STANDARD DEVIATIONS: Oh, K.

Greetings,

What's the problem?

Depression affects one in eight persons in the United States and is projected to become the second leading cause of disability in the world.

Meta-analysis of depression therapies indicate that two-thirds of patients fail to respond adequately to initial antidepressant medication.

Traditional antidepressant therapy can require months of dosing before any results are observed.

Why is ketamine the answer?

Ketamine is an anesthetic drug that has been found to rapidly and effectively reduce depression and suicidal ideation in a large number of depression-affected patients.

Ketamine got its start in Belgium in the 1960s as an anesthesia medicine for animals. The FDA approved it for humans in 1970. It was used in treating injured soldiers on the battlefields in the Vietnam War. Ketamine was found to be a good substitute for the side-effect riddled phencyclidine, or PCP. Unlike other anesthetics, ketamine doesn't slow the heart or breathing, so patients don't need to be on a ventilator to receive it. It has been used extensively as an anesthetic in many clinical settings and perhaps you've seen it in use when assisting on bone marrow collection. The anesthetic is given by IV and requires observation for treatment.

The feelings of unreality; visual and sensory distortions, are what led to its popularity as a club drug (K. Special K, Super K, Vitamin K, etc.). It is commonly injected, snorted, smoked, or added to drinks.

The FDA approved form for depression comes as a nasal spray (Spravato) and is dosed at a fraction of the IV amounts for anesthesia. For treatment-resistant depression, patients usually get the nasal spray twice a week for 1 to 4 weeks; then once a week for weeks 5 to 9; and then once every week or 2 after that. The nasal treatment is done in tandem with an oral antidepressant.

Does it work?

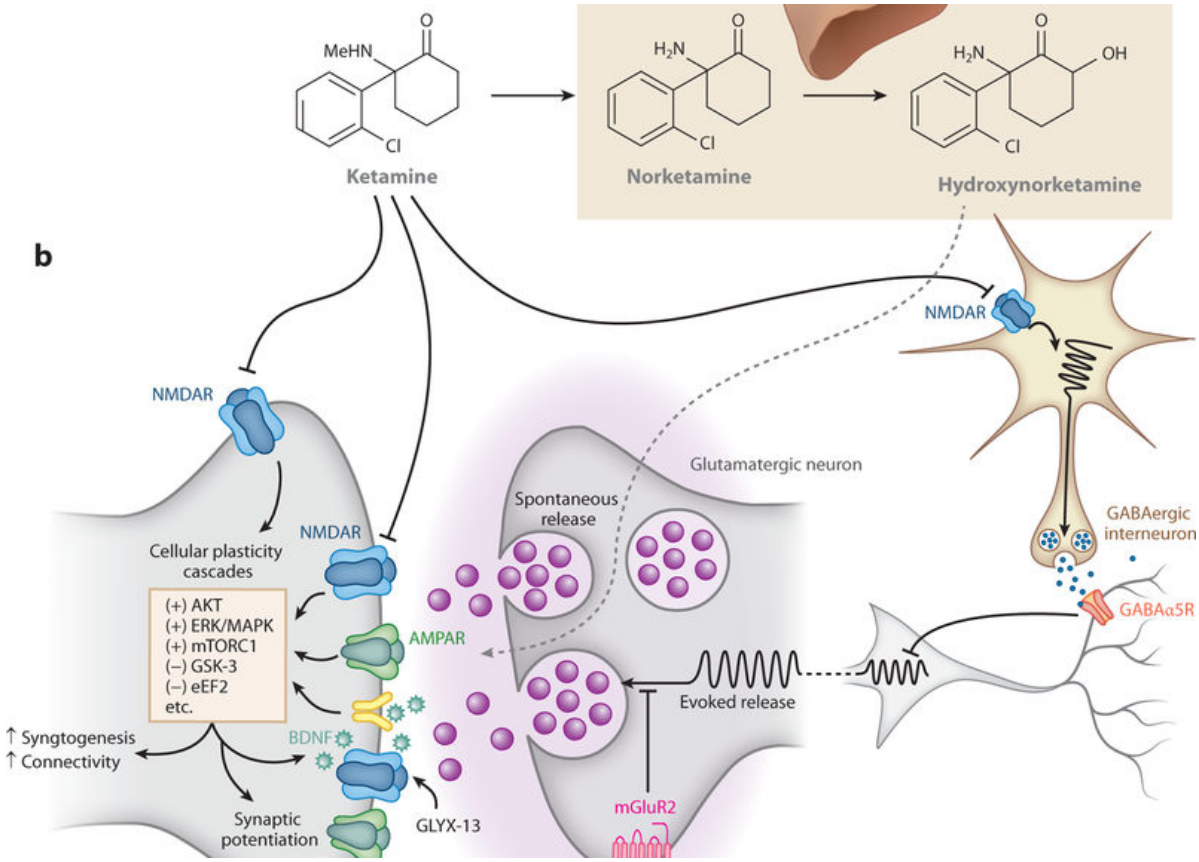
Around 70% of patients treated with ketamine report relief from depression. Treatment responses are almost immediate and tend to last. Trial results are indisputable when compared to placebo.

So, what's going on?

Like much of the science behind these disorders, ketamine seems to influence the neural synapse and the regulation of neurotransmitters to affect behavior and mental status. We're just not sure how.

When the nerves in the brain and spinal cord are constantly bombarded with signals indicating fear, anxiety, depression, or pain, the nerve cell becomes exhausted. Ketamine promotes a stimulation of nerve cell growth and proliferation.

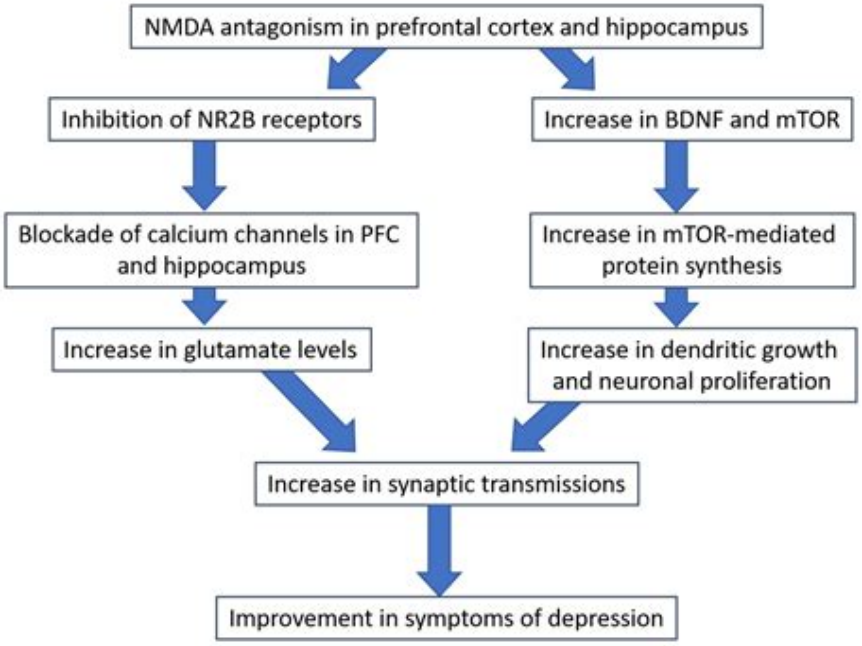
Synaptic activity, neural connections, and specific ion channels at the neural synapse all start firing within hours of supervised dosing. The nerve cell response to the neurotransmitter glutamate is a likely target of its activity. Here is a convoluted image (and alphabet soup):



{Ketamine stimulates protein synthesis and nerve cell growth.}

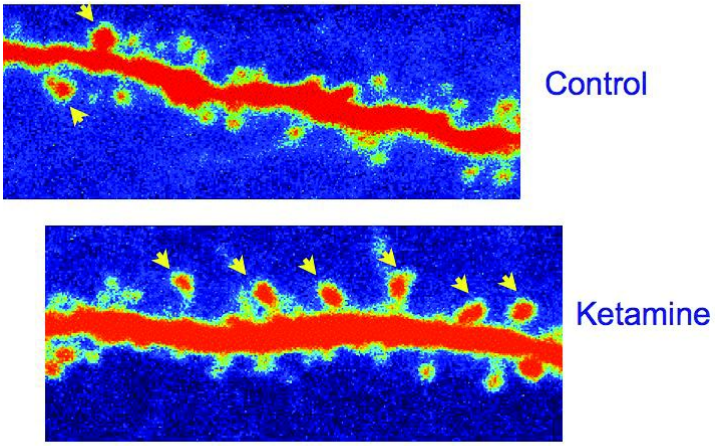
The take home message is that BDNF (Brain-Derived Neurotrophic Factor) is low in chronic stress and depression, leading to nerve atrophy/death. Ketamine kicks off a cascade of events that boost BDNF levels up, repairing the damage and inducing synaptogenesis.

Here it is in a simpler (sort of) chart:



{Ketamine is a NMDA antagonist.}

And, when we image synapses ….



{New synaptic activity is observed.}

While the exact biochemical processes in play are still being teased out, the action of ketamine is an observable increase in synaptic plasticity at the frontal cortex, the hippocampus, and other neural centers of importance to mood and behavior.

Major Mood Disorder (MDD) is widespread, with an estimated prevalence of 10-19%. The pathophysiology of MDD is poorly understood. Weak monoamine activity (serotonin, norepinephrine, dopamine) prevails as the presumptive cause; and reuptake inhibitors are the treatment in vogue. The major issue with these agents is that it takes several weeks to months to produce positive effect, which leaves the patient susceptible when suicide is an imminent concern.

The actions of ketamine to induce rapid antidepressant effects are in sharp contrast with the delayed effect onset of currently approved antidepressant treatments, which is particularly important in cases of patients where a lag in the onset of antidepressant action has been associated with increased risk for suicide.

The mechanism of action of ketamine's rapid antidepressant effect is unknown, but is thought to be related to its antagonism at the NMDA receptor and also involve, directly or indirectly, increasing synaptic potential.

Ketamine is a rapid-acting medication being re-purposed to treat both major depressive disorder and the depressive phase of bipolar disorder, and suicidality is also decreased. Positive effects are often seen within hours of administration. Ketamine has been shown to be very effective even in those with treatment-resistant depression. The discovery of antidepressive action of ketamine has been described as the single most important advance in the treatment of depression in over 50 years.

Have a great week and be safe,

Bryan