly normalized glutamate receptor levels and synaptic functioning in these mice, and partially normalized the GABAergic deficits. From the literature, we likewise know that chronic stress is linked both to reduced GABAergic signaling and to downregulation of NMDARs and AMPARs, and that potentiation of AMPAR signaling is a likely required step for ketamine's antidepressant mechanism of action (7,8,10). Taking a broader view, it seems likely that perturbation in the balance between excitatory and inhibitory signaling within key neural circuits that control motivated behavior and emotion regulation represents a common pathway to mood disorders, including major depression. The myriad routes to

these critical perturbations—via interactions between genetic, developmental, and environmental factors—leave a large search space for continued research.

Turning to the clinical trial reported by Singh *et al.* ([6](#)), this is the first report on the tolerability, safety, and efficacy of esketamine—the *S*-enantiomer of ketamine, which typically exists as a racemic mixture of *R,S*-ketamine. While previous clinical trials by academic groups have exclusively tested the racimate in mood disorder populations, the current report by Singh *et al.* from Janssen Research and Development represents an important step in the first large-scale drug development effort to bring ketamine to market for the treatment of major depression or TRD. The *S*-enantiomer—available as an anesthetic agent in the European Union—is reported to exhibit approximately threefold higher affinity for the NMDAR compared to the *R*-enantiomer. In this study, 30 patients with treatment-resistant unipolar depression were randomized in a 1:1:1 fashion to receive an intravenous infusion of 0.20 mg/kg or 0.40 mg/kg esketamine or saline placebo over 40 minutes. Change in depression severity measured using the Montgomery–Åsberg Depression Rating Scale 24 hours posttreatment represented the primary outcome. Beyond the primary endpoint, patients could receive a total of up to six treatment infusions (two under double-blind conditions and four more open-label). The authors report generally favorable tolerability of both drug doses, with 29 of 30 randomized patients completing the trial. Both esketamine doses were associated with transient dissociation, and 2 of 11 patients (~18%) randomized to the 0.40 mg/kg dose experienced a high level of dissociation during or immediately after the infusion that was classified as severe. Both doses of esketamine were associated with a large reduction in Montgomery–Åsberg Depression Rating score at 1 day posttreatment compared to placebo; response rates for the low and high dose were 67% and 64%, respectively—in line with response rates reported in trials of racemic ketamine in TRD ([1](#),[2](#)). As discussed previously elsewhere, the use of an inert placebo in ketamine studies is likely problematic because patients and investigators may be aware of the treatment assignment owing to the predictable dissociative effects of ketamine. In this regard, it may be worth noting that in both the current report and in the original Zarate *et al.* report the response rate under the (saline) placebo condition was zero. In contrast, a study comparing ketamine to the anesthetic benzodiazepine agent midazolam as a control condition in patients with TRD reported response rates of 64% and 28%, respectively ([2](#)). These data suggest that some proportion of the difference between efficacy under drug and control conditions is related to expectancy and other nonspecific factors in any given ketamine study. Measurement of this nonspecific component of the effect and identifying factors to mitigate it represents a major clinical science challenge for ketamine research moving forward.

The studies reviewed herein are a testament to the progress being made in the area of ketamine effects in mood disorders. Pitfalls and future obstacles to overcome are also evident. Beyond ketamine, the drive to discover and develop "ketamine-like" compounds as a new generation of antidepressant therapies is a particularly exciting result of the original ketamine work. For illustrative purposes, example

Table 1. Ketamine-Inspired Drugs Currently in Human Testing for Depressive Disorders

Target	Compound	Clinical Trial Phase	Sponsor
NMDAR (nonselective)	AXS-05	III	Axsome Therapeutics (New York, NY)
NMDAR (nonselective)	AVP-786	II	Avanir (Aliso Viejo, CA)/ Otsuka (Rockville, MD)
NMDAR (nonselective)	Esketamine	III	Janssen (Titusville, NJ)
NR2B Subunit	CERC-301	II	Cerecor (Baltimore, MD)
NR2B Subunit	GLYX-13; NRX-1074	II	Allergan (Coolock, Dublin, Ireland)
NR2B Subunit	AV-101	II	VistaGen (San Francisco, CA)

NMDAR, *N*-methyl-D-aspartate receptor; NR2B, *N*-methyl D-aspartate receptor subtype 2B.

glutamatergic compounds currently in human phase testing are listed in Table 1. A realistic optimism is warranted as we look toward the future of depression research and therapeutic development.

Article Information

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