Usage of Ketamine in Treating Resistant Depression: A Promising New Treatment Proven to Restoring Connections in the Brain

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etamine has long been used in the medical world as a dissociative anesthetic, a class of psychedelic drugs. However, since the early 2000’s, ketamine has appeared as a possible treatment for depression; specifically, treatment-resistant depression. Though there is no formal definition of treatment-resistant depression (TRD), the symptoms of TRD mimic the symptoms of major depressive disorder, except with the important distinction that the patient has failed to respond to at least one antidepressant treatment. Diagnosing treatment-resistant depression can be difficult since oftentimes patients are not given the proper treatment initially and therefore have not actually become treatment-resistant. Due to resistance to current treatments, scientists are in the process of developing other ways to address TRD, and ketamine has emerged as one of these potential treatments.

Our understanding of depression evolves each day. There are a few established hypotheses of what causes depression but one of the most agreed upon ideas is that the glutamate system is involved in the pathophysiology of major depressive disorder, and glutamatergic agents are suggested as novel antidepressants based on this hypothesis. We know of two ways in which ketamine is thought to ease symptoms of depression, both culminating in the eventual regeneration of synaptic connections in the brain. Firstly, when ketamine is administered, a chain reaction is induced by a blockade of N-methyl-D-aspartate (NMDA) receptors producing a surge of glutamate, leading to the acute activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA). This activation releases brain-derived neurotrophic factor (BDNF), a protein that ultimately catalyzes the activation of downstream synaptogenic signaling pathways. The other suggested mechanism of ketamine involves restoring the dopamine neuron population in various regions of the brain to relieve symptoms associated with downregulation of dopamine pathways, such as anhedonia and lack of motivation, which are common symptoms of depression. Clinical trials have suggested that by restoring these pathways, there is a self-reported amelioration of overall mood and relief of depression symptoms.

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The rapid symptom relief of these treatments is particularly beneficial in urgent situations and, therefore, expands their application. Esketamine is the current frontrunner in expanded applications due to its combination of safety and efficacy, while intranasal esketamine still remains the safer option due to the lesser dosage required to achieve therapeutic effects and thus the reduced risk of inducing an overdose.

An important factor to note is that women and men may experience ketamine treatment differently. Studies have shown that, though the response rate is similar, women may require a lower dosage than men in order to obtain therapeutic effects; in fact, according to recent research, women need only half the dosage that men require to attain equivalent therapeutic benefits. Furthermore, the side effects experienced differ by gender as well. Men have reported more adverse effects like depersonalization, amnesia, verbal learning deficits, subjective memory loss, and psychotic disorders, while women have reported increased nausea, headaches, and cognitive impairment disorders. These results are expected considering the differences in the ways sexes experience depression as well as other antidepressant treatments and should be taken into consideration when administering treatment.

Both ketamine and esketamine have been proven to be clinically effective, but in terms of widespread application, they are still in the early stages. However, research has proven that these treatments restore connections in the brain and have promising long term benefits, so there will surely be more trials to come. The rapid symptom relief of these treatments is particularly beneficial in urgent situations and, therefore, expands their application. Esketamine is the current frontrunner in expanded applications due to its combination of safety and efficacy, while intravenous ketamine poses too great a risk in terms of potential abuse and dissociative effects despite its greater levels of success in clinical trials. Esketamine requires a lower dosage and produces less severe risks which makes it the more desirable and practical treatment option, at least for the time being. There is a need for novel antidepressants now more than ever, and we are on the verge of a highly effective solution with continued trials involving both ketamine and esketamine.