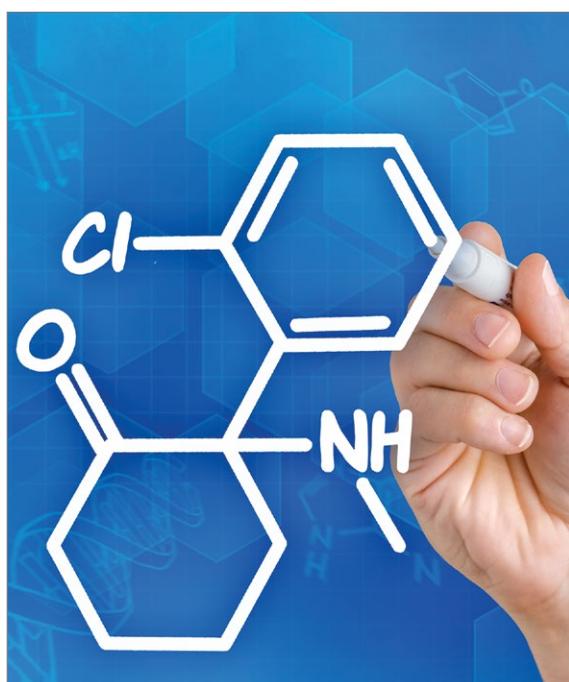


Ketamine/esketamine: Putative mechanisms of action



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Details of how these agents produce rapid antidepressant effects have been misrepresented

Since the FDA approved intranasal esketamine, there has understandably been significant dialogue, debate, and discussion about the possible mechanisms of action of its antidepressant effects. Ketamine, the racemate of esketamine and arketamine, has been used off-label since the late 1990s. The first study of IV ketamine’s rapid antidepressant activity was published in 2000.¹ In that study, 7 patients with major depressive disorder (MDD) were treated in a double-blind/placebo-controlled manner with IV ketamine or placebo. Researchers found a significant antidepressant effect within 72 hours with the administration of IV ketamine.

There is a tremendous number of publications related to ketamine, which creates a large reservoir of information to review in an attempt to piece together what we currently know about the mechanisms of action of ketamine/esketamine (K/ESK). A search of PubMed using the search word “ketamine” (October 8, 2019; www.ncbi.nlm.nih.gov/pubmed) produced a list of 4,869 articles just in the last 5 years; and the search words “ketamine and depression” produced a list of 1,221 publications over the same time period.

The FDA approval of intranasal esketamine in March 2019 was based on 5 phase III clinical studies (albeit not all were positive studies) and >9 years of intensive pre-clinical and clinical research on the efficacy and safety of intranasal esketamine in treatment-resistant depression (TRD). At the time the FDA approved it, esketamine had been studied in 1,700 patients with TRD, with 1-year safety data on approximately 800 patients. Despite this

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established data portfolio, critics of K/ESK continue to opine that we do not have enough long-term experience with these drugs, and some key opinion leaders continue to voice caution about the clinical use of K/ESK until we obtain more information and experience.

An article in the September 2019 issue *CURRENT PSYCHIATRY* by Epstein and Farrell² exemplifies my concern regarding the misrepresentation of significant details about what we know about the mechanism of action of K/ESK. Both K/ESK are certainly not “miracle cures,” and although I understand the use of this term in the article’s title, the continued use of this term to describe K/ESK in the article is detrimental. The authors caution about “miracle cures” ultimately proving to be harmful, and suggest that K/ESK could end up in the trash heap with Freud’s 1884 positive description of cocaine for depression and inducing insulin comas to treat patients with schizophrenia, a treatment used until 1960. These rogue treatments were used in the infancy of psychiatry, at a time when there was a paucity of treatments available in psychiatry, and only a primitive understanding of the brain.

Of greater concern to me is the authors’ simplistic and flawed description of the mechanism of action of ketamine. They state “based on available research, ketamine’s long-lasting effects seem to come from 2 mechanisms... activation of endogenous opioid receptors... [and] blockade of *N*-methyl-D-aspartate receptors.” In the spirit of scientific inquiry, I would like to explore the current evidence base of the putative mechanisms of action of K/ESK.

Ketamine: A plethora of studies

An impressive body of literature is attempting to piece together the complex and multidimensional neurophysiological mechanisms that result in ketamine’s rapid-acting antidepressant (RAAD) effect, which occurs as soon as 4 hours post-dose. A plethora of pre-clinical and clinical studies, including functional connectivity MRI scans in individuals with MDD, have provided a rough outline, albeit incomplete, of

ketamine’s mechanisms of action. Ketamine was discovered in 1962 by chemist Calvin L. Stevens, who was experimenting with novel molecular structures to find a replacement for phencyclidine as a safer dissociative anesthetic. After successful experiments in human prisoners in 1964, ketamine was further studied and became FDA-approved in 1970 as a dissociative anesthetic. Lacking respiratory depression and hypotension, which were common adverse effects of other anesthetics, ketamine became commonly used on the battlefield in the Vietnam War, and continues to be used as a dissociative anesthetic.

Following the publication of the Berman article¹ in 2000 that demonstrated apparent RAAD activity of IV ketamine, interest in ketamine’s use for TRD—a huge unmet need in psychiatry—skyrocketed. Since the FDA approval of iproniazid (a monoamine oxidase inhibitor) as the first medication approved to treat major depression in 1958, and the FDA approval of imipramine in 1959, all subsequent FDA-approved antidepressants have shared iproniazid/imipramine’s properties of modulating the monoamines serotonin, dopamine, and norepinephrine. The infamous Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial concluded that only 37% of patients with a major depressive episode achieve remission with their first antidepressant trial, and only 49% respond (50% improvement in symptoms).³ Ketamine/esketamine offered a novel mechanism of action, presumed to be related to the glutamate system, that demonstrated a clinical improvement in depressive symptoms in as few as 4 hours, with benefits that lasted up to 1 week after a single dose.

A model of how ketamine works

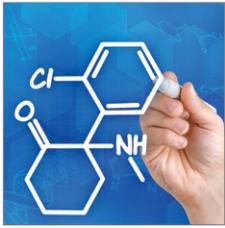
Numerous publications from preclinical and clinical research collectively have woven a putative model of how K/ESK may rapidly improve depression by ultimately increasing synaptogenesis in the human prefrontal cortex—a part of the brain known to atrophy in states of chronic stress and depression.⁴ What is well established is the noncompetitive antagonism of K/ESK

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**Ketamine/
esketamine may
rapidly improve
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How ketamine works

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Evidence that opioid receptors are necessary for ketamine's antidepressant effect comes from a single study

at the *N*-methyl-D-aspartate (NMDA) glutamate receptor, but this pharmacodynamic property may or may not be responsible, or even required, for the ultimate antidepressant effect 4 hours after administration. It has been shown that unlike anesthetic doses of K/ESK that inhibit glutamate, sub-anesthetic doses activate neuronal glutamate transmission in the prefrontal cortex.⁵

A significant body of evidence supports agonism of the glutamate alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor as an important step in the cascade of events that ultimately increases levels of the mammalian target of rapamycin (mTOR), which unleashes protein synthesis in synapses facilitating synaptogenesis. Pretreatment with AMPA receptor antagonists blocks the downstream effect of synaptogenesis.^{6,7} In support of this putative mechanism, hydroxynorketamine, a metabolite of racemic ketamine that has also demonstrated RAAD activity in a ketamine-like manner, is dependent upon AMPA glutamate receptor upregulation and activation, while not requiring activity at the NMDA-glutamate receptor.^{8,9}

A comprehensive model on the putative molecular cascade of events contributing to the antidepressant effect of ketamine has recently been published¹⁰ and mirrors the excellent previous review by Abdallah et al.¹¹ Hirota and Lambert¹⁰ propose that antagonism of interneuronal NMDA-glutamate receptors on GABAergic interneurons may result in a prefrontal cortex surge of glutamate, which increases agonism of the AMPA-glutamate receptor. This AMPA-glutamate receptor agonism has been shown to increase expression of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF),¹² both of which converge on increasing levels of mTOR, and the subsequent activation of mTOR, which putatively plays a role in increased production of scaffolding proteins and increased synaptogenesis, especially in the prefrontal cortex. In support of this model, during infusion and at 24 hours after a single ketamine infusion in individuals with MDD, functional connectivity MRI demonstrated an increase in global brain connectivity in the prefrontal cortex.^{13,14}

The demonstration of increased global connectivity in the prefrontal cortex of patients with MDD, both during ketamine infusion and at 24 hours post-infusion, supports the clinical observations in clinics treating patients with K/ESK.

Opioid receptors and ketamine

During the past year, there has been significant discussion in psychiatry about the possible role of the mu opioid receptor and opioid system activation in ketamine's RAAD effect. Remarkably, the literature supporting this hypothesis in humans is based on a single study by Williams et al.¹⁵ The authors' claim: "We now present the first evidence in humans that opioid receptors are necessary for ketamine's acute antidepressant effect." In fact, in my opinion, this single study, which has not been replicated, is highly flawed. It included 30 adults with TRD, but only 12 of the 14 participants who qualified for the planned interim analysis completed the double-blind crossover. The population studied was quite treatment-refractory; the average duration of MDD was 24.1 years, the average age at onset was 17.3 years, and the duration of the current depressive episode at the time of the study was 8.6 years. Most significant to me was the reason the study was terminated: "At the interim analysis, given the finding that the combination of ketamine and naltrexone was not only ineffective but also noxious for many participants, we decided to stop enrolling patients in the study." A distinct possibility is that the noxious adverse effects from the naltrexone impacted the participants' experience in a negative manner, dampening down any antidepressant effect from ketamine.

In the August 2019 issue of *Molecular Psychiatry*, these same authors published a second article¹⁶ with conclusions based solely on "a secondary analysis of" the data from the same 12 participants in their first publication. Williams et al¹⁶ concluded that naltrexone also decreases the anti-suicidal effects of ketamine. Without any additional data or clinical research, these same authors extrapolated their hypothesized opioid receptor activity of ketamine to

include it being responsible for ketamine's established anti-suicidal effects.

Mathew and Rivas-Grajales¹⁷ recently published a thoughtful critique and analysis of the study design and conclusions of the original Williams paper.¹⁵ They concluded that insufficient evidence exists to answer the question of how ketamine may interface with the opioid system, and they encourage further research into this important topic.

Two additional recent publications^{18,19} reported that naltrexone pretreatment did not attenuate the antidepressant effects of ketamine in their participants. Additionally, a recent publication in the anesthesiology literature²⁰ concluded that esketamine reversed respiratory depression that was induced by remifentanyl. From a clinical perspective, the most compelling argument against a direct mu opioid receptor mechanism for K/ESK is the lack of any craving, tolerance, or withdrawal in patients with TRD treated with K/ESK in numerous clinical publications comparing K/ESK with placebo. In the case of esketamine, during the 5 phase III clinical trials—including both short- and long-term studies—there was no signal for an opioid-like pharmacology. Significantly, both K/ESK are rapidly metabolized by the human body, and the typical dosing is 2 doses/week for the first month, then 1 dose/week for the next month, then 1 dose every week or less for the remainder of treatment.

Curiously, in the May 2019 issue of the *American Journal of Psychiatry*, Schatzberg²¹ (one of the co-authors of the prior 2 studies opining that ketamine has direct opioid system activation) wrote a "Reviews and Overviews" article in which he misrepresents the conclusions of an elegant study by Abdallah et al²² published in December 2018.

Abdallah et al²² added rapamycin, an immunosuppressant and a known inhibitor of mTOR, as a pretreatment to patients in a major depressive episode prior to infusion with IV ketamine. Their hypothesis was to see if the rapamycin decreased ketamine's rapid antidepressant response—putatively by inhibiting the effect of mTOR. Rather than decreasing ketamine's antidepressant effect, and in contrast to the placebo

pretreatment group, at 2 weeks post IV ketamine infusion, patients treated with rapamycin-ketamine had a longer duration/greater improvement in their depressive symptoms compared with the patients receiving placebo-ketamine (improvement of 41% vs 13%, respectively, $P = .04$). Abdallah et al²² hypothesized that the pretreatment with rapamycin provides anti-inflammatory benefits to the synaptogenesis resulting from ketamine, which protects the newly formed synapses and prolongs ketamine's antidepressant effect. Schatzberg²¹ came to a different conclusion than Abdallah et al,²² opining that because the rapamycin "failed to decrease ketamine response," this result debunks the role of mTOR as a mediator in the antidepressant effect of ketamine through synaptogenesis.

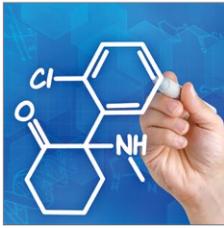
Much more to learn

We still have a great deal to learn about the mechanism of action of K/ESK. However, clinics that are augmenting antidepressants with K/ESK in patients with TRD report significant and rapid symptom improvement in some patients (personal communications). We still do not understand the actual mechanisms of action of antidepressants and antipsychotics, but this does not curtail their use and clinical benefits to our patients. Ketamine has been extensively studied. In the current appropriate climate of concern about the pervasive and lethal opioid epidemic in the United States, we must remain on solid scientific ground before attributing an opioid mechanism to a novel treatment that has already benefitted many of our most depressed and refractory patients.

Looking at the extensive published data over the past 20 years, a consistent model has emerged whereby glutamate agonism of the AMPA-glutamate receptor, both with and without antagonism of the NMDA-glutamate receptor, appears to set in motion a molecular cascade involving BDNF and VEGF, and ultimately increasing the activity of mTOR, with resulting synaptogenicity that increases global brain connectivity in the human prefrontal cortex. As we continue to understand the complexities

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Two additional recent publications reported that naltrexone pretreatment did not attenuate the antidepressant effects of ketamine



How ketamine works

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A better understanding of the antidepressant effects of ketamine might lead to novel molecular targets for drug development

Related Resources

- Mattingly GW, Anderson RH. Intranasal esketamine. *Current Psychiatry*. 2019;18(5):31-38.
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Drug Brand Names

Esketamine nasal spray • Spravato	Naltrexone • Vivitrol, ReVia
Imipramine • Tofranil	Rapamycin • Rapamune
Ketamine • Ketalar	Remifentanyl • Ultiva

and additional circuitries that are involved in the RAAD effect of K/ESK, the hope is that novel molecular targets for future drug development will emerge.

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Bottom Line

Extensive published data over the past 20 years has produced a consistent model to explain the putative mechanisms of action for the rapid antidepressant effects of ketamine and esketamine. We must remain on solid scientific ground before attributing an opioid mechanism to a novel treatment that has already benefitted many of our patients with treatment-resistant depression.