Overview

Ketamine is a dissociative class compound, with an FDA schedule III designation. It is indicated for and commonly used as an anesthetic medication. Ketamine has been found to be helpful for treating depression, even in individuals who have not responded to other interventions. It has a unique effect, in that it can work very rapidly, with individuals frequently seeing improvement in their depression within hours. However, ketamine response is not guaranteed and even in responders, there can be a high rate of relapse back to the depressed, state, even with repeat dosing that increases over time.

The ongoing beneficial effects of ketamine that can be realized include general mood improvement, lessening of anhedonia and reduction/resolution of suicidal ideation. Improvements to levels of anxiety and behavioral pattern of sleep, appetite and energy can also be realized. Ketamine has also demonstrated benefit in anxiety conditions, including PTSD, and may yield gains to patterns of obsessive thinking or rumination. Coupling these biological effects with psychotherapy and behavioral change is designed to maximize benefit and sustained gains.

Off-label use.

Ketamine does not have an indication for treatment of depression, anxiety of any other psychiatric condition by the FDA. Therefore, the provision of ketamine for these conditions is an 'off-label' use. This is a legal prescribing practice and occurs quite commonly. Almost twenty percent of all medications prescribed in the United States are prescribed for off-label use.

Mechanism

Ketamine operates on a receptor level as NMDA antagonist and regulates the availability of the neurotransmitter glutamate in the brain. The antidepressant effect appears to be mediated by downstream signal effects of AMPA receptors. A variety of other receptors are targeted and contribute to the acute and ongoing effects of treatment.

Route of Administration

Ketamine can be administered in a variety of ways: via an intravenous ketamine infusion (IV), an intramuscular injection (IM), a subcutaneous injection (SC) intranasally, sublingually and orally as a dissolving troche or oral dissolving tablet. Routes vary in the onset of action, bioavailability and clearing time through the system for each individual. While there is generally a predictable response based on past administration, it is possible that patient maybe experience variable physiological and subjective experiences with the same dose. Research has shown

that an intramuscular injection of ketamine is as effective as the same dose given by intravenous infusion.

Route	Bioavailability	Onset
IV	100%	1 min
IM	93%	1-5 min
Nasal	25-50%	30 minutes
Oral	17-24%	<30 minutes
Sublingual	24-30%	<15 minutes

Dosing protocols

There are a variety of dosing protocols in practice. Much research and attention has been focused on the provision of 0.5mg/kg of ketamine by IV infusion over 45 minutes, in a repeated series consisting of 2/week for 3 weeks. Other described protocols include provision of a single infusion, daily or weekly dosing by IV, IM, or oral routes.

There is significant ongoing research into the initial and maintenance protocol to define optimal response. Much attention is focused on the maintenance of response, noting that the drop off in response can approach 90% following a positive response. Combining psychotherapy with ketamine dosing serves to prolong effect by addressing behavioral and psychological factors that can perpetuate depression, anxiety and other distress states.

Effect

Ketamine effects can be designated as occurring at time of dosing – acute, and ongoing – beyond the time it takes for ketamine to metabolize physically, noting that longer acting metabolites persist upto a week.

The acute subjective effects of ketamine dosing can range from subperceptual disturbances in cognitive processing and body sensation to full dissociative states in which one feels separate from the body and thoughts dissolve fully. Research has shown that ketamine treatment without dissociation is as effective as treatment with dissociation. Dissociation is not required to achieve treatment success.

These experiences are classified as non-ordinary states of consciousness, and may represent novel experiences for patients. It is possible that some patients may experience a departure from their usual mind and physical state as

challenging or unsettling in the moment. The treatment environment, supportive therapist stance and dosing protocol is designed to optimize the positive nature of the subjective experiences.

The treatment dosage administered at Ketamine Treament Services is 0.5mg/kg. Studies have shown that higher doses do not increase the success rate of treatment. Most patients do not dissociate or have unpleasant feelings at this dose.

A more comprehensive description of dosing ranges and effects.

State	Features	Typical Ketamine Dose	Duration
Empathogenic Experience	Awareness of body; comfort and relaxation; reduced ego defenses; empathy, compassion, and warmth; love and peace; euphoria; mind is dreamy with non-specific colorful visual effects	Low sub-psychedelic dose similar to that used for anxiolysis and/or analgesia (0.25 mg/kg – 0.5 mg/kg IM, or 25 – 50 mg IM)	45-60 mins
Out-of-Body Experience (OBE)	Complete separation from one's body; significantly diminished ego defenses; visits to mythological realms of consciousness; encounters with non-terrestial beings; emotionally intense visions (e.g., deceased relatives, spirits); vivid dreams of past and future incarnations; re-experiencing the birth process	Medium psychedelic dose such as that used for mild conscious dissociative sedation (0.75 mg/kg – 1.5 mg/kg IM, or 75 mg – 125 mg IM)	45-60 mins
Near-Death Experience (NDE)	Departure from one's body; complete ego dissolution/loss of identity; experienced physical (body) and psychological (mind) death; experience being a single point of consciousness simply aware of itself; reliving one's life; aware of how actions have affected others, with moral judgment of self	High psychedelic dose such as that used for moderate to severe conscious dissociative sedation (2.0 mg/kg – 3.0 mg/kg IM, or 150 – 250 mg IM)	45-60 mins
Ego-Dissolving Transcendental Experience (EDT)	Ecstatic state of the dissolution of boundaries between the self and external reality; complete dissolution of one's body and self (soul); transcending normal mass/time/space continuum; collective consciousness; unity with Nature/Universe; sacredness	Rare in low doses (0.25 mg/kg – 0.5 mg/kg IM, or 25 – 50 mg IM), more common in high psychedelic doses (2.0 mg/kg – 3.0 mg/kg IM, or 150 – 200 mg IM)	45-60 mins

Ketamine Psychedelic Psychotherapy: Focus on its Pharmacology, Phenomenology, and Clinical Application: Journal of Transpersonal Studies. Volume 33. Issue 2.

Medical clearance for treatment:

Prior to administration of ketamine, a patient will need to be medically cleared for treatment by a provider at Smith Family MD. Medication optimization of blood pressure is needed based on the sympathetic activation effects of ketamine. An EKG may be required in instances where there has been arrhythmia or a history of cardiovascular issues. Patient with a history of cystitis or other bladder issues may need to be cleared by urological consultation, noting the rare but potential significant adverse effect of cystitis.

Adverse and side effect associated with treatment:

The most common side effects associated with ketamine are nausea, vomiting, dizziness, diplopia, drowsiness, dysphoria, and confusion. There are reports of emergence phenomenon for approximately 6% to 12% of patients. Rarely, patients experience hallucinations.

A complete list of side effects follows:

Allergic: anaphylaxis, breathing difficulties, facial, lip, throat and tongue swelling, hives
Cardiovascular: arrhythmias, blood pressure, is frequently elevated, bradycardia, hypotension, left ventricular dysfunction in patients with heart failure, respiratory\cardiac arrest
Gastrointestinal: anorexia, nausea, and vomiting
Muscular: muscle stiffness and spasms/tonic-clonic movements resembling seizures, enhanced skeletal muscle tone
Neurologic: confusion, seizures
Ophthalmologic: diplopia, increased intraocular pressure, nystagmus
Psychiatric: amnesia, anxiety, confusion, depression, disorientation, dysphoria, dissociative state (patients may not be able to speak or respond purposefully to verbal commands), emergence phenomena/delirium (6% to 12% in different studies and can last for up to 3 hours) including hallucinations, flashbacks, unusual thoughts, extreme fear, excitement, and irrational behavior, insomnia, physical and psychological dependence, addiction when used recreationally. (Drug dependence and tolerance may develop after prolonged use. Withdrawal symptoms may occur if stopping ketamine suddenly.)
Respiratory: apnea, increased laryngeal, and tracheal secretions, laryngospasm, airway obstruction in infants (may not be drug-related), respiratory depression
Skin: (infrequently) at the site of injection, local pain, and erythema, morbilliform rash

Ketamine increases sympathetic tone in the vasculature and can raise blood pressure, which has associated risks with adverse outcomes linked to stroke and arrhythmias, resulting in loss of function and possibly death.

Ketamine has limited suppression of respiratory drive, however it is rarely reported to cause laryngospasm, particularly in pediatric populations.

Ketamine has been associated with cystitis, a painful and potentially irreversible bladder condition. Cystitis has been generally reported in higher doses and more frequent uses, particularly in substance abusing population.

Ketamine has a risk of abuse and tolerance. It generally has low reinforcement properties and no physiological withdrawal syndrome. Therefore, it is atypical for patients to crave use and demonstrate behaviors to obtain it. Some patients exhibit tolerance (needing higher doses for the same effect).

An emergence phenomena, in approximately 10-20% of cases, has been reported in which a patient may experience subjective distress with psychological or physical restlessness. In these instances, treatment with low dose anxiolytic medication has been beneficial.

There are also rare psychological and psychiatric risks associated with treatment, notable switching into mania for bipolar patients, who may not yet be diagnosed as such. While rarely described, it is possible that sustained perceptual disturbances, alternations in cognition, reality testing or subjective distress stemming from treatment may persist beyond that acute treatment.

Management of Adverse Effects:

Intervention may include provision of anti-hypertensive medication, medication for nausea, or medication for anxiety. Management of cardiorespiratory symptoms is beyond the scope of our office practice and will be handled by activation of the EMS system in coordination with the local Emergency Department. In the event of psychological distress, treating provider may deliver of anxiolytic medication or antipsychotic medication in oral or intramuscular formulation. The treating provider reserves the right to activate emergency response systems, ie. call 9-11, if it is determined by clinical judgment that patient safety requires a higher level of care than can be provided in the office.

Preparation

Prior to treatment:

- Patients are expected to abstain from all substance use for a period of 48 hours; including alcohol tobacco, cannabis, illicit substances.
- In certain instance, a urine toxicology screen may requires prior to treatment, including on the day of treatment
- No dietary intake for least 4 hours prior treatment. A small intake of water is permitted
- Hold medication that may raise blood pressure – ie. stimulants
- Continue on anti-hypertension and diabetic medication, with dose of adjustment of insulin based on dietary intake adjustment.

Standard course experience with treatment

Preparation: 0-15 minutes

- Evaluation of mindset and readiness for treatment
- Blood pressure screening, with treatment for parameter of 150/90mm Hg
    - Pt with blood pressure above the threshold will need to take medication to control blood pressure on the day of treatment and possibly during the course of treatment. Clonidine is available in oral formulation
- Confirmation that an after-care/support person is available for pick-up from office.
- Completion of depression and related screening forms

Dosing: Onset 15-30 minutes

- Ketamine 0.5mg/kg is injected intramuscularly in the deltoid or tricep muscle of the arm.

Trance state: 30-45 minutes: Generally restful, volitionally non-verbal, supported by soothing music and eye shade to minimize light effect

- Patient will typically experience a heaviness in the physical body, possibly with the loss of sensation, followed by a separation from the usual state of cognitive processing, such that verbal expression may become limited and even absent.
- Patients are generally rousable to an alert and interactive state, and will be checked in on by verbal cue to determine if there are any concerns.
- Some patients may experience unfamiliarity with this state that is disconcerting – perhaps in the heaviness/floating sensation, vertigo like sensation, physical discomfort (nausea), the presentation of distressing psychological material
- During treatment blood pressure will be checked every 15 minutes either manually or by automated monitor.
- Patient also consents to allow for video monitor of the experience in order to assure safety and mutually mitigate concern for behavior that may be aversive, intrusive or experienced as such by the patient in an altered state of awareness. – ie. a gentle hand placed on the shoulder.
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<u>Integration Phase: 30-45 minutes: Opportunity for reflection and discussion</u>

- Patient will be engaged verbally to describe experience and potentially engage in discussion of thoughts, emotional states and physical sensations. Patients may prefer silence in this period, and thoughts recorded by physician notations, or use of a the patient's private recording device – ie. audio on phone.

<u>Disengagement from treatment</u>

At any point in the treatment course, the patient may disengage from the defined and recommended process – ie. sit up and take off the eye shade. However, patients will not be allowed to leave the office on their own until 90 minutes after dosing of ketamine. The patient may request that the defined after-care support assume custody at any point during the treatment, with full release into care to be determined by the physician providing care / administering the dose.

After-care

Patients agree to establish an after-care support person for 4 hours following treatment. Patient will leave the clinic in the care of this person. Patient agrees not to drive a motorized vehicle, ride a bicycle, or exercise vigorously for 8 hours following treatment. A light meal is recommended following treatment.

Ongoing treatment

The patient will be engaged in an ongoing and concurrent treatment with a medical provider at Smith Family MD, a psychiatrist and/or psychologist, as deemed appropriate by the physician providing ketamine treatment. The termination or interruption of this collaborative treatment may result in termination of ketamine associated therapy.

Final declaration

In signing this agreement, I recognize that I have an established a treatment relationship with Dr. Scott Smith. I understand that sharing or selling my prescribed medications to another person is a crime and grounds for immediate dismissal from treatment. I understand that I have alternative treatment options beside ketamine for my condition. I understand that I may not respond or have a favorable response to ketamine treatment and there are risks associated with the treatment, some of which may be permanent.

Treatment may be terminated by Dr. Smith based on clinical factors, including and not limited to concerns for poor fit with treatment, likelihood of response, lack of compliance with care, concern for diversion, patient behaviors and risk factors exceeding tolerance of his practice, and lack of sufficient collaborative support by the treatment team. Provision of treatment does not automatically imply future treatment.

MD / Physician providing treatment:	Patient receiving treatment:

Name: _____	Name: _____
Signature: _____	Signature: _____
Date: _____	Date: _____

Ketamine Treatment Services
990 Lake Hunter Circle, Ste 101b
Mount Pleasant SC 29646
843-972-8136