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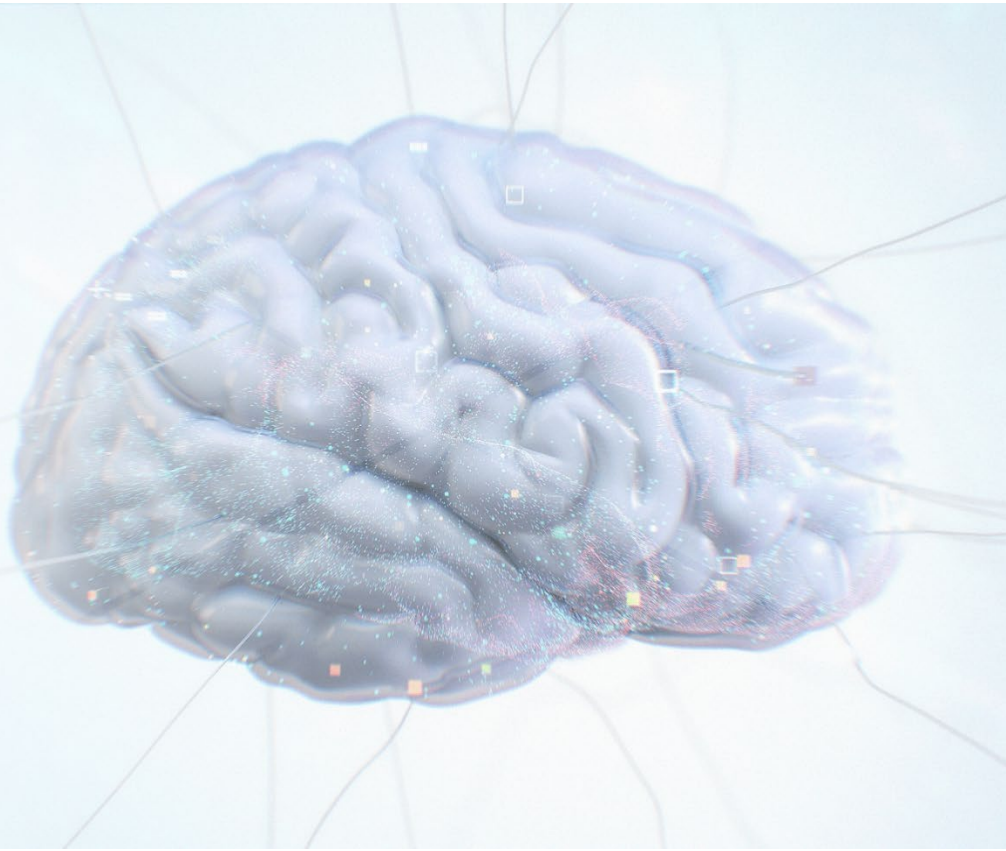
The Evolving Science of Ketamine



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Ketamine Uses

While Ketamine has been around since the 1950's, new therapeutics applications continue to bloom before our eyes[1]. Originally applied as an anesthetic in veterinary patients, its use quickly expanded to use in human anesthesia and in the past 80 years has been investigated to treat chronic pain, seizures, headaches, alcohol, and substance abuse[2]. More recently, it is being studied to treat depression[3], help with neuroprotection,[4] and even promote synaptic elasticity[5].

Chronic Pain Management

Although ketamine acts on multiple aspects of pain expression, *Hocking and Cousins* noted that research of ketamine as an agent for chronic pain management has lagged[6, 8]. In turn, this may be due to the lack of robust results in chronic pain management, with the authors concluding that ketamine might be a reasonable "third-line" option when first - and second-line options have failed. In another meta-analysis, ketamine across multiple chronic pain syndromes in refractory patients provided short term benefits, with the authors noting bias in most of the studies they evaluated[7]. Blonk et al arrived at a similar conclusion with oral ketamine for pain management describing it has had a lack of evidence and a poor safety profile, recommending its oral use be limited to an add-on agent in refractory complex chronic pain patients[8].

Refractory Epilepsy and Status Epilepticus

In addition to its use in chronic pain management, ketamine has additionally been evaluated for use in refractory epilepsy. Based on the fact that ketamine can be used in anesthetic doses for status epilepticus (SE), *Borsato et al*. performed a National Library of Medicine (NLM) database search for the use of low dose ketamine for refractory epilepticus, but found none[9]. Consequently, the authors reported the successful use of initially intravenous (IV) ketamine and later conversion to oral ketamine in patients with refractory seizures. The authors noted that IV ketamine at doses of 0.25-0.5 mg/kg/hr was more prone to cause drug-related side effects, whereas the use of oral ketamine in doses ranging from 500mg to 2000mg, divided into 2 to 4 doses per day, could likely present a better tolerated option, especially in combination with individualization based on Cytochrome P450 profiles. *Alkhachroum et al*. further demonstrated in 68 super-refractory SE (SRSE) patients between 2009 and 2018 that ketamine decreased seizure burden by at least 50% within 24 hours in 55 patients, then complete cessation in 43 patients. Later, *Jacobwitz et al*. in a single-center retrospective study, found that IV ketamine in doses ranging from 1 to 7mg/kg/day was effective in neonatal and pediatric patients with few adverse events[10,11]. Of interest, it was also noted that ketamine was more effective when initiated first rather than being added after the therapeutic failure of midazolam.

Applications in Migraine Therapy

Because of its effect on NMDA receptors and its use in acute and chronic pain, ketamine is a natural therapeutic consideration for migraines. Indeed, a few studies have looked at mostly intravenous administration but also intranasal administration of ketamine for various types of migraines[12-16]. In a double-blind, randomized parallel trial, 18 patients were prescribed 25mg of intranasal ketamine whereas 30 patients were administered 2mg of midazolam for migraine with prolonged aura. Ketamine statistically decreased severity of the migraines, but not the duration of the aura[12]. Seventy-seven patients in a retrospective review received intravenous ketamine after unsuccessful inpatient and outpatient aggressive treatment of chronic migraines. Of these patients, 71.4% demonstrated an acute response but no long-term benefit from the ketamine intervention[13]. Yet another retrospective review of 6 patients showed that all 6 patients reported a decrease of >6 points, on a scale of 0-10, after receiving IV ketamine, in doses ranging from 0.12 to 0.42mg/kg/h for outpatient refractory migraines[14]. With that said, a double-blind, placebo-controlled study of 34 patients (=17 ketamine, =17 placebo), demonstrated that the administration of IV ketamine at a dose of 0.2mg/kg did not show any improvement in migraines and more side effects than placebo[16].

Substance Abuse Disorder and Mechanism of Action

Because of its application to pain management, it is likely not surprising that ketamine has been associated with abuse. However, what is surprising is that, ironically, it has also been studied for its use in substance abuse disorder (SUD) (i.e. alcohol, heroin, and cocaine) by reducing cravings. While the mechanism of action for this application is not well elucidated, it appears to be related to ketamine affecting neuroplasticity via NMDA receptor antagonism. This in turn increases AMPA receptor insertion, thereby reversing decreased glutamatergic transmission associated with addiction and depression[7]. Anecdotal evidence since the 1990s in the U.S. has demonstrated

promising evidence of its application, mostly intramuscularly, for this use while previous, poorly structured studies in the USSR, and later the U.S. showed robust results for ketamine in SUD[18-22]. More recent studies have fortified these arguments with more robust results. One study indicated that 3 doses of intravenous ketamine (n=8) (dose of 0.41mg/kg to 0.71mg/hg) within 48 hours reduced the amount and frequency of cocaine use within 4 weeks of the study compared to baseline. Another study compared a single dose of ketamine (=0.71mg/kg/dose) to midazolam (=0.025mg/kg/dose), with ketamine showing a 67% reduction in cocaine use compared to midazolam[23,24].

Treatment-Resistant Depression and Neuroplasticity

While these many applications are fantastic, even more exciting are some of the newer applications of ketamine, which include depression, neuroprotection, and synaptic plasticity. Indeed, the isomer of ketamine, (S)-ketamine, also known as esketamine, is commercially available as a nasal spray indicated for treatment resistant depression. The first placebo-controlled, double-blind trial published study looking at the use of ketamine for depression dates to 2000 and the team of Berman et al[25]. They demonstrated in 7 patients that a single dose of ketamine (=0.5mg/kg) vs placebo provided significant improvement within 72 hours of infusion for treatment resistant depression (TRD). This publication was significant because it opened the doors to the role of NMDA and glutamate in the pathophysiology of depression. Since that time, many other published studies, as well as the work done to justify the approval of esketamine, have further demonstrated the value both of intravenous and nasal ketamine for rapidly mitigating TRD and providing an effect that can last over 7 days after administration[27-31].

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