

# KETAMINE FOR TREATMENT-RESISTANT DEPRESSION: A NEW ADVOCATE

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## ABSTRACT

Current alternatives for the treatment of major depressive disorder lack efficacy and have a delayed onset of action. Recently, the glutamatergic neurotransmission system has been noted to play an important role in the pathophysiology of this disorder. Ever since the first report of the antidepressant effects of the N-methyl-D-aspartate receptor antagonist, ketamine, research has been redirected to novel therapeutic targets. With this rapidly growing evidence of a fast-acting antidepressant such as ketamine, as well as its efficacy in treatment-resistant cases of depression, off-label use has become popular in certain settings. In this article, the clinical antidepressant properties of ketamine in relation to the glutamate hypothesis of depression are discussed, to highlight the breakthrough of these findings in the development of novel therapeutic strategies and provide a clearer view of its benefits and potential harms. (REV INVES CLIN. 2018;70:65-7)

**Key words:** Ketamine. Treatment-resistant. Depression. N-methyl-D-aspartate.

## INTRODUCTION

Major depressive disorder (MDD) is a leading cause of disability worldwide<sup>1</sup>. The limited efficacy of existing treatments contributes to the burden and public health costs related to depression, with only about 67% of patients achieving clinical remission after 4 steps of combined treatment<sup>2</sup>. Moreover, current antidepressants have a limited mechanism of action involving mostly monoaminergic neurotransmission and have a prolonged delay in onset of action, a major limitation in the clinical setting. In this article, the current evidence regarding ketamine's

preclinical and clinical evidence in the treatment of depression is discussed to provide a clearer view of its benefits and potential harms.

The monoamine hypothesis of depression in which a deficient synaptic concentration of neurotransmitters produced depressive states, seemed to provide a simple and clear understanding of depression pathophysiology, mostly due to the initial mechanisms of early antidepressants<sup>3,4</sup>. However, two important questions remained to be answered: why is there a delayed onset of clinical response, and why are more than one-third of the patients unresponsive? A few theories

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addressing these gaps should be mentioned. In the first place, if not an absolute deficiency of monoamines were to blame for depression; the adaptive responses of certain types of monoamine receptors (specifically 5-HT<sub>1A</sub> autoreceptors) could explain the delayed clinical response<sup>4</sup>. However, more importantly, preclinical and clinical studies have found that chronic stress, as seen in MDD, produces alterations in glutamatergic neurotransmission and intracellular signaling, leading to decreased levels of key neurotrophins such as the brain-derived neurotrophic factor (BDNF) and leading to negative morphological changes observed in MDD patients<sup>3,4</sup>. Thus, it has been noted also that chronic administration of antidepressants increases the expression of BDNF and induces neuroplasticity in areas involved in MDD (such as the hippocampus and the prefrontal cortex)<sup>3,4</sup>. This late effect could explain the delay of onset of typical antidepressants.

Now, how to face the failure to achieve a response in one-third of the patients? Current understanding of the neurobiology of MDD includes relations between the hypothalamic-pituitary-adrenocortical axis, inflammatory modulators, neurotrophic factors, and functional and structural variations of neural regions<sup>5</sup>. Thus, it could be said that MDD originates from a maladaptive response to chronic stress, leading to diminished expression of neurotrophic factors, and the dysregulation of key networks within the brain (some modulated by monoamines). However, recently, there has been a shift of interest from this monoaminergic hypothesis to an earlier imbalance in the excitatory/inhibitory transmission involving glutamate and GABA<sup>6</sup>. The observation of fast-acting antidepressant properties of certain modulators of glutamate neurotransmission has opened a new avenue in MDD therapeutics. Since the publication of the first controlled clinical trial showing a rapid and robust antidepressant response following a single dose of intravenous ketamine at a 0.5 mg/kg dose over 40 min<sup>7</sup>, there has been rapidly growing evidence supporting this claim<sup>8</sup>. Through activation of the mammalian target of rapamycin signaling, inhibition of glycogen synthase kinase-3 beta, along with enhanced expression and release of BDNF in preclinical studies, ketamine seems to exert its antidepressant effects on patients who were previously unresponsive to regular treatments<sup>9</sup>. Furthermore, it has been recently noted that N-methyl-D-aspartate receptor antagonism by ketamine may block

the lateral habenula bursts, releasing its inhibition onto monoaminergic reward centers, suggesting another mechanism for its rapid antidepressant effects<sup>10</sup>.

Unlike current antidepressants that may take several weeks until clinical improvement of depressive symptoms, a single administration of intravenous or intranasal racemic ketamine (usually at 0.5 mg/kg) achieves a greater response within the 1<sup>st</sup> h, peaking at 4 h, and lasting up to 7 days after the administration<sup>8</sup>. Described side effects have also been found to be transitory (disappearing minutes after the administration), and not serious.

These observations offer a new target for research when investigating MDD. Every aspect of depression could now include and address the glutamatergic system when considering the genesis, course, and treatment, including diagnostic and response biomarkers<sup>6</sup>.

When analyzing these findings from a clinical perspective, it is to be noted that the importance of these results does not only lie in the strength of ketamine's antidepressant efficacy in controlled settings, but also may help face daily problems for the treatment of MDD if proven to be safe. In the first place, and only considering treatment-resistant depression a great number of patients may find relief that could not be achieved with any other antidepressant intervention. This response would also be achieved within hours, increasing the likelihood of satisfaction and encouragement among patients and practitioners. Moreover, when facing psychiatric emergencies such as potential suicide, this rapid response could provide the needed solution (Table 1). With the limitations of current antidepressant therapies potentially solved, the personal, social, and economic burden of MDD could be diminished dramatically.

Although these findings may seem more than encouraging, we should aim to answer certain questions before the implementation of therapeutic regimens involving ketamine outside of clinical trials. Some of these issues have been pointed out earlier the efficacy and safety of repeated ketamine treatments (since relapse generally occurs during the 1<sup>st</sup> week after intervention), the diversion of its use and potential increase in ketamine dependence, and the possibility of public discouragement because of unexpected or currently unknown side effects<sup>11</sup>. Although its

Table 1. Ketamine's clinical antidepressant properties and points of concern

Antidepressant properties	Concerns
Efficacious in treatment-resistant MDD	Long-term side effects (such as ulcerative cystitis)*
Rapid onset of action	Misuse potential*
Prolonged response and remission	Increasing off-label use
Rapid reduction of suicidality	Insufficient safety and efficacy data
Useful in MDD and BD	
Transitory mild side effects	

\*Observed when using higher doses at more frequent intervals<sup>12,14</sup>.  
MDD: major depressive disorder; BD: bipolar disorder

misuse (in much larger and frequent doses) may lead to similar consequences seen in other substance use disorders<sup>12</sup>, it has shown to be safe and well tolerated in a controlled medical setting, and at subanesthetic doses needed for its antidepressant effects<sup>13,14</sup>. These aspects seem more relevant now, as off-label administration of ketamine has become more popular in some countries, disregarding some necessary cautions that should be considered.

## CONCLUSION

Without a doubt, ketamine has proven to be a new advocate for mental health research and therapeutics. After over half a century without novel targets for MDD treatment, the observation of ketamine's rapid antidepressant effects in treatment-resistant depression has become a promising field that could represent a breakthrough in the understanding of MDD, and the possibility of reducing some of the major personal and global burden that depression is responsible for. It seems imminent then that a new era of different acting antidepressant strategies is upon us, and it is our responsibility to make a critical analysis of the potential benefits and harm inherent to novel therapeutics.

## CONFLICT OF INTEREST

Rodrigo Pérez-Esparza has served as a speaker for Janssen (Johnson & Johnson).

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