Ketamine for depression: evidence, challenges and promise

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Major depressive disorder and bipolar depression are among the most prevalent and disabling mental disorders worldwide. Real-world effectiveness trials in major depressive disorder have underscored that most pharmacological options target monoamines, which are involved in a minority (15-20%) of synaptic contacts in the mammalian brain.

Most synapses (~50%) use the amino acid glutamate as their primary neurotransmitter, and preclinical models of depression have implicated aberrant glutamatergic neurotransmission for 25 years (1). More recently, the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine was shown to produce rapid and robust antidepressant effects in patients with treatment-resistant major depressive disorder and bipolar depression (2-7).

EVIDENCE

Ketamine is a non-competitive NMDA receptor antagonist that works as an open channel pore blocker at the phencyclidine binding site, thereby preventing the flux of cations (primarily calcium) and neuronal excitation/depolarization.

Several randomized, placebo-controlled trials of sub-anesthetic dose ketamine infusions (0.5 mg/kg for 40 min) have been conducted in individuals with major depressive disorder, including those with treatment-resistant depression (2-4). Sub-anesthetic dose ketamine also has similar antidepressant efficacy in treatment-resistant bipolar depression subjects maintained on mood stabilizers (5), and has not demonstrated increased affective switching to hypo/mania over placebo (8).

Ketamine has also been shown to rapidly reduce suicidal thinking (6,7). Because few evidence-based treatments for suicidality exist – none of which have rapid onset – ketamine may be a promising rapid-acting antidepressant treatment option in emergency and acute inpatient psychiatry.

Finally, repeated sub-anesthetic dose ketamine infusions have demonstrated preliminary efficacy and safety/tolerability in brief trials (9).

All the aforementioned placebo-controlled trials have used racemic ketamine mixtures. The S-enantiomer (S-ketamine/esketamine) has three- to four-fold greater affinity for the NMDA receptor, which may permit lower dosing to preserve antidepressant efficacy while limiting undesirable side effects.

Non-intravenous modes of ketamine administration have also been studied (intramuscular, subcutaneous, oral, sublingual and intranasal), with mixed efficacy but typically fewer side effects than intravenous infusion.

Specific ketamine metabolites have also been shown to correlate with antidepressant response (10); some have affinity for non-NMDA receptors (e.g., antagonism of alpha 7 nicotinic acetylcholine receptors) (11), which may also contribute to their antidepressant mechanism of action.

In that regard, ketamine's antidepressant mechanism has been an active topic of preclinical and clinical investigation. Ketamine-induced NMDA receptor antagonism of inhibitory gamma-aminobutyric acid (GABA)ergic cortical interneurons has been shown to release tonic inhibition of excitatory (glutamatergic) pyramidal neurons to increase synaptic glutamate release (acute "glutamate surge") (12). Because postsynaptic NMDA receptors are blocked, synaptic glutamate can then preferentially bind to and activate alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (13). Postsynaptic membrane depolarization then initiates intracellular second messenger/signal transduction cascades, resulting in some or all of the following: mammalian target of rapamycin (mTOR) activation (14), increased brain-derived neurotrophic factor (BDNF) translation and secretion (15), and glycogen synthase kinase-3 (GSK-3) inhibition (16). These acute molecular and cellular responses to ketamine stimulate synaptic plasticity.

Clinical neurobiological studies have focused on more amenable units of analysis, namely genetics, peripheral measures, and neuroimaging (including sleep electroencephalography). Some of them may be critical mediators of antidepressant response to ketamine, including BDNF genotype, circulating BDNF levels, acute changes in central glutamate levels, synaptic potentiation, and circuit-level de/synchronization (17).

CHALLENGES

Although a handful of psychiatrists and anesthesiologists are currently administering ketamine in office-based outpatient settings, significant challenges exist for ketamine's potential broader dissemination in treating major depression. First, ketamine is not approved by the U.S. Food and Drug Administration (FDA) for any depressive disorder; this lack of indication may hamper dissemination, with concomitant public health implications.

Yet, for ketamine to be more widely disseminated clinically, standardization of best practices must be put in place for optimal mode of administration, dosing and frequency. Several studies are currently investigating alternative modes

of administration (e.g., intranasal esketamine), but none are comparing different modes head-to-head.

For optimal dosing, with the exception of a small (N=4), placebo-controlled, crossover study (18), all randomized controlled trials in both treatment-resistant major depressive disorder and bipolar depression have used the same dose (0.5 mg/kg). However, ketamine's antidepressant dose-response is currently being investigated in a multi-site, psychoactive placebo-controlled, parallel-design trial with midazolam 0.045, ketamine 0.1, ketamine 0.2, ketamine 0.5, and ketamine 1.0 mg/kg infusions.

It should also be noted that, because antidepressant response to ketamine is typically short-lived, evidence-based strategies to maintain response/prevent relapse are critical for clinical practice. The most logical and potentially efficacious strategy is repeated dosing ("boosters"), similar to maintenance therapy in electroconvulsive therapy (ECT). However, few published studies exist of repeated ketamine infusions in active major depressive disorder (9,19,20), and these have typically only offered <10 infusions over 12-21 days. Notably, the risk for abuse and potential long-term side effects – for instance, cognitive sequelae, urinary cystitis – may increase manifold with repeated dosing. These risks necessitate close clinical follow-up and/or appropriate consultation.

Oral glutamatergic modulators are also reasonable strategies to prevent relapse. In a four-week, randomized, placebo-controlled trial, the oral glutamatergic modulator riluzole did not maintain ketamine's antidepressant effect over placebo, but the effect size was large (d=0.78), suggesting that the study might have been underpowered (21). D-cycloserine, a partial agonist at the NMDA receptor glycine site, demonstrated preliminary efficacy for treatment-refractory bipolar depression in a small (N=7), open-label, eight-week study in which a daily escalating dose of the drug followed the administration of sub-anesthetic dose ketamine (22). In addition, ketamine co-administration with standard oral antidepressants/mood stabilizers has shown preliminary efficacy in preclinical studies (23,24), but has not yet been investigated in controlled studies in humans.

In initial trials, ketamine had a large-to-very-large antidepressant effect, with maximal efficacy within 24 hours and relapse often within one week. Nevertheless, ketamine's antidepressant efficacy difference was exaggerated by minimal response to the inert placebo (intravenous saline).

In the largest randomized controlled trial to date with a psychoactive placebo (intravenous midazolam), ketamine still separated at 24 hours post-infusion. Ketamine's drug difference, however, was not as great, due to the more typical placebo response for a major depressive disorder trial (4). Although a better placebo than saline, midazolam also has its flaws – for instance, minimal acute dissociative side effects – that may compromise the integrity of the blind in savvy patients. Future research challenges include developing a better control condition than midazolam and formally assessing randomization expectancies.

Another potential hurdle is the identification and replication of enriched subgroups with augmented antidepressant response to ketamine. Our group has identified several non-overlapping clinical predictors of ketamine's antidepressant efficacy, including increased body mass index, family history of alcohol use disorder in a first-degree relative, and dimensional anxious depression (25).

In addition to these clinical descriptive parameters, several genetic, central neurobiological, and peripheral measures have also been shown to correlate with ketamine's antidepressant efficacy (26,27). Nevertheless, few studies have combined measures/datasets in order to increase predictive power and detect smaller effects. Due to the heterogeneity of major depressive disorder, this combinatorial approach may best be undertaken by forming a multi-site ketamine depression consortium to maximize the sample size of enriched subgroups for prospective mechanistic studies.

Another issue of concern is that a sensitive and specific human biomarker of glutamate function – for instance, an NMDA receptor subunit positron emission tomography (PET) ligand – has yet to be developed. In an *in vitro* model system, intracellular second messenger/signal transduction mediators and effectors hypothesized to be critical to ketamine's antidepressant efficacy (e.g., mTOR phosphorylation and inhibition of eukaryotic elongation factor-2 kinase (eEF2)) may also reflect glutamate receptor engagement. Again, such systems would not only improve our understanding of ketamine's antidepressant mechanisms, but would also prove very useful for glutamate-based drug screening.

Although several depression-like induction paradigms have been developed in healthy volunteers – for instance, acute monoamine reduction (reserpine, dietary tryptophan depletion) and "sickness syndrome"-like induction (lipopolysaccharide) – these models have yet to be tested and/or reported as ketamine-responsive.

Ketamine also enhances resiliency to stress in rodent models of despair (28,29) and may have analogous effects in humans. This may facilitate the rapid screening of candidate glutamate-based drugs in healthy volunteers, thereby reducing resource allocation to drugs likely to fail early in the clinical pipeline.

In summary, a sensitive and specific ketamine-responsive model system remains a substantial challenge for future research.

PROMISE

The discovery of ketamine's rapid and robust antidepressant efficacy has provided hope for patients with treatment-resistant depression and depression researchers alike. This promise is two-fold: a) the identification of novel glutamate-based mechanisms of disease and treatment response in depressive disorders; and b) the availability of a first-in-class, rapid-acting antidepressant medication. Ketamine's preliminary efficacy for suicidality, where swift onset and significant

response are absolutely vital, also provides promise as a prototypical anti-suicidal treatment.

Finally, in addition to adult treatment-resistant major depressive disorder and bipolar depression, ketamine has also demonstrated preliminary efficacy and/or is currently being studied in other disorders, which may ultimately extend its utility in clinical practice. These include pediatric/adolescent depression and behavioral dysregulation, autism, obsessive-compulsive disorder, post-traumatic stress disorder, and depression comorbid with alcohol dependence.

Acknowledgements

Funding for this work was provided by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health, a NARSAD Independent Investigator grant, and a Brain & Behavior Mood Disorders Research Award to C.A. Zarate. The authors thank the 7SE research unit and staff for their support. I. Henter provided excellent editorial assistance.

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DOI 10.1002/wps.20269