

Ketamine:

An FDA-Approved Alliance Between Therapists and Physicians

Clary Tepper, PhD & Eric Tepper, MD

Who are these people, anyway?

Clary Tepper, PhD

- Clinical psychologist in private practice
- Core faculty and director of clinical training in the doctoral program in psychology at California Northstate University in Sacramento
- Director of clinical training at Catalyst Integration for Health (a mental-health ketamine practice)



Eric Tepper, MD

- Board-certified family medicine physician in private practice
- Medical director of Catalyst Integration for Health (a mental-health ketamine practice)

NOTE TO SELF: add professional headshots



Quick overview of ketamine (The Cliff Notes version, or the TL;DR)

- <> Ketamine is a prescription medication (commonly administered as a shot or a nose spray)
- <> APA and ASKP guidelines: Should be administered in a medical setting with medical monitoring
- <> It is a two-hour treatment that takes place while the client relaxes in a recliner in a private room
- <> On average, clients receive 6 - 8 treatments of ketamine (then they are done—usually in a matter of weeks)
- <> Ketamine is most effective when used in addition to psychotherapy, not instead of
- <> The client continues to work with their regular, ongoing therapist
- <> Ketamine repairs the brain—it increases brain flexibility and builds neural connections in the brain
 - <> That brain repair help treat depression, anxiety, trauma, OCD, grief, and suicidal ideation
- <> Neural-synaptic growth starts within hours, and people start to feel better quickly (often by the next day)
- <> The neural growth from the ketamine facilitates rapid progress in therapy

A brief history of antidepressants

First discovered in 1952 by accident

Spawned the serotonin hypothesis (AKA the monoamine hypothesis), which is that serotonin, norepinephrine and dopamine are the “actors” of depression

Led pharmaceutical companies to create MAOIs, TCAs, SSRIs, NRIs, SNRIs

Differences were seen in side effects and tolerability, but not efficacy



Other medical ways to treat depression

ECT: Developed in the 1930s

Highly effective but significant side effects

Still used today

TMS: FDA approved in 2008

Well tolerated, but time intensive

Questions about efficacy

Ketamine: FDA approved in 1970 as an anesthetic agent

A new formulation of ketamine (esketamine) was FDA approved in 2019 for depression

Other formulations of ketamine (not just esketamine) also show excellent efficacy in treating depression, anxiety, OCD, trauma, and suicidal ideation

Mental health doses are much smaller than anesthesia doses



Why ketamine?

The incidence of major depression is growing exponentially

Previous medications only work on monoamines (serotonin and norepinephrine)

<> It takes weeks—or months—before they start to work

<> They do not work for approximately $\frac{1}{3}$ of people who take them

Ketamine starts to work within hours

<> People generally report feeling better the next day

<> Ketamine is not an ongoing treatment—clients generally get 6-8 treatments
(so their course of ketamine is usually done within a few weeks)

<> A rapid decrease in suicidality is seen—this is a significant breakthrough



STAR D trial

2006: Federally-funded trial of 4,041 people with major depression

Used SSRIs, SNRIs, NRIs, thyroid, and mood stabilizers

Results: First medication—a little over one third of people got better

Second medication—a little less than a third of people got better

Third med—only 14% got better, and those that got better relapsed after an average of 3.1 months

They did not include psychotherapy in the trials



Who would have thought that
therapists and physicians could
work together?!

How is ketamine different?

Works completely differently than all other antidepressants

Does not follow the monoamine hypothesis (the serotonin hypothesis)

Ketamine works by blocking the NMDA glutamate receptor, leading to increases in BDNF and GDNF (these are growth factors for the brain that help with brain repair)

This helps treat depression, anxiety, trauma, OCD, and suicidal ideation



Impact of BDNF and GDNF on psychotherapy

BDNF and GDNF are “growth factors”

Growth factors help repair the brain, **growing new connections among brain cells** (called synaptogenesis) and **increasing brain flexibility** (called neuroplasticity)

This repair process means clients are primed and ready to make progress in psychotherapy



Timing of the therapy session:

Most neural growth is seen in the 48 hours following a ketamine treatment

This is the ideal time for the client to schedule a session with their therapist

Therapist evaluation: Is the client psychologically ready for ketamine?

Ketamine helps dissolve defenses

This can be unsettling for the client

It helps with mental blocks in trauma therapy

Are they ready to go further



Clients with OCD should be actively working on symptoms

Otherwise they just feel more comfortable with their OCD symptoms

Who is a good candidate for a ketamine eval?



Depression

Grief

Anxiety

Trauma

OCD

Suicidal ideation



Thought disorders

Racial and ethnic issues

Rates of mental illness—estimates vary

Less likely to receive care for mental health concerns

BIPOC are not well represented in studies on ketamine

Lower levels of BIPOC participation in ketamine research than other groups in biomedical research

May be related to inequities in criminal justice system

Race-based trauma not included in DSM-V criteria for PTSD



If race-based trauma was included in PTSD criteria, more people would qualify for studies on how ketamine helps heal trauma, and more could get help for this type of trauma

LGBTQA: Unmet needs

Sexual minority adults are approx 3x more likely to experience a major depressive episode as individuals who identify as straight

More than 12 million adult Americans who identify as LGBTQA are experiencing “mental health challenges”



What the ketamine treatment looks like

Once a therapist thinks the client is psychologically ready for ketamine, they refer the client to a medical provider at a ketamine practice

The client gets a medical evaluation to make sure they can safely receive ketamine

If they are deemed appropriate for ketamine, the client receives ketamine in the medical office

- The American Psychiatric Association and the American Society of Ketamine Physicians say that all ketamine treatments should be administered in a medical office under medical supervision

There are multiple different routes of administration—this will be discussed later

The client relaxes in a recliner in a private room during the treatment

The client often feels spacey, floaty, and dissociated for the first 45 minutes (though not always)

During the 2nd hour of the treatment, the client's vitals and sensorium return to normal

When the treatment is complete (after two hours), the client will need to have someone drive them home

Clients (on average) receive six to eight treatments in total, then they are done

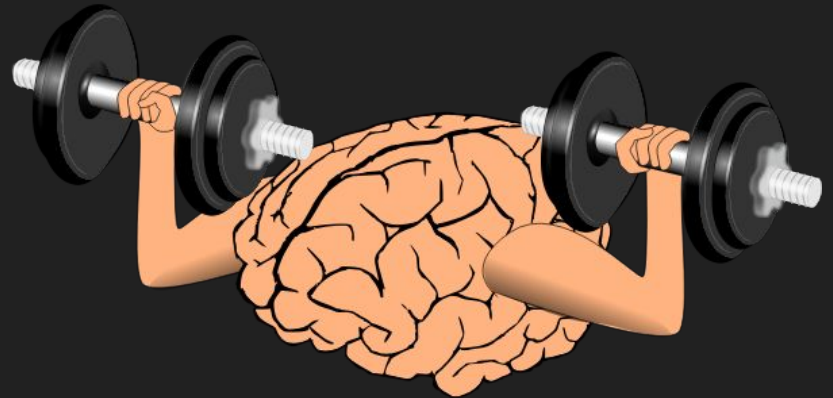
Now the fun begins!

Within hours of receiving ketamine, neural growth begins

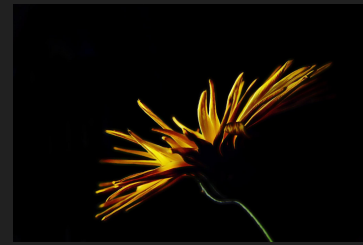
Most people report feeling better the next day

The next 48 hours is a great time for therapy (neural growth is skyrocketing)

Neuroplasticity increases and synaptogenesis begins—yes, this means brain cells are growing!



Various roles the therapist can take



The therapist can join the client at the medical practice while their client gets ketamine

Most clients are too spacy and “out of it” during the first 45 minutes of the treatment to be able to talk coherently (though this varies by client)

Some clients want to talk during the second hour of the treatment (while they are waiting for their vitals to return to normal)

Some clients like to journal during this hour and bring the journal to their next therapy session

OR

The therapist can schedule a session with their client during the 48 hours after the ketamine treatment (when the most neural growth is seen; that growth helps the client make new, rapid progress in therapy)

Routes of administration: Is ketamine a pill?



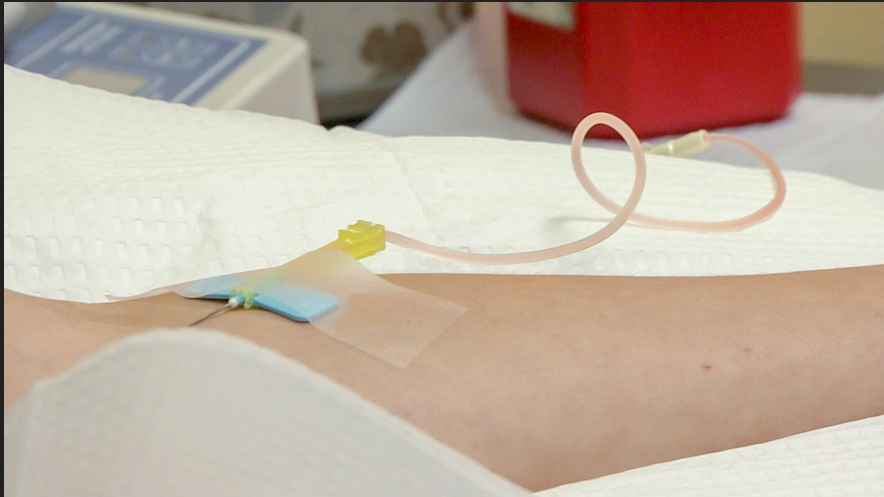
Short answer:

NO

There are three routes of ketamine administration

1. Intravenous (IV) and intramuscular (IM) ketamine (a simple shot)

These are the most bioavailable (93-100%) and consistent



Three routes of ketamine administration, continued

2. Intranasal

This nose spray formulation is also called esketamine (brand name Spravato)

The bioavailability is 30-50% and is highly effective

The absorption varies with technique and nose condition

This formulation is FDA-approved for major depressive disorder and suicidal ideation

It is also commonly used to treat anxiety, trauma and OCD,
all of which are perfectly legal but considered “off label”



Three routes of ketamine administration, continued

3. Oral ketamine (sublingual) “troche”

Compounded by a pharmacy

Dissolves under the tongue

Absorbed through the cheeks and tongue

It tastes bad (reeeeeeally bad) so people tend to swallow it instead of holding it in their mouth as instructed

Swallowed ketamine is ineffective . . . but still causes sedation and other side effects



The bioavailability of oral ketamine is low—less than 20%—and highly variable due to swallowing

We stopped using troches at our practice because we didn't find them to be all that effective

Does ketamine even work?



Effectiveness in treating depression

<> Single infusion: 7.95 point drop in MADRS scores vs midazolam

<> Repeat treatment: Up to 25.7 pt MADRS drop

<> Superior effect compared to venlafaxine monotherapy, olanzapine/fluoxetine combination, fluoxetine monotherapy, quetiapine augmentation, nortriptyline monotherapy, lamotrigine augmentation, ECT and rTMS

<> Both IV and intranasal similar with a 6-fold increased odds of antidepressant response at 24 hours compared to placebo

Oral/sublingual--???



Looks like ketamine was effective for this little guy

Effectiveness in treating anxiety disorders



50% decrease in HAM-A scores after once-weekly or twice-weekly injections of ketamine

In people with OCD, therapy is required to decrease thoughts, compulsions, and behaviors (otherwise people just feel more comfortable with their OCD)

Side effects: Everything has side effects, which is why we medically monitor people taking ketamine

Most side effects are mild, but since severe reactions can occur, we have oxygen, an AED, and emergency blood pressure medications on hand at our ketamine practice

- <> Central nervous system: Alterations in body image/mood, floating sensations, vivid dreams, hallucinations, delirium, purposeless movement, drowsiness, increased intraocular pressure, increased intracranial pressure, increased muscle tone, memory impairment (long-term use/abuse)
- <> Gastrointestinal: Nausea and vomiting, hepatic damage (from long-term oral use)
- <> Cardiovascular: Increase in blood pressure and heart rate, arrhythmia
- <> Pulmonary: Respiratory failure
- <> Misc: Lacrimation, salivation, ulcerative cystitis (long term oral use)

Most are minor and resolve within two hours of ketamine administration

Can easily be handled by a physician in the medical office

There is excellent long term safety with IV/IM and intranasal ketamine

(when used appropriately)



People often feel sleepy after getting ketamine

Most **commonly-seen** side effects

Minor: Feeling dissociated, tired, or “out of it”

More serious: Increased blood pressure—no one should ever take ketamine unless their vitals are being monitored

- Clients who arrive for a ketamine session with unusually high blood pressure will not be able to get ketamine that day

Some clients experience nausea—this can be pre-treated by the physician (thus eliminating this side effect)

Side effect worth noting: motor skills are affected, and clients will need someone to drive them home (it is important that clients plan for this in advance)

Most side effects are gone within two hours of ketamine administration

Evaluation: Is ketamine working for my client?

Need good collaboration between the therapist and the physician to evaluate if ketamine is helping the client

Dosing: How much and how often

Time for a medication break

or

Time for a tune-up/booster dose

Ketamine may help the client to feel better biologically; are they doing the psychological work to learn how to think and live differently





Summary

Ketamine is not based on the serotonin hypothesis (the monoamine hypothesis)

The most bioavailable forms of ketamine are 1) a shot (or an IV) or 2) a nose spray (esketamine, AKA Spravato)

Ketamine is highly effective for depression, anxiety, trauma, OCD, grief, and suicidal ideation (should **not** be used on anyone with a thought disorder)

When a therapist thinks their client is psychologically ready for ketamine, they refer them to a physician at a ketamine clinic for a medical evaluation

A physician prescribes and administers the ketamine in a monitored medical setting

The client continues to see their regular therapist

Neural growth skyrockets during the 48 hours after the ketamine treatment, so that is the ideal time for the client to schedule a session with their therapist

The end

