Ketamine for Depression

Reference Guide for Health Professionals

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Ketamine is a popular anesthetic drug that has a strong affinity to the NMDA receptors in the brain. It is an FDA approved drug primarily used in a hospital setting. At doses of 2mg/kg, Ketamine is a safe and effective induction drug for anesthesia.

Ketamine is also often used in labor and delivery as an adjunct to spinal anesthesia during a cesarean section at one time intravenous dose of 30-50mg. It is also used in the emergency department for procedural sedation and pain management.
At Oklahoma Ketamine Center, we provide low ketamine sub-anesthetic dose for treatment of moderate to severe depression. For depression treatment, a fraction of the doses used in a cesarean section is used over 50-60 minutes. Patients do not lose consciousness and often spend time listening to music or on their phones. There are some who choose to nap during the treatment.
Patients who have gone through the Ketamine treatment have experienced drastic and long lasting relief in depression symptoms. The Beck's Depression Inventory Scale is used to track their progress. On average, most of the patients who are depressed score around 34-38 (Severe). After the first series of infusions are finished (usually over a two week period), the patients' scores range from 0-6. Beck's scale range from 0-10 for about 90 days after the initial series. The scores gradually increase and therefore, maintenance infusions are required every 90 days to maintain depression relief.

There are plenty of research articles which showcase these same results. A few selected abstracts are also provided in this informational booklet.
A common misunderstanding with Ketamine clinics is the sense that Ketamine replaces the need for a healthcare provider. This could not be farther from the truth. These patients are required to make their regular appointments and often must increase frequency in order to be tested for Ketamine maintenance. Simply adding the Beck's scale to your patients' routine appointment is all that is needed.

You decide when they need to return for their "boost" infusion (typically once every 90 days).
Another popular misconception is the notion that Ketamine will interact with current prescribed depression medications. Ketamine interacts with the neurotransmitter Glutamate and can be taken along with any current FDA approved depression medications.

Patients who receive Ketamine at Oklahoma Ketamine Center continue to take all of their currently prescribed medications. It is up to you to decide whether they can be taken off any medication.

All patients undergo very strict guidelines prior to Ketamine treatment. Drug screenings and thorough
examination of patient history is required. Ketamine is not for every patient. The exclusion criteria will disqualify patients in the program such as a history of uncontrolled seizures or hypertension.

We typically expect patients to have experienced at least one or two FDA approved depression medications with little to no success before being referred to our clinic. No depression medication should be stopped while on Ketamine therapy (the drug *Memantine* can decrease the effects but is rarely seen in depression patients' medication lists).
Ketamine is very safe at low doses. Patients will be educated on what to expect during their infusions. The patients who fall asleep during their treatment experience vivid dreams. Most find this very pleasant (Note that the extremely low doses will not produce a "high" and as such is not addictive or habit forming). Unlike most medications, Ketamine does not have to be "tapered." It can be initiated and stopped abruptly without any issues. Patients typically experience a little blurry vision after the infusion and therefore, will require to have someone with them to drive them home.
If you decide to refer patients to our center, they must satisfy an extensive checklist to ensure safety. Ketamine has successfully treated all spectrums of depression ranging from PTSD to schizophrenia along with suicidal ideation.

Your patients will come to our center under your orders to be monitored by our anesthesia provider (Typically a Doctor of nurse Anesthesia or CRNA). Vital signs are monitored every 5 minutes and include NIBP, Pulse Oximeter, and EKG.
Summary

1.) Ketamine is an old anesthetic drug with drastic positive effects on depression and anxiety

2.) Ketamine is an adjunct to your current therapy and patients must continue to follow up with routine appointments

3.) Safe to use along with any current FDA approved depression medicines including Lithium

4.) Tremendous patient satisfaction as illustrated by the Beck's Inventory Scale

5.) Highly backed by random control trials and peer reviewed studies (abstracts included in this booklet)
6.) Opens up new avenues for patient volume (Many PCP's want to send patients to our center for Ketamine therapy but our clinic only accepts referrals by a licensed health care provider.)
Abstract

Ketamine safety and tolerability in clinical trials for treatment-resistant depression
Ben Wan et. al. 2015

OBJECTIVE:
Ketamine has demonstrated rapid antidepressant effects in patients with treatment-resistant depression (TRD); however, the safety and tolerability of ketamine in this population have not been fully described. Herein we report the largest study to date of the safety, tolerability, and acceptability of ketamine in TRD.

METHOD:
Data from 205 intravenous (IV) ketamine infusions (0.5 mg/kg over 40 minutes) in 97 participants with DSM-IV-defined major depressive disorder (MDD) were pooled from 3 clinical trials conducted between 2006 and 2012 at 2 academic medical centers. Safety and tolerability measures included attrition, adverse events (AEs), hemodynamic changes, and assessments of psychosis and dissociation.

RESULTS: The overall antidepressant response rate, defined as a ≥ 50% improvement in Montgomery-Asberg Depression Rating Scale score, was 67% (65 of 97 participants). Four of 205 infusions (1.95%) were discontinued due to AEs.
The overall attrition rate was 3.1% (3 of 97). In the first 4 hours after the infusion, the most common general AEs were drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. Approximately one third of individuals experienced protocol-defined hemodynamic changes. Ketamine resulted in small but significant increases in psychotomimetic and dissociative symptoms (all P < .05). There were no cases of persistent psychotomimetic effects, adverse medical effects, or increased substance use in a subgroup of patients with available long-term follow-up information.

CONCLUSIONS:
In this relatively large group of patients with TRD, ketamine was safe and well tolerated.
Mechanisms underlying differential effectiveness of memantine and ketamine in rapid antidepressant responses
Gideons et. al. 2013

Ketamine is an NMDA receptor (NMDAR) antagonist that elicits rapid antidepressant responses in patients with treatment-resistant depression. However, ketamine can also produce psychotomimetic effects that limit its utility as an antidepressant, raising the question of whether the clinically tolerated NMDAR antagonist memantine possesses antidepressant properties. Despite its similar potency to ketamine as an NMDAR antagonist, clinical data suggest that memantine does not exert rapid antidepressant actions for reasons that are poorly understood. In this study, we recapitulate the ketamine and memantine clinical findings in mice, showing that ketamine, but not memantine, has antidepressant-like effects in behavioral models. Using electrophysiology in cultured hippocampal neurons, we show that ketamine and memantine effectively block NMDAR-mediated miniature excitatory postsynaptic currents in the absence of Mg(2+). However, in physiological levels of extracellular Mg(2+), we identified key functional differences between
ketamine and memantine in their ability to block NMDAR function at rest. This differential effect of ketamine and memantine extends to intracellular signaling coupled to NMDAR at rest, in that memantine does not inhibit the phosphorylation of eukaryotic elongation factor 2 or augment subsequent expression of BDNF, which are critical determinants of ketamine-mediated antidepressant efficacy. These results demonstrate significant differences between the efficacies of ketamine and memantine on NMDAR-mediated neurotransmission that have impacts on downstream intracellular signaling, which we hypothesize is the trigger for rapid antidepressant responses. These data provide a novel framework on the necessary functional requirements of NMDAR-mediated neurotransmission as a critical determinant necessary to elicit rapid antidepressant responses.
Abstract

Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Murrough et. al. 2013

OBJECTIVE:
Ketamine, a glutamate N-methyl-d-aspartate (NMDA) receptor antagonist, has shown rapid antidepressant effects, but small study groups and inadequate control conditions in prior studies have precluded a definitive conclusion. The authors evaluated the rapid antidepressant efficacy of ketamine in a large group of patients with treatment-resistant major depression.

METHOD:
This was a two-site, parallel-arm, randomized controlled trial of a single infusion of ketamine compared to an active placebo control condition, the anesthetic midazolam. Patients with treatment-resistant major depression experiencing a major depressive episode were randomly assigned under double-blind conditions to receive a single intravenous infusion of ketamine or midazolam in a 2:1 ratio (N=73). The primary outcome was change in depression severity 24 hours after drug administration, as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS).
RESULTS:
The ketamine group had greater improvement in the MADRS score than the midazolam group 24 hours after treatment. After adjustment for baseline scores and site, the MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% confidence interval [CI], 3.20 to 12.71). The likelihood of response at 24 hours was greater with ketamine than with midazolam (odds ratio, 2.18; 95% CI, 1.21 to 4.14), with response rates of 64% and 28%, respectively.

CONCLUSIONS:
Ketamine demonstrated rapid antidepressant effects in an optimized study design, further supporting NMDA receptor modulation as a novel mechanism for accelerated improvement in severe and chronic forms of depression. More information on response durability and safety is required before implementation in clinical practice.
Abstract

Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review
Iadarola et. al. 2015

Current pharmacotherapies for major depressive disorder (MDD) and bipolar depression (BDep) have a distinct lag of onset that can generate great distress and impairment in patients. Furthermore, as demonstrated by several real-world effectiveness trials, their efficacy is limited. All approved antidepressant medications for MDD primarily act through monoaminergic mechanisms, agonists or antagonists with varying affinities for serotonin, norepinephrine and dopamine. The glutamate system has received much attention in recent years as an avenue for developing novel therapeutics. A single subanesthetic dose infusion of the noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has been shown to have rapid and potent antidepressant effects in treatment-resistant MDD and BDep. In a reverse translational framework, ketamine's clinical efficacy has inspired many preclinical studies to explore glutamatergic mechanisms of antidepressant action. These studies have revealed enhanced synaptic plasticity/synaptogenesis via numerous molecular and cellular mechanisms: release of local translational inhibition of brain-derived neurotrophic...
factor and secretion from dendritic spines, mammalian target of rapamycin activation and glycogen synthase kinase-3 inhibition. Current efforts are focused on extending ketamine's antidepressant efficacy, uncovering the neurobiological mechanisms responsible for ketamine's antidepressant activity in biologically enriched subgroups, and identifying treatment response biomarkers to personalize antidepressant selection. Other NMDA receptor antagonists have been studied both preclinically and clinically, which have revealed relatively modest antidepressant effects compared with ketamine but potentially other favorable characteristics, for example, decreased dissociative or psychotomimetic effects; therefore, there is great interest in developing novel glutamatergic antidepressants with greater target specificity and/or decreased adverse effects.
Abstract

Augmentation Therapy With Serial Intravenous Ketamine Over 18 Months in a Patient With Treatment Resistant Depression.
Hassamal et. al. 2015

Major depressive disorder is a severe illness that affects 3% to 7% of adults annually in the United States. About 30% of these individuals are refractory to multiple treatment trials. Recent reports have found a significant and almost immediate improvement in depressive symptoms after single or multiple ketamine intravenous infusions (IVIs) in such patients. We present the case of A.B., a patient with treatment-resistant depression (TRD) including to subgenual deep brain stimulation, who went into remission after augmentation with 6 ketamine IVIs (0.5 mg/kg) over a 3-week period. However, she had a reemergence of depressive symptoms 4 months later and received a second series of 3 ketamine IVIs over the course of a week. A.B. again went into remission and maintained this for the next 8 months. At this time, she experienced a reemergence of depressive symptoms and was treated with the third series of ketamine IVIs (3 infusions over the course of a week).
Because A.B. has now been in remission for 6 months. A.B. has received a total of 12 ketamine IVIs over the course of 18 months. No significant adverse events have occurred. To our knowledge, this is the first case of long-term ketamine efficacy as augmentation therapy in TRD over the course of 18 months. There is a need for studies examining the long-term management of TRD with IV ketamine. Guidelines for maintenance ketamine IVIs in TRD also need to be developed.
Abstract

A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression.
Diagranados et. al. 2010

CONTEXT:
Existing therapies for bipolar depression have a considerable lag of onset of action. Pharmacological strategies that produce rapid antidepressant effects—for instance, within a few hours or days—would have an enormous impact on patient care and public health.

OBJECTIVE:
To determine whether an N-methyl-D-aspartate-receptor antagonist produces rapid antidepressant effects in subjects with bipolar depression.

DESIGN:
A randomized, placebo-controlled, double-blind, crossover, add-on study conducted from October 2006 to June 2009.

SETTING:
Mood Disorders Research Unit at the National Institute of Mental Health, Bethesda, Maryland. Patients Eighteen subjects with DSM-IV bipolar depression (treatment-resistant).
INTERVENTIONS:
Subjects maintained at therapeutic levels of lithium or valproate received an intravenous infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo on 2 test days 2 weeks apart. The Montgomery-Asberg Depression Rating Scale was used to rate subjects at baseline and at 40, 80, 110, and 230 minutes and on days 1, 2, 3, 7, 10, and 14 post infusion.

MAIN OUTCOME MEASURES:
Change in Montgomery-Asberg Depression Rating Scale primary efficacy measure scores.

RESULTS:
Within 40 minutes, depressive symptoms significantly improved in subjects receiving ketamine compared with placebo (d = 0.52, 95% confidence interval [CI], 0.28-0.76); this improvement remained significant through day 3. The drug difference effect size was largest at day 2 (d = 0.80, 95% CI, 0.55-1.04). Seventy-one percent of subjects responded to ketamine and 6% responded to placebo at some point during the trial. One subject receiving ketamine and 1 receiving placebo developed manic symptoms. Ketamine was generally well tolerated; the most common adverse effect was dissociative symptoms, only at the 40-minute point.

CONCLUSION:
In patients with treatment-resistant bipolar depression, robust and rapid antidepressant effects resulted from a single intravenous dose of an N-methyl-D-aspartate antagonist.
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