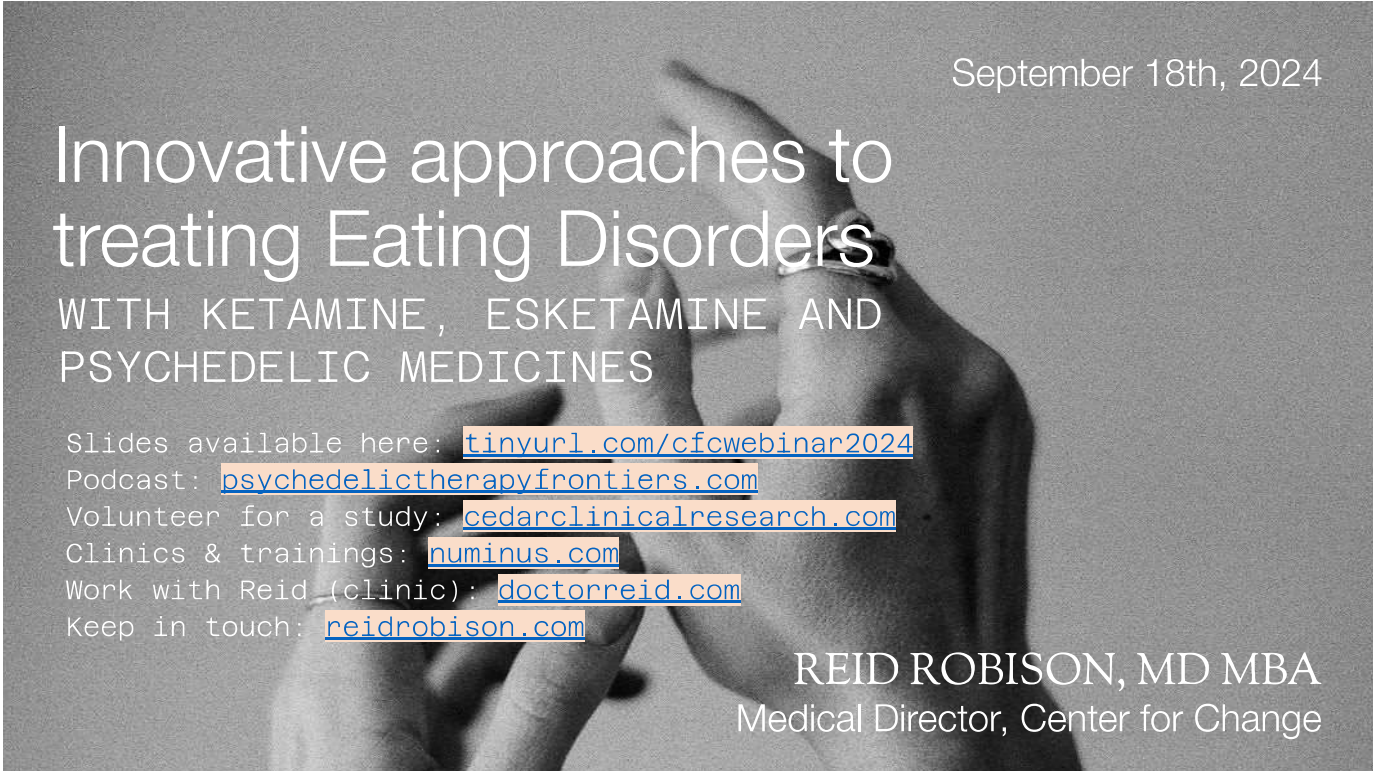




September 18th, 2024

Innovative approaches to treating Eating Disorders

WITH KETAMINE, Esketamine AND PSYCHEDELIC MEDICINES

Slides available here: tinyurl.com/cfcwebinar2024

Podcast: psychedelictherapyfrontiers.com

Volunteer for a study: cedarclinicalresearch.com

Clinics & trainings: numinus.com

Work with Reid (clinic): doctorreid.com

Keep in touch: reidrobison.com

REID ROBISON, MD MBA
Medical Director, Center for Change

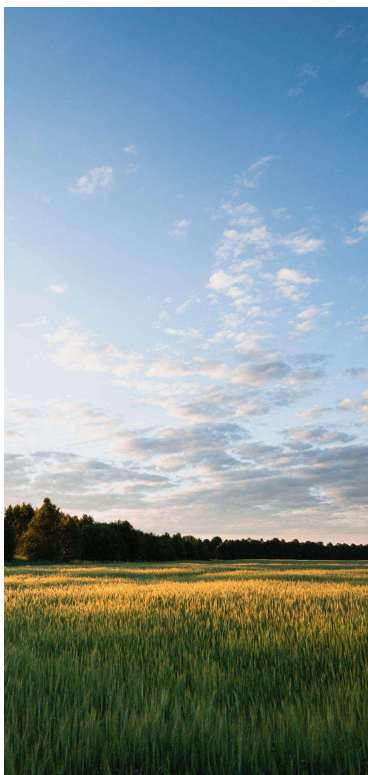
A review of the research:

1. How common are eating disorders?
2. How are current treatments doing?

EATING DISORDER PREVALENCE:

What do the big/recent studies say?

- 2020 Harvard report:
 - **9% of the U.S. population** will experience an eating disorder within their lifetimes
- 2023 review/meta-analysis:
 - **Disordered eating in 22% of children and adolescents** (ages 6-18)
 - n=63,181 from 16 countries
 - Used 5-item Sick, Control, One, Fat, Food (SCOFF) questionnaire
 - In young adulthood: 5.5-17.9% of young women, 0.6-2.4% of young men



Eating disorders are increasing, but more people are seeking treatment.

A review of worldwide data found that eating disorder diagnoses more than doubled from 2000-2018. This was consistent across regions, age groups, & genders.

The overall incidence of eating disorders among teen girls & young women 15.3% in 2020 in comparison to previous years. (Zipfel 2022)

Global eating disorder prevalence increased from 3.5% to 7.8% between 2000 and 2018. (Galmiche 2019)

According to a 2021 study, the number of people entering inpatient treatment for an eating disorder doubled between 2018 and 2020. (Asch 2021)

Amid the COVID-19 pandemic, healthcare providers noticed a particularly significant uptick in the number of people seeking treatment for eating disorders.

→ 70% increase in call/chat volume in national hotlines since the pandemic started

FROM A REVIEW OF THE PAST DECADE OF RESEARCH (Miskovic-Wheatley 2023)

- AN
 - Full recovery & weight restored: 21.8% to 70.1%
 - Predictors of good outcome: AN-R (over AN-BP), younger age, no pharmacotherapy, shorter duration of illness, higher baseline BMI
- BN
 - Binge/purge abstinence in 29.9% (those who start treatment) to 35.4% (those who completed treatment)
 - Predictors of good outcome: Lower levels of shape/weight concern, less severe co-morbid depression
- BED
 - Binge abstinence in ~50.9% (in both those who start and those who complete)



PHARMACOTHERAPY:

- AN has no FDA-approved meds
- BN has one (Prozac)
- BED has one (Vyvanse)

While depression commonly occurs with most eating disorders, traditional antidepressants (i.e. SSRIs) often lack efficacy in AN.

→ Prolonged & severe starvation in AN leads to changes in brain structure & function (i.e. in the hippocampus)
(Treasure 2020, Keeler 2020)

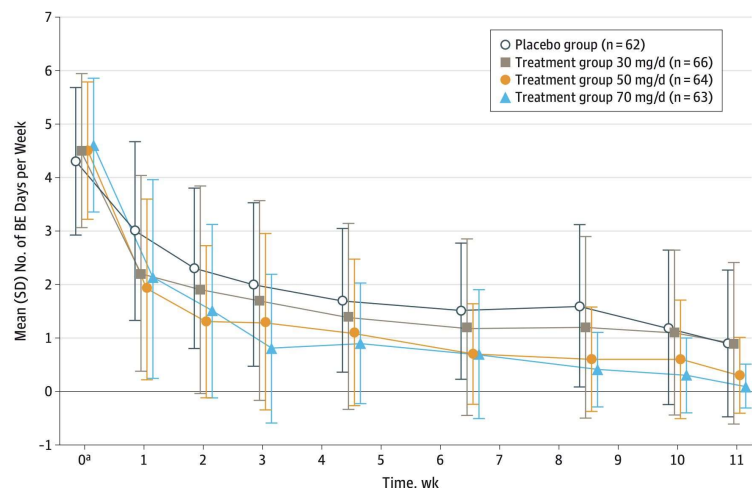
→ Those with SE-AN+TRD are 6x more likely to remain unrecovered years later (Franko 2018)

Prozac (fluoxetine) for Bulimia Nervosa

- Double-blind, placebo-controlled study (Halmi 1992)
 - 382 patients were randomly assigned to receive fluoxetine or placebo at a dose of 20mg or 60mg x 8 weeks
 - 20mg fluoxetine group:
 - reductions in binge episodes & vomiting compared with placebo (45 vs. 33% and 29 vs. 5%, respectively).
 - 60mg group had even greater improvement:
 - 67% reduction in binge eating and a 56% reduction in vomiting.

Vyvanse (lisdexamfetamine) for BED

- Randomized, double-blind, placebo-controlled trial (McElroy 2015)
 - n=255
 - 30mg, 50mg, 70mg/day
 - Baseline to week 11 (binge episodes/week):
 - PBO: -3.3
 - 30mg: -3.5
 - 50mg: -4.1
 - 70mg: -4.1



What potential medications are being explored for Eating Disorders?

TRP-8803 for BED

- TRP-8803 is a proprietary formulation of IV-infused psilocin
 - Addressing the drawbacks of oral psilocybin.
 - It provides faster onset times, better control over the psychedelic experience, and reduced treatment durations compared to traditional methods.
 - Currently undergoing phase II clinical trials for binge eating disorder (and fibromyalgia)





INITIAL DATA:

TRYP's Phase II Trial of Psilocybin for BED

The first use of psilocybin in conjunction with psychotherapy as a therapeutic intervention for BED.

Initial data from the first patient dosed The patient exhibited:

- Reduced overall anxiety
- Reduced anxiety around food
- Reduced compulsion to overeat
- Improved self-image and confidence.

These positive changes in behavior translated to significant weight loss at four weeks. There were no drug-related adverse events.

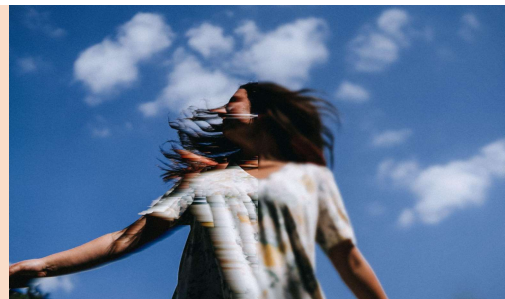
Imperial College: AN Psilocybin protocol published in 2021

PROTOCOL:

20 female participants will receive 3 oral doses of psilocybin (up to 25 mg) over a 6-week period delivered in a therapeutic environment and supported by psychological preparation & integration.

OUTCOMES:

- Psychopathology at 6 month follow-up
- Readiness/motivation to engage in therapy
- fMRI brain changes baseline-endpoint
- Changes in EEG activity (including a neuronal plasticity marker)



"In the core you are always yourself, but during an eating disorder you lose yourself. . . looking back I was just a hollow kind of body. . . you lose yourself in the process but you find yourself again and you also create new. . . I reinvented myself but then I also reconnected with what I always was."

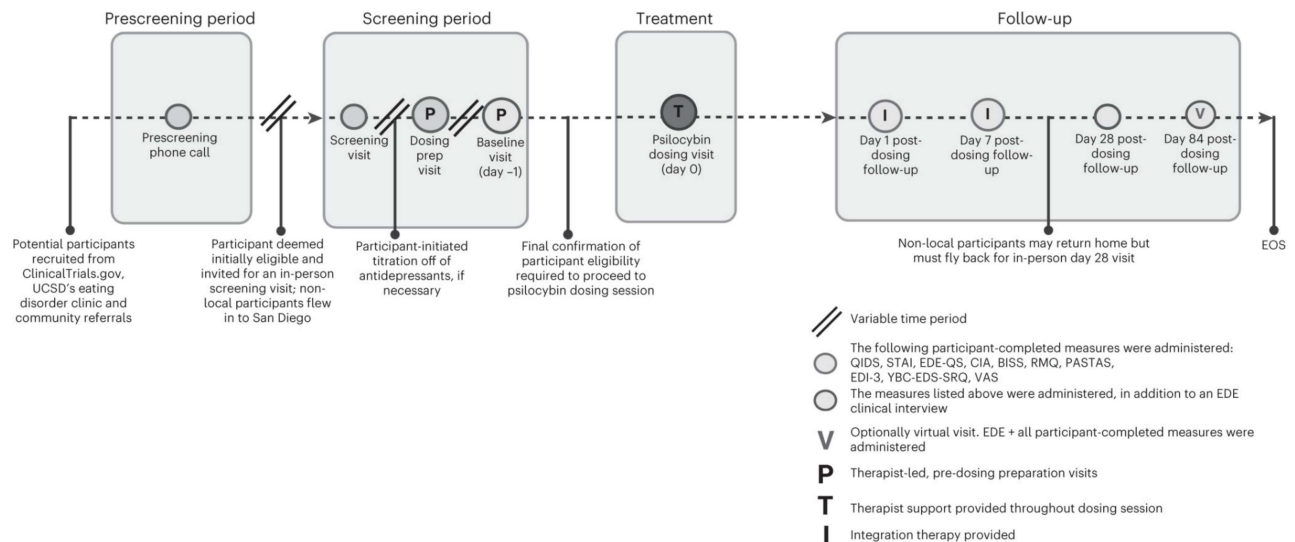
(Focus group 2, A1)

UCSD / COMPASS

Psilocybin for Anorexia Trial

PRELIMINARY RESULTS (Peck 2023):

- 10 patients with anorexia received a single 25 mg dose of synthetic psilocybin (~3.5 grams of dried psilocybin)
 - 30% of participants had clinically significant reductions in eating disorder symptoms after one month. At 3 months, this rose to 40%.
 - Participants experienced significant reductions in body shape concerns at 1-month follow-up.
 - 90% of participants found the experience to be meaningful and therapeutic.
- Psilocybin therapy was well-tolerated and no serious adverse events were reported.



(Peck 2023)

TNX-1900 for BED



- TNX-1900 (intranasal potentiated oxytocin) is in phase II development under investigator-initiated INDs at MGH as a candidate for adolescent obesity, binge eating disorder, (and bone health in autism, as well as at the University of Washington for social anxiety disorder.
- TNX-1900 is a drug-device combination product, based on an intranasal actuator device that delivers oxytocin into the nasal cavity.
- Tonix's formulation is believed to increase specificity for oxytocin receptors relative to vasopressin receptors as well as to enhance the potency of oxytocin *
- Oxytocin, when delivered via the nasal route, concentrates in the trigeminal system resulting in binding of oxytocin to receptors on neurons in the trigeminal system.
- With TNX-1900, the addition of magnesium to the oxytocin formulation enhances oxytocin receptor binding as well as its inhibitory effects on trigeminal neurons and resultant craniofacial analgesic effects.
 - "Preliminary Data Show that Oxytocin Decreases Impulsivity and Reduces Food Intake"



MDMA-Assisted Therapy for Anorexia Nervosa & Binge Eating Disorder

PROTOCOL:

WEEKS 1-3

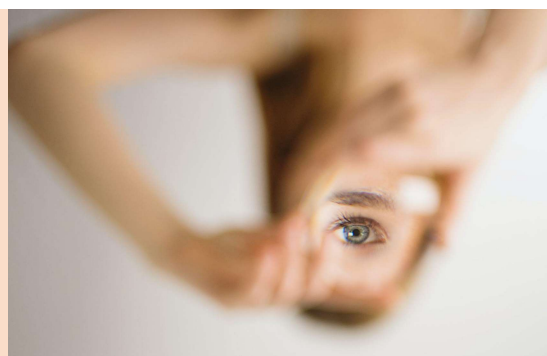
Three participant preparat sessions (individual and with caregiver)

WEEKS 4-12

Three 8-hour experimental sessions

Six individual integration sessions

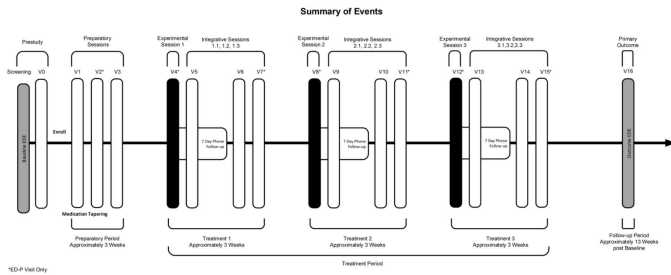
Three individual + caregiver integration sessions



MED1: An open-label, multi-site Phase 2 study of safety and feasibility of MDMA-assisted psychotherapy for eating disorders:

- 12 participants with Anorexia Nervosa
- 6 participants with Binge Eating Disorder

MAPS MED1 Study: MDMA for AN & BED (w/ fMRI add on study)



fMRI Investigator Initiated Sub-Study

To understand the neural circuitry that underlies the therapeutic effect of MDMA in AN-R in particular, a pilot functional magnetic resonance imaging (fMRI) Investigator Initiated Sub-Study (IIS) will be conducted using a select cohort of AN-R ED participants at pre-selected study sites in efforts to identify neuroimaging biomarkers of treatment response. This IIS will be conducted at the Hartford Hospital/Institute of Living in Hartford, Connecticut with Dr. Mirjana Domakonda as Clinical Investigator. Details regarding this IIS are listed separately in the fMRI IIS protocol.

Dose Selection

This study will examine the safety and feasibility of three open-label Experimental Sessions of psychotherapy assisted by flexible doses of MDMA for ED-Ps along with associated non-drug preparatory and integrative psychotherapy. Similar MDMA doses to those proposed in this study have been safely used in previous studies sponsored by MAPS.

Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 mg	40 mg	80 mg to 120 mg
2	80 mg or 120 mg	40 mg or 60 mg	80 mg to 180 mg
3	80 mg or 120 mg	40 mg or 60 mg	80 mg to 180 mg
Total Cumulative Dose			240 mg to 480 mg

*A supplemental dose will be administered unless contraindicated or refused by the ED-P. Observed response, safety, and tolerability of the previously administered dose, and discussion with the participant will all be taken into consideration as potential contraindications to the supplemental dose, and when considering escalating the initial dose in the 2nd and 3rd Experimental Sessions.

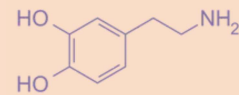
A little
neurobiology
tangent...

SEROTONIN

PLAYS A ROLE IN:

Mood & anxiety changes
Appetite
Sleep
Obsessionality
Temperament regulation
Aggression, impulsivity, suicidality
Sexual desire & function
Memory & learning
Harm avoidance / behavioral inhibition

- Impacts 40 million brain cells
- Up to 95% resides within our gut



DOPAMINE

In anorexia, for example:

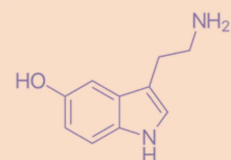
- No spikes of dopamine with eating, so food is not pleasurable and can instead feel anxiety-provoking.
- Underfiring in nucleus accumbens lead to no reinforcement of pleasure with decisions.

In binge eating disorder:

- Spikes come in anticipation of eating
- Hyper-responsiveness to food as reward

FUNCTION

- Helps control out reward & pleasure center
- Aids in decision making
- Helps regulate movement & emotional response



ACETYLCHOLINE

Caudate Nucleus

- Regulates goal directed behavior & habits
- Flexibility

Putamen:

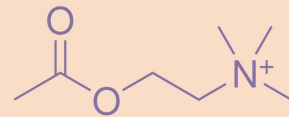
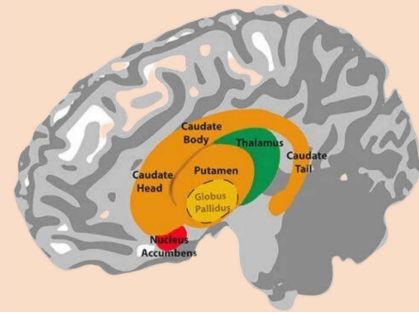
- Modulates rigid habitual behavior
- Transforms new action into automatic behavior (like learning to ride a bike)

Nucleus accumbens (NA):

- Part of the reward systems

NA + Caudate Nucleus:

- Allow us to learn new tasks



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The Evolution of Dopamine

Evolution has stumbled on dopamine as a way to get people to find things likely to propagate their genes—like sex and eating—highly rewarding, and thus reinforces the mechanism. This was all well and good when calorie-rich donuts were hard to come by, and nearly all of our energy was involved in procurement of food and propagation of our species.

Neurobiology of Binge Eating & Restricting

Normally when we're hungry, food is more rewarding (dopamine) vs. when we're full (Avena 2008, Bragulat 2010).

- When restrictive eating follows a binge, the binge becomes more rewarding. Post-binge guilt leads to further restriction, reinforcing the high reward of binge eating (Carr 2011)

In bulimia, reward pathways (and binge-purge type of anorexia) are more active than controls when viewing food (Brooks 2011)

- Recurrent purging may decrease acetylcholine in the brain, where high levels signal something unpleasant. (Avena 2012)

In anorexia, there is decreased reward sensitivity when exposed to food, and increased fear/punishment (Harrison 2010)

- Significant shift toward higher emphasis on long-term weight loss than immediate reward (Kaye 2013)
- Some religions/cultures see denial of pleasure as a good thing, but when truly physically hungry, shifting focus in the brain to drive for thinness can keep people stuck for years.

When we lose weight, we lose it from the entire body, not just where we want it to.
→ The brain, as the fattiest organ in the body, is highly sensitive to malnutrition.

These traits exist before eating disorders and persist after recovery:

- Those who binge eat are more likely to abuse drugs/alcohol (Ross 1999)
- Those with restrictive eating tend to report higher levels of ascetic behaviors (Keating 2012)

Neurobiology of Eating Disorders: ACETYLCHOLINE

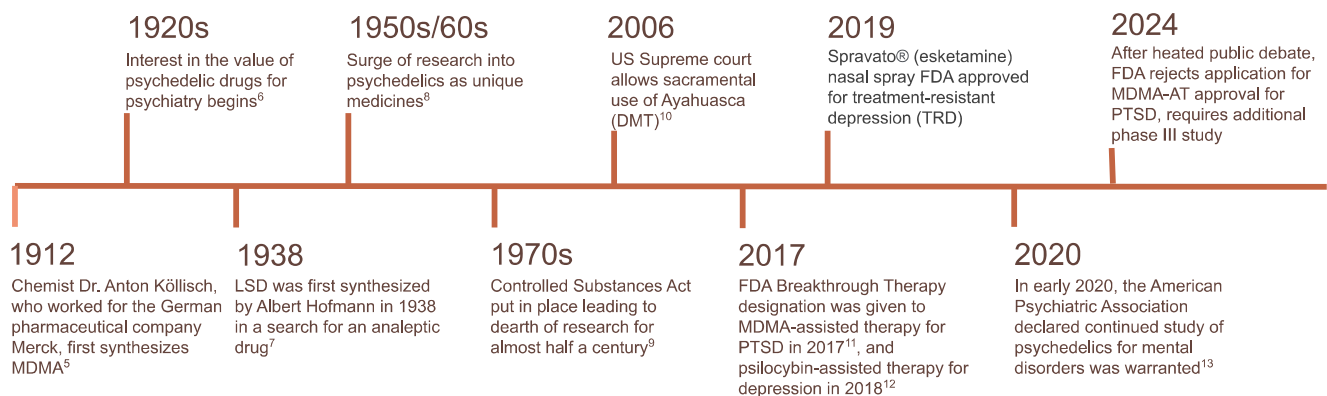
Individuals with anorexia have been characterized by an altered cholinergic system with a decrease in the release of acetylcholine.

- The caudate is responsible for goal-directed behavior:
 - Cholinergic dysfunction in the caudate promotes habit formation and maladaptive behavior.
- The putamen modulates rigid habitual behavior:
 - Habits emerge from goal-directed behavior after behaviors become automatic as a result of repetition.
 - Habits are driven by environmental stimuli and are independent of outcome.

“Dysregulation of habit formation is key to eating disorders...” (Therfall 2012)

Psychedelics & Eating Disorders

WESTERN HISTORY OF PSYCHEDELICS



Positive effects of psychedelics on depression and wellbeing scores in individuals with eating disorders

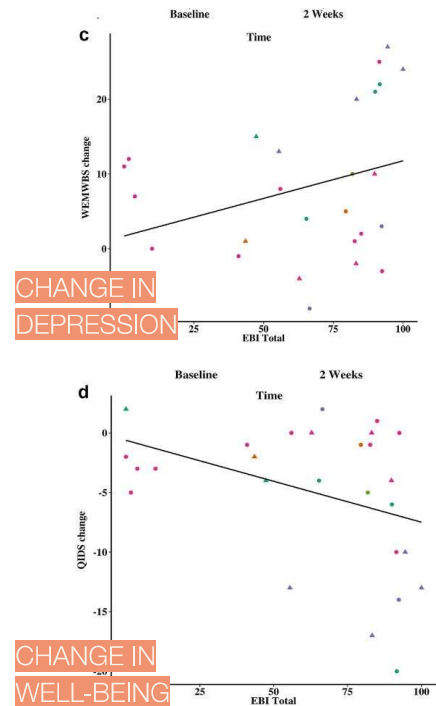
Data collected online from people planning to take a psychedelic.

38 participants reporting a lifetime ED diagnosis completed depression & wellbeing measurement scales 1-2 weeks before & after their psychedelic experience.

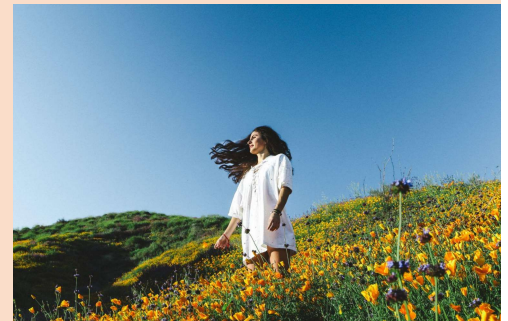
RESULTS:

- Significant improvements in depression and wellbeing scores following the psychedelic experience.
- Marginal evidence of a correlation between emotional breakthrough and the relevant mental health improvements.

ML Spriggs, H Kettner, RL Carhart-Harris, 2020



HOW PSYCHEDELICS MAY HELP WITH EATING DISORDERS



Though theoretical mechanisms of action of psychedelic medicines are still being investigated, a growing body of research points towards the following ways they may help people with eating disorders:

- 1) The potential to alleviate symptoms that relate to serotonergic signaling and cognitive inflexibility
- 2) The induction of desirable brain states that might accelerate therapeutic processes (and make eating disorders therapies easier to receive)

“We need to reframe the question. It’s not necessarily, ‘How do we treat anorexia?’”. Instead, the problem we need to address is, “How do we help people engage in the process of recovery?”

Meg Spriggs, PhD
Centre for Psychedelic Research, Imperial College London

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Components of Psychedelic-Assisted Therapy



PREPARATION SESSION

- Medical screening & education
- Establish rapport & obtain consent
- Set treatment goals



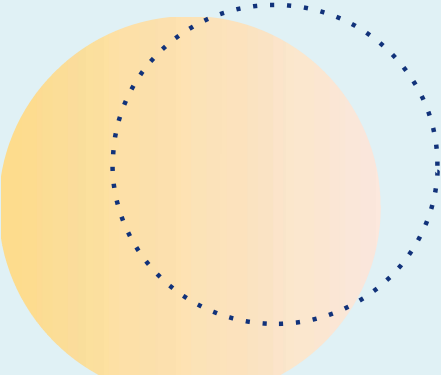
DOSING SESSION

- (4-6 dosing sessions)
- Intention setting prior to dosing
- Brief/limited processing afterwards



INTEGRATION SESSION

- Within 1-2 days of dosing session
- Explore material that emerged
 - Draw connections and meaning related to intentions and day-to-day life

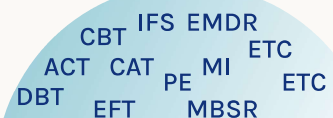


How Therapy Works

(Process > Method)

Boiling down the alphabet soup of Psychotherapy (aka how to change your mind... and your patterns)

- Let's start with the WHY
 - Why are we doing this? What are we 'treating'? What is our goal?
- It all boils down to these: **ENTRENCHED MALADAPTIVE PATTERNS**
 - Patterns of behavior (response) that get us in trouble (maladaptive)
 - There's a reason why these patterns are entrenched (sticky)
 - As patterns, they're likely to recur



CBT IFS EMDR
ACT CAT PE MI ETC
DBT EFT MBSR

Where do these entrenched maladaptive patterns come from?

- If it's hysterical, it's historical (aka causal misattributions from childhood)
 - Childhood traumas and adversities
 - Not just traumas – also not understanding a human event that occurred in front of your eyes in childhood, that is carried on as a schematic memory
 - **Triggers are friends to follow** (they show you the path... your work)
 - If you wait long enough (or take a psychedelic :), transference heats up, old patterns surface
 - Then you have something to work with

How Change Occurs

Mechanism #1: Extinction

- Pavlovian conditioning
 - For example, If you're a combat veteran with PTSD and you startle every time there's a loud noise.
 - If you reactivate that startle mechanism with a loud noise, but do it in a safe & supported place, then the cortex learns the war is over, you don't need that startle reflex, everything is ok (aka corrective experiences)
 - The cortex sends inhibitory signals into the midbrain, and blocks the expression of the fear response (even though amygdala still lights up)
- Extinction is not necessarily permanent
- Useful mechanism of change for very repetitive responses

How Change Occurs

Mechanism #2: Memory Reconsolidation

- When the original pattern of the neural networks that represent this pattern are in a state of activation, AND there's new information that the person is exposed, then there's a prediction error
 - For a period of several hours, the new information can reprogram the neural networks in such a way that the prediction is erased & a new one takes its place
- The activation of the old pattern needs to be fairly vivid for this to occur
- More of a lasting (even permanent) mechanism of change

How Change Occurs

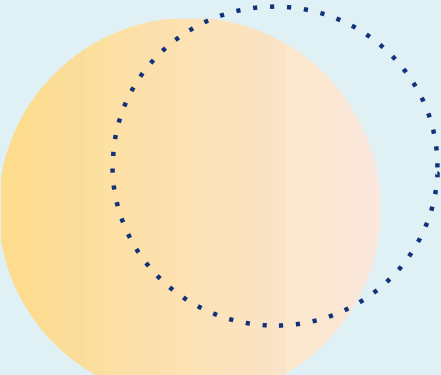
Mechanism #2b: Corrective Emotional Experiences

- Described by Alexander and French in 1946
- When a client in therapy gets into a situation where they're expecting a certain negative response from the therapist (for example, they think they're going to be judged or thrown out of therapy)
 - This creates a prediction error, aka a golden opportunity for extinction or rememory consolidation to take place
- One of the core tenets of emotion-focused therapy
 - And one of the two main ways of transforming emotion
 - New lived experience with a supportive other is healing
 - Disconfirms pathogenic beliefs
 - Provides interpersonal soothing



More Therapy Thoughts

- 95% of mental activity is going on outside of our conscious awareness
 - Explains why cognitive approaches alone don't always work
- Core values (part of an internalized system of self control that other mammals don't have) are *much more challenging* to change in therapy
 - When we're doing things that aren't "good according to our values", we feel shame/guilt
 - They start in the cortex but end up in the limbic system (and therefore have a lot of motivational power)
 - Shame is the distance between current self-evaluation and your core values
- Cognitive dissonance: Theory by Festinger that proposes inconsistency among beliefs or behaviors leads to an uncomfortable psychological tension (dissonance)
 - The brain then changes one of the inconsistent elements to reduce the dissonance and restore harmony



How Psychedelics Work

(Process > Method)

A Unifying Brain Theory (aka “the Free Energy Principle” and the Entropic Brain)

- It's about uncertainty reduction: biological systems resist a natural tendency to disorder
- The brain is constantly generating and updating a mental model of the environment that tries to predict upcoming sensory input using “prior beliefs”
- The predictive models are layered on top of each other in a hierarchy
 - The model is used to generate predictions of sensory input that are compared to actual sensory input
 - The higher levels send predictions down the hierarchy
 - The lower levels report sensory input data up the hierarchy
- This comparison results in prediction errors that are then used to update and revise the mental model
 - When the top down predictions don't match the bottom-up sensory input, the model either:
 - Updates its “priors” based on the new sensory information, or
 - Ignores the sensory inputs and maintains its “prior beliefs”



REBUS: RELaxed Beliefs Under pSychedelics Aka How Psychedelics “Relax” Tightly-held Prior Beliefs

- Initial ‘blast’ of 5-HT_{2A}R stimulation has a residual influence on brain network dynamics and associated cognition.
 - This is thought to have a ‘loosening’ or ‘lubricating’ influence on rigid thinking and this is hypothesized to be conducive to improved psychological wellbeing (Carhart-Harris 2016)
- Psychedelics relax the weight of held beliefs/rules/restrictions, allowing them to be more readily changed
 - Psychedelics “heat up” the brain, increasing plasticity and weakening the influence of prior beliefs
 - As the brain “cools”, the hierarchy re-forms, though perhaps in a new configuration than before
 - Explains how lasting changes may persist after the substance is gone
- Psychedelics show particular promise for conditions associated with too-rigid thought patterns
 - i.e. “disorders that may rest on particularly rigid high-level priors that dominate cognition.”
 - In these conditions, new information can't revise the existing story of how things are, because strong priors suppress the new info before it can update anything.
- Psychedelics relax the strong top-down “prior beliefs” (i.e. ‘I can't eat that because it will make me fat’) and boost the bottom-up sensory inputs (i.e. intuitive, mindful eating)

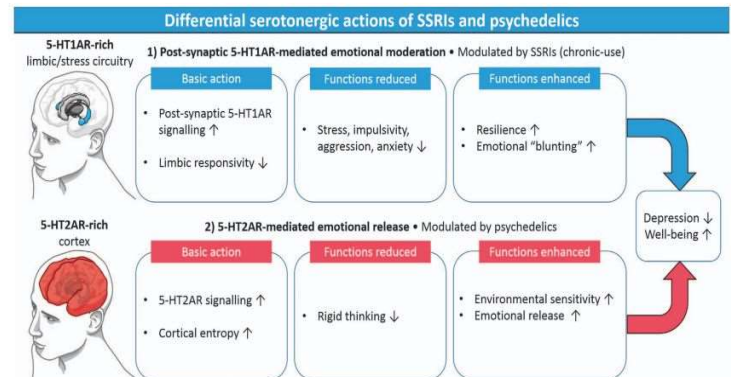
A TALE OF TWO SEROTONIN RECEPTORS: Psychedelics vs. SSRIs

SSRIs

5-HT_{1A} receptor signaling --> reduced limbic responsiveness, aka emotional blunting.

Psychedelics

5HT_{2A}R signaling → enhanced sensitivity + emotional release, combined with psychological support = therapeutically potent



The therapeutic potential of psychedelic drugs
RL Carhart-Harris and GM Goodwin

The **serotonin 5-HT_{2A}R** receptor is expressed all over the brain, particularly in regions associated with cognitive functions and social interactions. Stimulation of this receptor has been directly linked to cognitive flexibility, enhanced imagination, and creative thinking.

Psilocybin



History of psychiatry

Psilocybin in the treatment of anorexia
nervosa: The English transition of a French
1959 case study

La psilocybine dans le traitement de l'anorexie
mentale : la traduction en anglais d'une étude
de cas française de 1959

Vincent Verroust^{a, b, c, d}, Rayyan Zafar^e, Meg J. Spriggs^e

Psilocybin is a psychotropic molecule that is a partial agonist of serotonin 2A receptors and is the main psychoactive compound in hallucinogenic mushrooms. After the observation in 1953 in Mexico of ritual practices involving ingestion of such mushrooms, psilocybin was chemically characterized and synthesized in 1958 thanks to the collaboration between the *Muséum national d'Histoire naturelle* in France and the Sandoz pharmaceutical laboratories in Switzerland. The interest of this substance in psychiatric therapy was then evaluated for the first time at the Sainte-Anne Hospital in Paris, by the team of Professor Jean Delay. Among the patients who received this substance was a 35-year-old woman who was hospitalized for compulsive manifestations emblematic of anorexia nervosa and who experienced an immediate and lasting improvement. The original 1959 article (published in the *Annales de la Société Médico-Psychologique*) gives details of the patient's family background, biography and clinical examination. It then outlines the observations after two injections of psilocybin four days apart, in particular the autobiographical verbal statements that allowed the patient to understand the psychogenesis of her illness. After a long hiatus, psilocybin is once again the subject of medical research, with clinical trials now underway assessing psilocybin in the treatment of anorexia nervosa ([NCT04505189](#); [NCT04052568](#); [NCT04661514](#)) and this 1959 case study, is the first known demonstration of the safety and efficacy of psilocybin treatment of anorexia nervosa. This case study thus provides an interesting insight into possible therapeutic mechanisms and is of great interest to the field moving forward.

Single-Dose Psilocybin for MDD



In this phase 2 clinical trial, 104 adult participants were randomized to receive a single dose of psilocybin or niacin placebo administered alongside psychological support.

Prior to dosing, each participant spent 6-8 hours with study therapists preparing for their experience. The dosing session lasted 7-10 hours and was conducted in a comfortable room under staff supervision. Following this, subjects completed a 4-hour integration session.

RESULTS

- The improvements in depression symptoms in the psilocybin group were observed within 8 days of psilocybin dosing and those improvements were maintained across the 6-week follow-up period.
- On average, participants who received the single dose of psilocybin had a 19.1-point drop in the MADRS depression scale compared with the placebo group, who experienced a 6.8-point drop, a 12.3-point difference.
- At the 6-week endpoint, about 60% of the people who took the psilocybin dose had a response, meaning they'd had a 50% reduction in their starting depression score, and 44% of them were in remission, meaning that their score had dropped to a level that is close to how people function when they're not depressed.
 - Only 20% of the niacin people had a response at week six, and only 11% of the niacin people had remission.

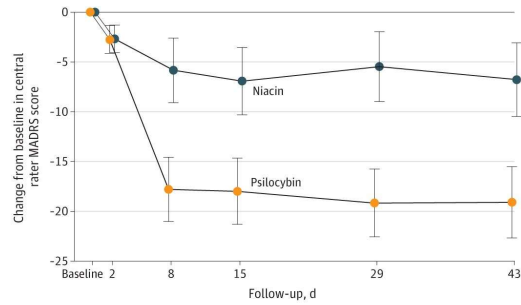
(Raison et al., 2023)

QUESTION

What is the efficacy and safety of single-dose psilocybin in patients with major depressive disorder?

CONCLUSION

A 25-mg dose of psilocybin was associated with a clinically significant sustained reduction in depressive symptoms and functional disability, without serious adverse events.



POPULATION

52 Women
52 Men



Adults aged 21-65 years
with major depressive disorder
with current episode ≥ 60 days

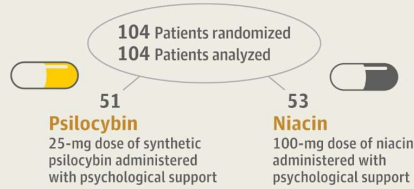
Mean age: 41 years

LOCATIONS

11
Research sites
in the US



INTERVENTION



PRIMARY OUTCOME

Difference in change in mean Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to day 43 (range, 0-60; higher scores indicate more severe depression)

FINDINGS

Mean change in score from baseline

Psilocybin

-19.1 (95% CI, -22.7 to -15.5)

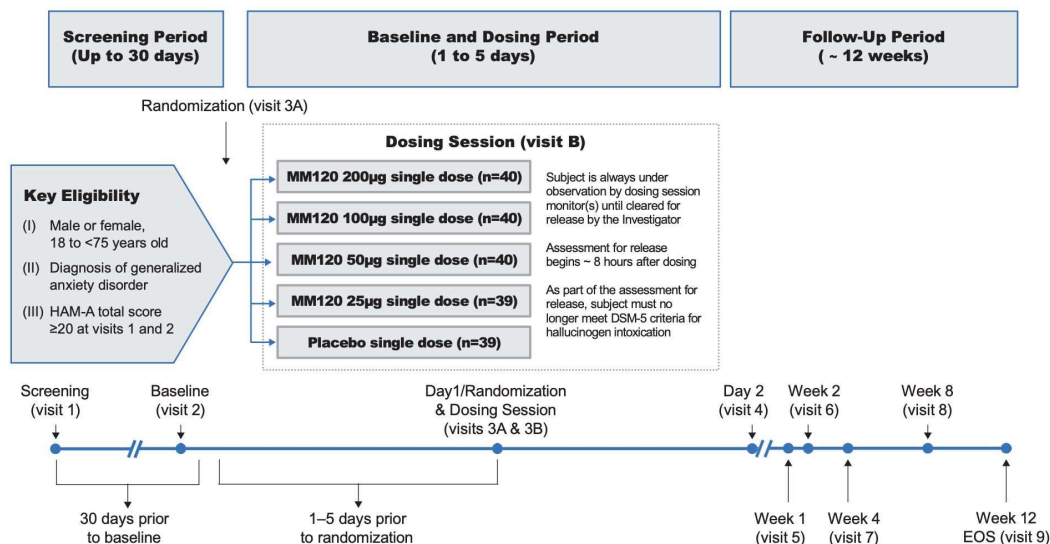
Niacin

-6.8 (95% CI, -10.5 to -3.1)

Psilocybin was associated with significantly reduced MADRS scores vs niacin:

Mean between-group difference in change in score, **-12.3** (95% CI, -17.5 to -7.2); $P < .001$

LSD



RAPID AND DURABLE RESPONSE TO A SINGLE DOSE OF MM120 (LYSERGIDE) IN GENERALIZED ANXIETY DISORDER: A Dose-Optimization Study

- Phase 2b multi-center, randomized, double-blind, placebo-controlled dose-finding study
 - evaluated the effect of 4 doses of MM120 (25, 50, 100, or 200µg) compared to placebo in 198 individuals with moderate-to-severe GAD
- A single dose of MM120 at 100µg and 200µg was sufficient to produce significant improvement in anxiety symptoms
 - as early as day 2 after dosing**
 - sustained through week 12**
- First study to demonstrate a benefit 1 day after treatment** in participants with GAD.
 - While benzodiazepines have shown acute efficacy in patients with GAD, they have dependency and other risk factors.
 - In a meta-analysis of 21 placebo-controlled trials for GAD, medications in current use demonstrated only modest benefits, with an overall Cohen's d effect size of 0.39
 - In comparison, at week 4, MM120 100µg exhibited an effect size of 0.88
 - Indicating **a greater therapeutic benefit with MM120 than any currently approved therapy** in GAD
 - without the burden of daily medication.
- The 7.6-point reduction in HAMA-A with MM120 100µg at week 4 is more than 2x that observed with other GAD treatments, including the recommended first-line treatments.
- The improvement in anxiety symptoms with MM120 100µg was sustained through week 12
 - Demonstrates the durability of the response despite participants having received only 1 dose of the treatment.
- At week 4, 78% of participants showed a HAM-A response, and 50% were in remission.
 - These rates are higher than what has been previously reported with escitalopram, paroxetine, and sertraline.

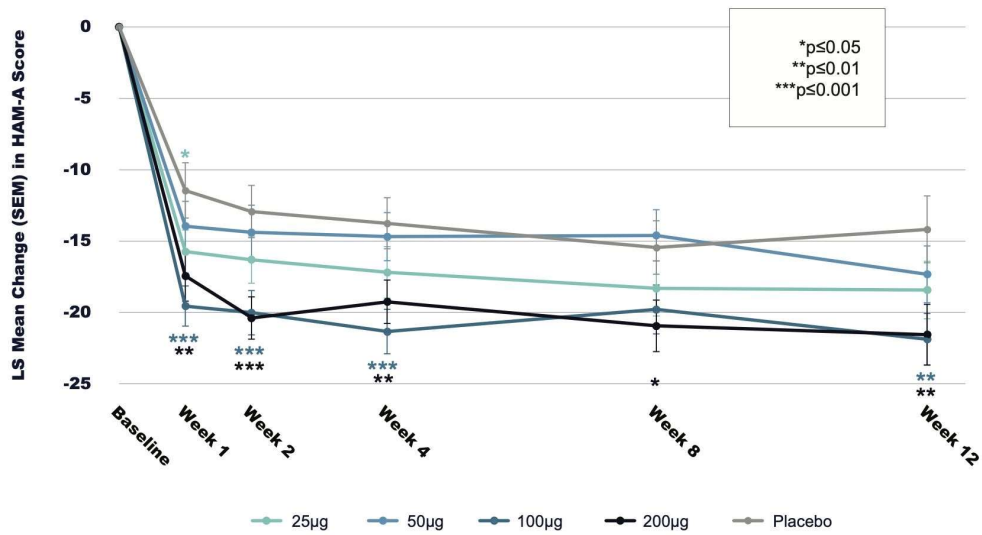
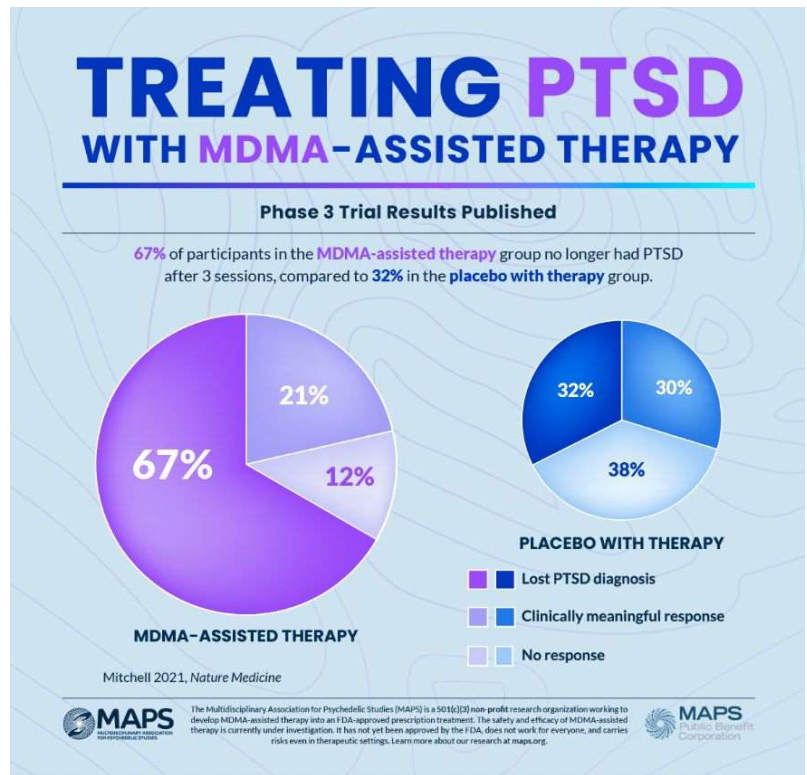


Figure 3: Least-Squares Mean Change From Baseline in HAM-A
 The MM120 100µg and 200µg groups demonstrated statistically and clinically significant reductions in HAM-A from baseline to week 12.

MDMA

Phase III study results: MDMA

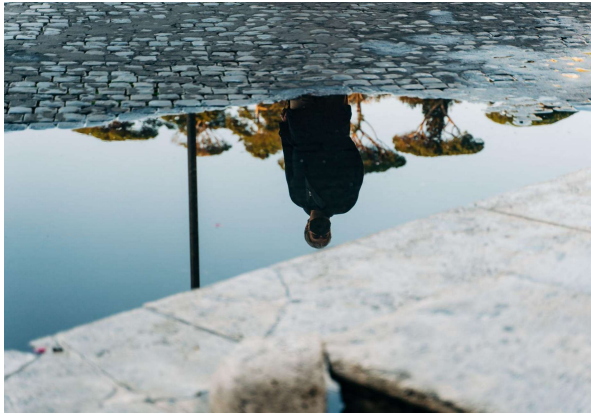
- 90 participants
 - Duration of PTSD diagnosis:
 - 14.8 years



Why MDMA for eating disorders?

- 1 TRUST: MDMA increases oxytocin levels, which may strengthen the therapeutic alliance
- 2 FEAR REDUCTION: MDMA increases ventromedial prefrontal activity and decreases amygdala activity, which may improve emotional regulation and decrease avoidance
- 3 EMOTIONAL ENGAGEMENT: MDMA increases norepinephrine release and circulating cortisol levels, which may facilitate emotional engagement and enhance extinction of learned fear association

MDMA-assisted therapy significantly reduced eating disorder symptoms of adults with severe PTSD in a randomized placebo-controlled trial.



90 individuals with severe PTSD received treatment in a double-blind, placebo-controlled pivotal trial of MDMA-AT.

At baseline, 15% of the PTSD participants had EAT-26 scores in the clinical range (≥ 20), and 31.5% had scores in the high-risk range (≥ 11) despite the absence of purging or low weight.

RESULTS:

After study completion, there was a significant reduction in total EAT-26 scores among MDMA group compared to placebo ($p = .03$).

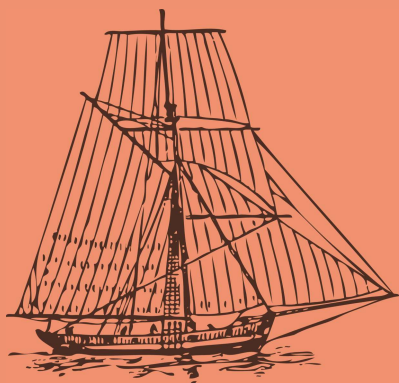
There were significant reductions in total EAT-26 scores in women with high EAT-26 scores ≥ 11 and ≥ 20 following MDMA.

(Mitchel et al., 2021)

Ketamine

KETAMINE: From anesthesia to psychiatry

- 1950s PCP was in use as an anesthetic but left people in a psychotic state
- 1962 Developed by Calvin Stevens at Parke Davis Labs
- 1965 Professor Edward Domino conducts 1st human studies
Calls ketamine a potent psychedelic; coins the term “dissociative anesthetic”
- 1970 Approved for human use by the US FDA in 1970 for anesthesia
Widely used in Vietnam war as a battlefield anesthetic
- 2000 First controlled study of ketamine for major depressive disorder (MDD)
- 2019 Spravato (esketamine) nasal spray FDA approved for treatment-resistant depression (TRD)



PSYCHONAUT

coined by Ernst Jünger which in 1970
which means “Sailors of the soul”

Psychonauts were known to
“Seek altered states of consciousness to
search for truth in the unconscious mind”

KETAMINE'S PSYCHEDELIC HISTORY

- 1950s Sensory deprivation tank developed by neurophysiologist Dr. John Lilly: "Does the brain need external stimulation to remain conscious?" Lilly built the world's first isolation tank to find out. And true to form, he was the first test subject. He'd soon learn that no, the brain didn't go unconscious when devoid of sensory input – it tripped.
- 1970s Late 60s, early 70s, ketamine street use commenced – exploring one's mind & escaping trauma from Vietnam War. Term "psychonaut" was coined.
- 1978 First books written on ketamine as a psychedelic, i.e. *Journeys into the Bright World* by Marcia Moore – *"Why are the 'mind-manifesting' drugs still regarded with so much fear? Can it be because modern science still lingers on the threshold of the unconscious, hesitating to knock too loudly for fear of what might be revealed if the door should open?" (Moore, 1978, p. 4)*
- 1990s Ketamine rises in popularity as a party drug – becomes classified as schedule III by DEA
- 1994 Ketamine studied as a model of psychosis/schizophrenia

THE PSYCHONAUT YOU'VE NEVER HEARD OF...

John Lilly: "Well, I discovered that dolphins have personalities and are valuable people. I began to wonder about the capabilities of whales, which have much larger brains.

There's a threshold of brain size for language as we know it, and as far as I can make out it's about 800 grams. Anybody below that, like the chimpanzee or the gorilla can't learn to speak a language. But above that threshold language is acquired very rapidly, as in a baby. Well, this means that the dolphins' lives are probably as complicated as ours. But what about their spiritual life? Can they get out of their bodies and travel? Are they extraterrestrial? I asked those kinds of questions. Most people wouldn't ask them.

So I took ketamine by the tank at Marine World in Redwood City. I got into the tank, and I had a microphone near my head and an underwater speaker that went down into the dolphin tank. My microphone hit their loudspeaker underwater. So I waited. Then I began to feel that I was in direct contact with them, and when one of them whistled, a long whistle, it went from my feet right up to my head. I went straight out of my body. They took me to the dolphin group mind. Boy, that was scary! I shouted and carried on. I said, "I can't even handle one dolphin, much less a group mind of dolphins!"

So instead of that they put me into a whale group mind, and when you have an experience like that, you realize that some of the LSD experiences may have been in those group minds, not in outer space at all. Since then I suspect that they're all ready to talk and carry on with us if we are not so blind. So we open up pathways to them with ketamine, LSD, swimming with them, falling in love with them, and them falling in love with us. All the non- scientific ways."

3 Brain Pathways to Induce Hallucinations

- 1) Activation of dopamine D2 receptors (D2Rs) with psychostimulants
- 2) Activation of serotonin 5HT2A receptors (HT2ARs) with psychedelics
- 3) Blockage of glutamate NMDA receptors (NMDARs) with dissociative anesthetics

	PSYCHOSTIMULANTS (cocaine, amphetamine)	DISSOCIATIVE ANESTHETICS (PCP, ketamine)	CLASSIC PSYCHEDELICS (LSD, psilocybin)	SCHIZOPHRENIA (paranoid)
MECHANISM	D2R activation	NMDAR blockage	5HT2AR activation	D2R activation & NMDAR blockage
TYPE OF HALLUCINATION	Auditory	Visual	Visual	Auditory
TYPE OF DELUSION	Paranoid	Mixed	Mystical	Paranoid
BEHAVIOR	Agitation	Social withdrawal	Mystical feelings	Variable
INSIGHT	No	Some	Yes	No

(Pang 2016)

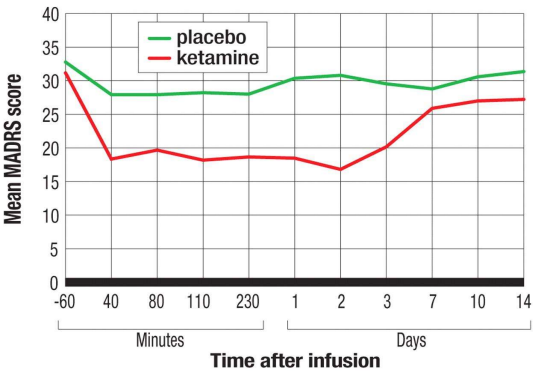
USES OF
KETAMINE

ON LABEL USES

Anesthesia

OFF-LABEL USES:

- Chronic Pain
- Major depressive disorder
- Suicidality
- Post-traumatic stress disorder (PTSD)
- Bipolar I and II depressive phases
- Obsessive-compulsive disorder (OCD)
- Psychological reactions to physical illness
- Personality disorders
- Substance use disorders
- Eating Disorders



Source: Carlos Zarate Jr., M.D., et al., Archives of General Psychiatry, August 2010

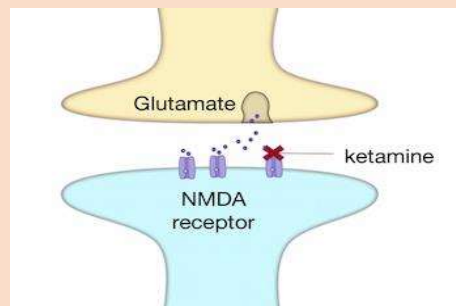
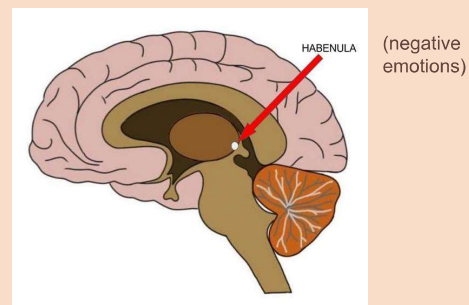
Treatment	Effectiveness
Ketamine Infusion	50-70%
Electro Convulsive Therapy	50-60%
Multiple Antidepressants	48%*
Single Antidepressant	36%*
Sugar Pill/Placebo	32%

“Recent data suggest that ketamine, given intravenously, might be the most important breakthrough in antidepressant treatment in decades.”

THOMAS INSEL, MD
Director National Institute of Mental Health

How Does Ketamine work?

- 1) Blocks NMDA receptors and inhibits the effect of glutamate in the brain (the main excitatory neurotransmitter)²⁶
- 2) Glutamate plays a role in “long-term potentiation” (neurons that fire together, wire together)²⁶
- 3) Turns off “burst mode” in the lateral habenula (stress / negative emotions)²⁶



Yang et al., Nature 2018

Ketamine's Uses in Psychiatry



PSYCHEDELIC

Ketamine-Assisted Psychotherapy (KAP)

IM or IV journeys in the ketamine room, with brief therapy before and after, and psychotherapeutic integration sessions in between



PSYCHOLYTIC

Ketamine-Assisted Psychotherapy (KAP)

Lozenges or nasal spray taken before the session to facilitate openness & deeper work, with the therapist present for the entire session.



PSYCHIATRIC

Ketamine or Spravato (esketamine) as a medical intervention.

In office, usually starting at twice a week then decreasing frequency as tolerated. Home maintenance dosing optional (lozenge or nasal spray).

KETAMINE FOR EATING DISORDERS

Indication	Study Sample	Treatment Protocol	Results	Citation
AN	n = 15 Avg age: 33,3	2–15 IV infusions at 20 mg/h for 10 hr + nalmeferene	9 responded & had prolonged remission with 2-9 infusions. Response associated with a decrease in compulsion score.	Mills et al., 1998
AN + depression	n = 1 Age: 29	9 IV infusions at 0.5mg/kg over 40 min	Partial remission/reduction in depression and suicidality	Dechant et al., 2020
AN + depression	n = 1 Age: 29	4 infusions at 0.75 mg/kg titrated to 1.2 mg/kg over 45 min + keto diet	Reduced depression & obsessive/compulsive tendencies after dose 4. Complete & sustained recovery for 6 mo after.	Scolnick et al., 2020
BN (binge/purge type)	n = 1 Age: 21	18 IV infusions at 0.5 mg/kg over 40 min + therapy	Complete and sustained remission of ED symptoms	Ragnhildstveit et al., 2021
Anorexia & binge/purge ED with TRD	n = 4 Avg age: 36.8	5–9 IV or IM doses at 0.5 mg/kg titrated to 0.9 mg/kg over 30–90 min	Clinically meaningful changes in depression and modest changes in anxiety & disordered eating.	Schwartz et al., 2021
AN-BP; AN/EDNOS + depression; BN-BP	Review	IV and IM ketamine	Results are encouraging & suggest therapeutic value—but limited to case series & reports on AN. More research needed.	Ragnhildstveit et al., 2021
AN/BN + comorbid depression & anxiety	n = 5 Avg Age: 32,2	4 weekly IM injections in a group-setting	4/5 had significant depression improvements. 2/5 had significant improvements in anxiety.	Robison et al., 2022

....KETAMINE FOR EATING DISORDERS

Indication	Study Sample	Treatment Protocol	Results	Citation
AN + depression	n = 4	IM ketamine & IN esketamine (3-23 doses)	All reported subjective decreases in depression, but only those given esketamine had reductions in PHQ-9 score over time. Weight remained stable with no SAEs.	Keeler, et al., 2023
ED + comorbid psychiatric diagnoses	n = 2 Ages: 14-19	KAP – SL ketamine, followed by IM ketamine + therapy	Experienced symptomatic & functional improvements. Treatment was well-tolerated.	Wolfson et al., 2023
AN (recovered but with persistent ED thoughts & behaviors)	n = 5	Ketogenic diet + 6 ketamine infusions over 6 months	Significant improvements in clinical impairment, eating concerns, shape & weight concerns, acceptance of self & body, social & emotional connection. Weight remained stable, except for one participant who relapsed 4 mo after treatment and off TKD.	Calabrese et al., 2022
Chronic & enduring AN	n = 2	Ketogenic diet + ketamine infusions	Led to complete & durable remission in both patients.	Scolnick & Beckwith, 2023

Treatment of compulsive behavior in eating disorders with ketamine

20mg/h of IV ketamine for 10h with 20mg twice daily nalmefene (as opioid antagonist) to treat 15 chronic ED patients, all resistant to several other forms of treatment.

RESULTS:

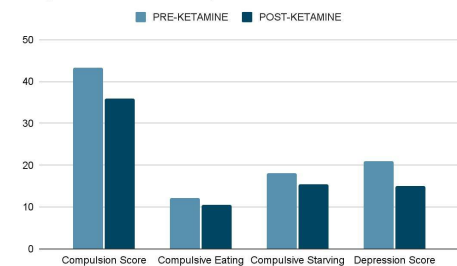
9 (responders) showed prolonged remission when treated with 2-9 infusions at intervals of 5 days to 3 weeks.

- Clinical response was linked to a significant decrease in Compulsion:
Before ketamine: 44.0 +/- 2.5; After ketamine: 27.0 +/- 3.5

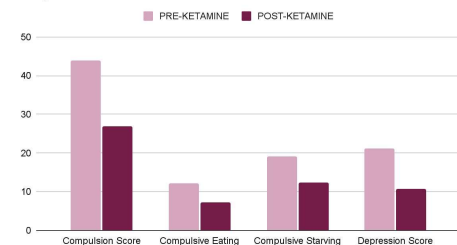
6 patients were non-responders

- No significant response to at least 5 infusions

Responders and Non-Responders



Responders



(Mills et al., 1998)

Group-Based KAP (G-KAP) for eating disorders

Novel group-based KAP protocol developed and tested out at a residential eating disorder treatment center (Center for Change):

- * Groups of 4 adults with weekly group preparation, processing and integration + individual integration sessions
- * Collaborative care model with G-KAP integrated with multidisciplinary team (medical, dietary, specialized ED therapy, family therapy...)

STUDY OUTCOMES

Improvements in depression & anxiety (PHQ-9, GAD-7 scores)

G-KAP was well-tolerated and safe

Feasibility of implementing G-KAP for patients in residential treatment center

Reduced cost when using a group-based format

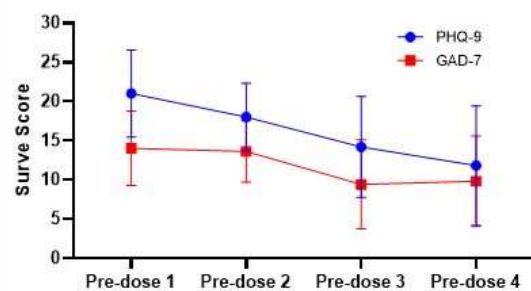
Paper published in May 2022

(Robison et al., 2022)

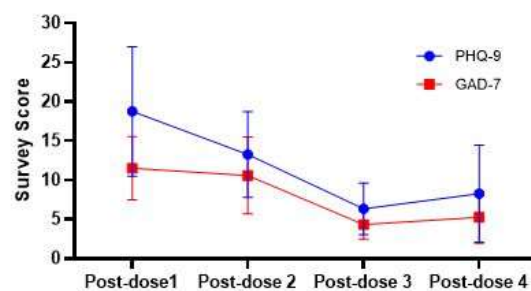


RESULTS: G-KAP for eating disorders

Mean pre-dose survey scores



Mean 4-hour post-dose survey scores



FIGURES: Mean pre-dose and 4-hour post dose PHQ-9 and GAD-7 scores for the 5 participants receiving IM ketamine treatment across the 4-week study period

PHQ-9 = Depression score GAD-7 = Anxiety score

(Robison et al., 2022)

“Trying ketamine allowed me to see the possibility of a life I could have. While the effects did not last, my very first experience snapped me out of a state of life-long, deep disconnection that I didn't even know I had been experiencing. Suddenly, I was able to live in the world in the way people had always described it. Though I am still trying to figure out how to attain that level of connection after catching a glimpse, that one experience was so essential. I could finally feel hunger and fullness cues. I felt what it's like to live in a body, instead of living a short distance from it. I felt connected to others and genuinely cared about their well-being. I felt human for the first time in a long time.”

– G-KAP PARTICIPANT

Pilot study of KAP for anorexia nervosa, with caregiver involvement

Focuses on developing of self-regulation and emotion-processing skills. This increases self-efficacy and confidence in patient's own ability to move through stress/distress.

Emphasizes the benefit of caregiver/family support and involvement.

PROTOCOL

Preparation: 2-3 sessions (caregiver involvement if appropriate)

Ketamine dosing: Intention-setting before & processing after

Caregiver skills development: Emotion coaching sessions provided to caregivers concurrently

Integration: 1-2 sessions (caregiver involvement if appropriate)

(Robison et al., UNPUBLISHED DATA)



KAP+Caregiver support for Anorexia

5 patients with moderate-severe anorexia attended 9 total sessions.

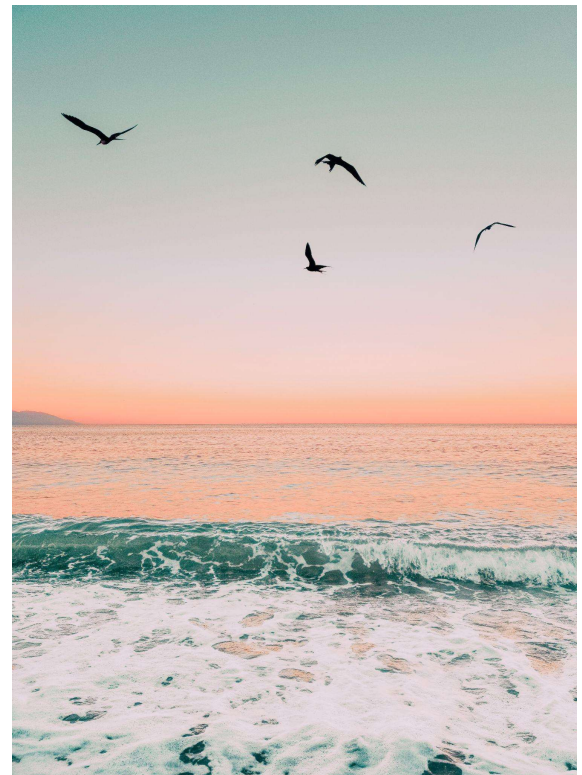
Ketamine was delivered IM with dose ranges of 40-100mg.

Caregivers/support persons attended two virtual coaching sessions to learn & practice skills to support the patient at home.

RESULTS:

Scale	Avg Score Before	Avg Score After
Depression (PHQ-9)	16	11.8
Anxiety (GAD-7)	14.2	9.2
Eating Disorder (EDE)	4.15	3.3
Embodiment (EES)	68.4	80

(Robison et al., UNPUBLISHED DATA)



“ The alleviation of suffering through an experience of the sacred has a central role in health & healing across many traditions. This long history suggests that a spiritual perspective on healing suffering & mental illness may offer promise and balance to Western medicine.

Podrebarac, O'Donnell, Mennenga, Owens, Malone, Duane, & Bogenschutz (NYU Dept of Psychiatry)

Thank you

Slides available here: tinyurl.com/cfcwebinar2024

Podcast: psychedelictherapyfrontiers.com

Volunteer for a study: cedarclinicalresearch.com

Clinics & trainings: numinus.com

Work with Reid (clinic): doctorreid.com

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