Healing Trauma, Addiction and Depression with Psychedelic-Assisted Psychotherapy

LARRY LEEMAN MD, MPH

NEW MEXICO AAFP WINTER CONFERENCE

FEBRUARY 27, 2021

Disclosure

- No financial disclosers
- MDMA and Psilocybin are schedule 1 drugs not currently FDA approved for clinical use outside of FDA supported research
- Ketamine is approved as anesthetic and is being used "off-label" for depression and PTSD with support from physician groups including APA

Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse.

Schedule III drugs, substances, or chemicals are defined as drugs with a moderate to low potential for physical and psychological dependence.

Learning Objectives

- Understand the relationship between trauma and addiction.
- Describe the potential mechanisms by which psilocybin, MDMDA, and ketamine assisted psychotherapy can improve mental health.
- Discuss the current models of ketamine use for treatment resistant depression and PTSD.
- Understand the therapeutic approach and evidence supporting the use of MDMA assisted psychotherapy for PTSD in veterans.
- Understand the therapeutic approach and evidence supporting the use of psilocybin assisted psychotherapy for depression, end of life care, and addiction.

Why is a Family Physician trained in Addiction Medicine interested in using Psychedelic drugs for his patients?

- Medical Director UNM Milagro Program
- 150 women a year with opioid or other substance use disorders in pregnancy
- Model program with integrated prenatal care and substance abuse counseling/medication assisted treatment (MAT) in family medicine clinics including caring for women during delivery and newborns at risk of Neonatal Opioid Withdrawal Syndrome
- Continuity model where women often have physician of their choice at birth
- Pilot doula program
- High proportion of women in remission for opioid use disorder at time of birth

Association of Opioid Use disorder with PTSD

- Prevalence of PTSD among women with substance use disorders estimated to be as high as 50-60%, compared to 12% among pregnant women without substance use disorders
- Pregnant women who are diagnosed with PTSD are more than twice as likely to use substances as those without trauma history
- PTSD difficult to "cure" with options including SSRI medications (e.g. sertraline and fluoxetine) , EMDR, prolonged exposure and cognitive behavioral therapies

Goodman DJ, et al . A Multidisciplinary Approach to the Treatment of Co-occurring Opioid Use Disorder and Posttraumatic Stress Disorder in Pregnancy J Dual Diagn. 2015;11(3-4):248-57

Postpartum Relapse

- We "successfully" treated opioid use disorder in pregnancy with medication assisted treatment (buprenorphine and methadone) and counseling but the underlying trauma remains
- High incidence of childhood sexual and physical abuse and other Adverse Childhood Events (ACES)
- Postpartum is high risk time for relapse
- Presence of PTSD and postpartum depression are risk factors for relapse

Gopman S. Obstet Gynecol Clin North Am. 2014 Jun;41(2)

Epidemics of despair

- Opioid use disorder and other addictions
- Post-traumatic Stress Disorder
- Gun violence
- Suicide
- Mass criminalization
- Homelessness

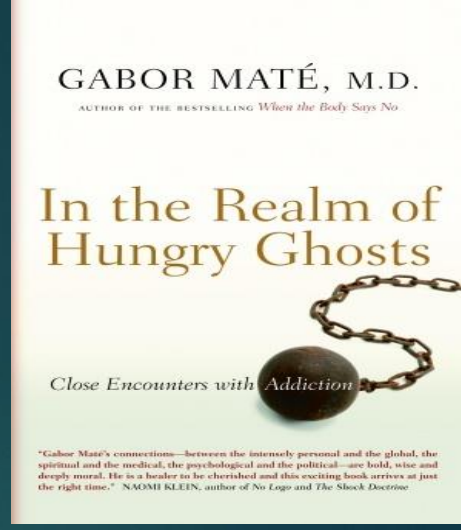
Societal factors and epidemics of despair

- Adverse Childhood Events: ACES
- Economic and health disparities
- Veterans from endless wars
- Mass incarceration from “war on drugs”
- Climate change catastrophe looming

Opioid Use Disorder in Pregnancy and intergenerational transmission

- May be epigenetic transmission based on exposure during pregnancy and effects of stress hormones but not proven
- Environmental deprivation if parents have substance abuse disorders
- Sexual abuse as factor in PTSD clusters in families
- Children may be placed in foster care due to parental OUD even if no other evidence of abuse or neglect- varies by state reporting laws and practices
- Mass incarceration since OUD viewed as crime rather than public health/medial approach
- Other Adverse Childhood Events

Links between trauma and addiction



"Not all addictions are rooted in abuse or trauma, but I do believe they can all be traced to painful experience. A hurt is at the centre of all addictive behaviours. It is present in the gambler, the Internet addict, the compulsive shopper and the workaholic.

The wound may not be as deep and the ache not as excruciating, and it may even be entirely hidden—but it's there. As we'll see, the effects of early stress or adverse experiences directly shape both the psychology and the neurobiology of addiction in the brain."

Gabor Mate MD
Canadian Family Physician
Author: In the Realm of Hungry Ghosts: Close Encounters with Addiction


I am more than my addiction.
Fighting for those I love,
fighting for my life.
BOLD FUTURES
Artwork by: Nani Chacon - 2014.

MDMA

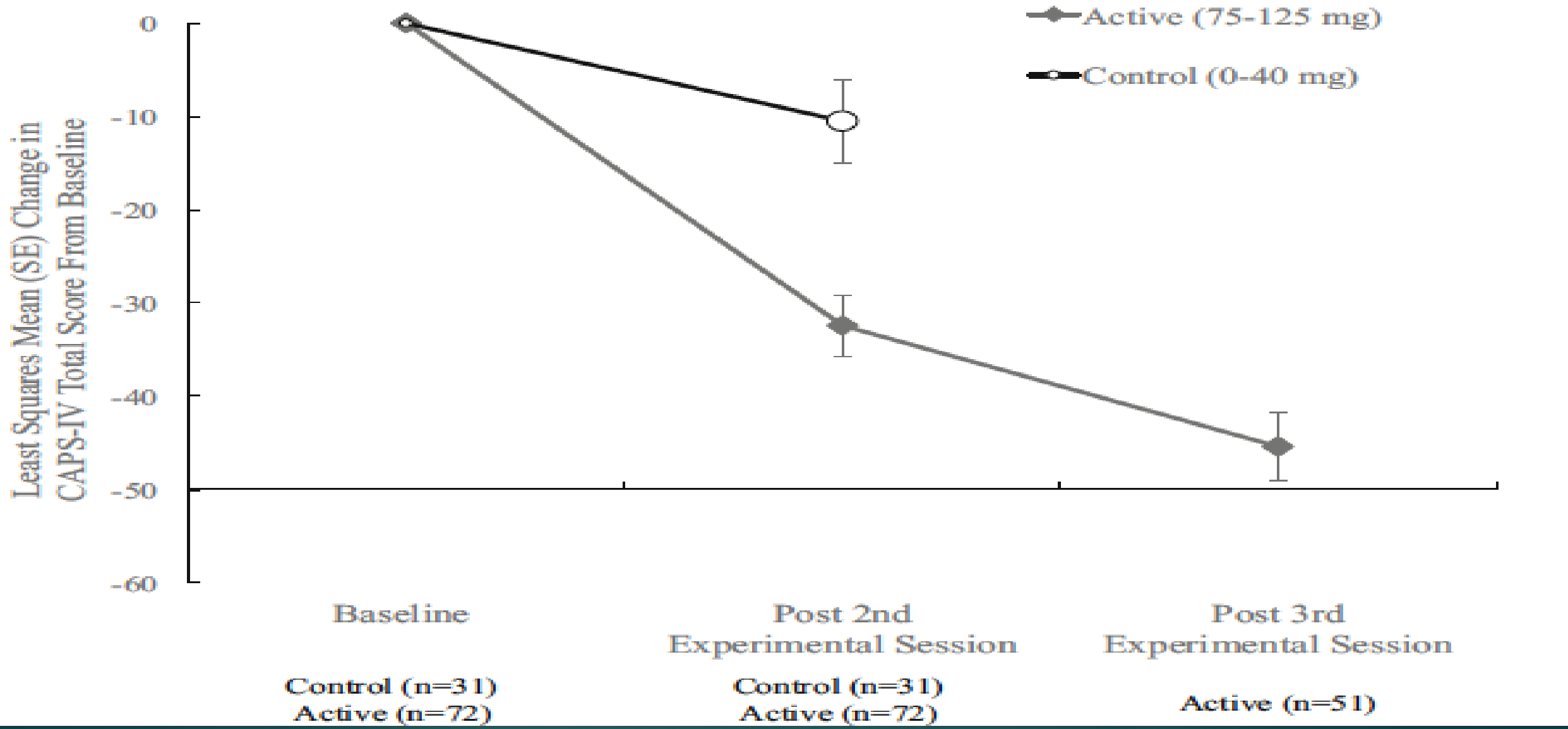
- 3,4-methylenedioxymethamphetamine (*MDMA*): a derivative of amphetamine
- Properties of stimulant and psychedelic but not a "classic" psychedelic
- "Entactogen" — a drug that can increase self-awareness and empathy
- Synthesized 1912 and used legally by psychotherapists from 1976 to 1985
- Made its way to recreational use as "Ecstasy" and popularized at raves
- DEA responded by categorizing as schedule one drug in 1985 despite testimony from psychiatrists and psychotherapists of benefits.

Pooled analysis of Six Phase 2 RCTs of MDMA for PTSD

- All subjects had >6 months PTSD
- 31 controls; 74 had active medication (MDMA)
- Active dose MDMA (75 to 125 mg) vs. placebo/control (0-40 mg)
- 2 or 3 eight-hour MDMA or control psychotherapy sessions spaced one month apart
- Preceded by 3 90-minute psychotherapy sessions prior to MDMA and 3 to 4 after each MDMA or control session
- All psychotherapists went though week-long MDMA psychotherapy training

Mithoefer MC, et al . MDMA-assisted psychotherapy for treatment of PTSD. Psychopharmacology 2019

MDMA AND CAPS-IV Total Score From Baseline



Proportion of subjects meeting CAPS IV Diagnostic Criteria for PTSD after two sessions

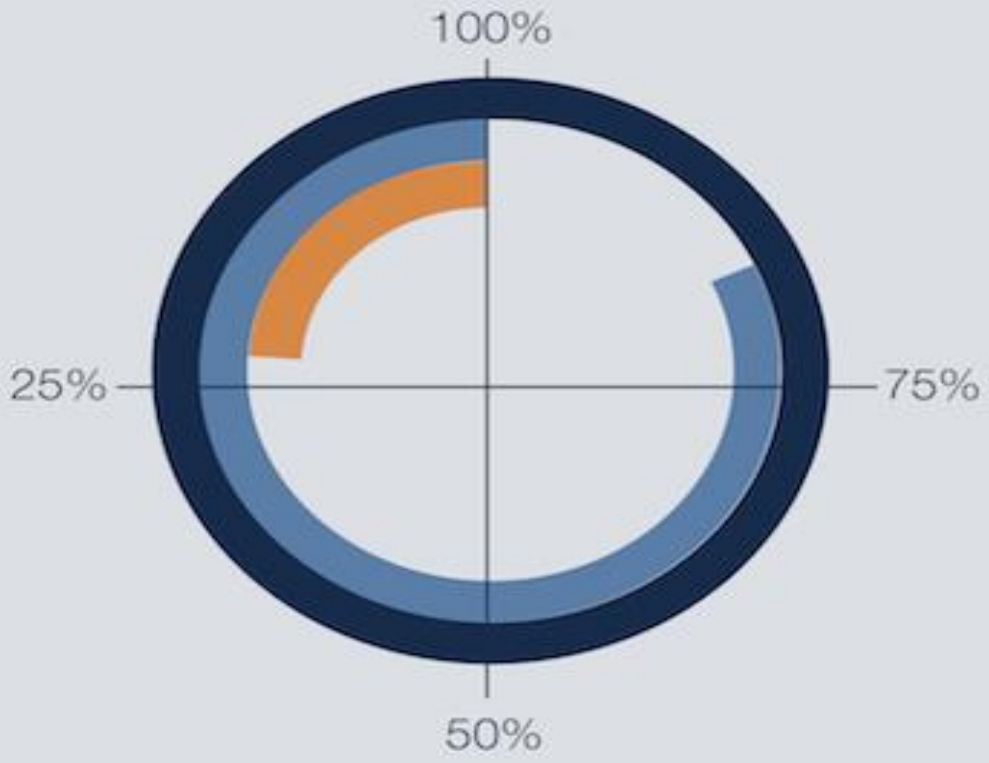
	CONTROL n=31	Active MDMA n=72
Yes	24. (77.4 %)	33 (45.8%)
No	7 (22.6 %)	39 (54.2%)

- Compares favorably to trauma based therapies for treatment of PTSD in veterans
- 6-72% of combat veterans still meet PTSD criteria after cognitive processing therapy or prolonged exposure therapy

Mithoefer MC, Feduccia AA, Jerome L, Mithoefer A, Wagner M, Walsh Z, Hamilton S, Yazar-Klosinski B, Emerson A, Doblin R. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. Psychopharmacology 2019 Sep;236(9):2735-2745

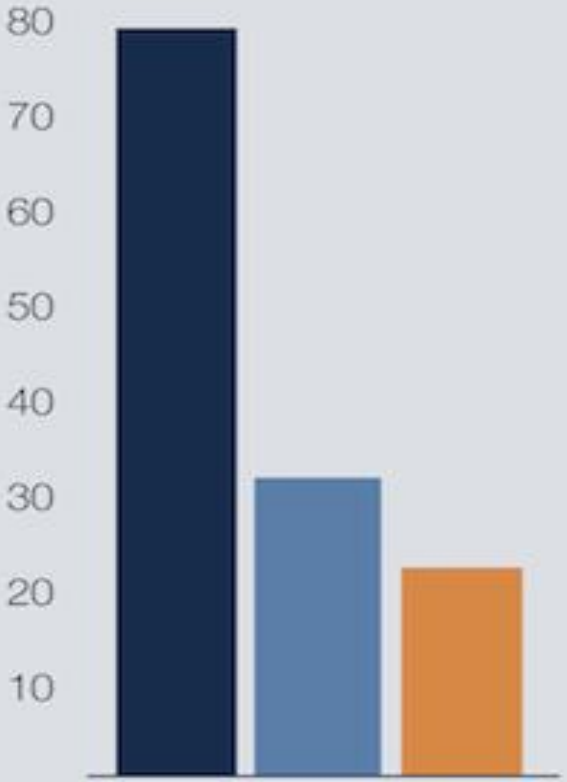
Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. *JAMA*. 2015;314(5):489–500

Percent of Subjects Qualifying for PTSD Diagnosis



- Before treatment
- Psychotherapy alone
- MDMA-Assisted Psychotherapy

Severity of PTSD Symptoms (CAPS Score)



- Before treatment
- 2 months after treatment
- 3.8 years after treatment

TREATING PTSD
WITH MDMA-ASSISTED PSYCHOTHERAPY

Posttraumatic Stress Disorder (PTSD) is a widespread and devastating illness for which we urgently need more effective treatments. **Could non-profit research offer hope?** The controlled use of MDMA in a psychotherapeutic setting is an important step in the treatment of PTSD.

What is PTSD?

Posttraumatic Stress Disorder (PTSD) can be a chronic, devastating illness that severely impacts quality of life. Sufferers often struggle to maintain healthy lives and relationships.

PTSD involves changes in the brain. Patients have decreased activity in the hippocampus and **prefrontal cortex** (areas associated with memory and learning) and increased activity in the amygdala (associated with fear).

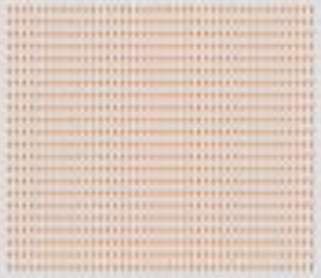
1 in 7 U.S. service members returning from Iraq and Afghanistan suffers from PTSD.

PTSD can be caused by:

What is MDMA-Assisted Psychotherapy?

A treatment that combines psychotherapy with the administration of MDMA, which catalyzes the therapeutic process.

MDMA is not Ecstasy. Substances sold illegally under the name "Ecstasy" often do not contain MDMA and sometimes contain harmful adulterants.



No drug is without risks. MDMA has been administered to over **780 human subjects in clinical studies** with only one serious adverse event.

MDMA is a synthetic compound that decreases **fear and defensiveness** while increasing **trust and empathy**, making it easier for patients to be comfortable between the extremes of fear and avoidance.

MDMA increases the release of **oxytocin and prolactin** (hormones associated with trust and bonding), allowing patients to discuss their memories openly.

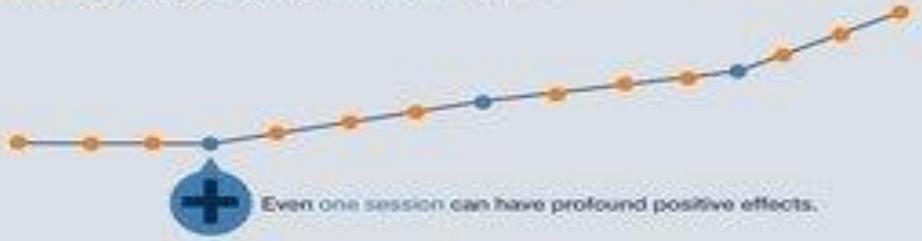
MDMA significantly **decreases activity in the left amygdala,** associated with fear and traumatic memory. It may also increase interpersonal trust without inhibiting access to emotions or senses.

MDMA is not the therapy in itself, but a **tool for the therapist and patient.**

How does MDMA-Assisted Psychotherapy work?

MDMA can make it easier for people with chronic, treatment-resistant PTSD to confront their traumatic memories.

Both FDA-approved PTSD treatments require patients to take drugs daily for years or even the rest of their lives. **But** MDMA is only administered a few times.

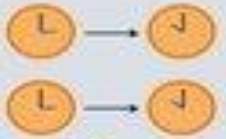


Even one session **can have profound positive effects.**

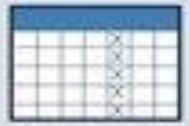
Current Results

In a study of the efficacy of MDMA-assisted psychotherapy for treating PTSD:

subjects were given either **MDMA** or placebo



during 2 **8-hour** sessions, **3-5 weeks** apart



along with **weekly** non-drug psychotherapy sessions

83% of participants were no longer diagnosed with PTSD at the 2-month follow-up.

Even more importantly, a long-term follow-up conducted a mean of 3.8 years later showed that the benefits were (on average) maintained over time.

Comparison of Sertraline, Paroxetine and MDMA for PTSD

	Sertraline		Paroxetine		MDMA	
	CAPS-2 (sertraline–placebo)[a]	Dropout %	CAPS-2 (paroxetine–placebo)[a]	Dropout %	CAPS-IV (MDMA–control)[b]	Dropout %
Study 1	–6.8 (effect size 0.31)	29.3%	–14 (effect size 0.56)	35.5%	–26.2 (effect size 0.9)	7.6%
Study 2	–9.8 (effect size 0.37)	28.4%	–11 (effect size 0.45)	39.0%	–	
Study 3	–		–6 (effect size 0.09)	33.0%	–	

[a]*Effect sizes were not reported in FDA statistical package for paroxetine. Placebo subtracted effect. Size were determined from CAPS scores by calculating the change from baseline divided by the standard deviation.*

[b]*Primary endpoint was 1–2 months after 2–3 blinded experimental sessions.*

Feduccia AA, Jerome L, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R.. Front Psychiatry. 2019 Sep 12;10:650

MDMA Assisted psychotherapy for PTSD for veterans

Video link: https://www.youtube.com/watch?v=RWIc4vRFoYY

Start until 2:41

MDMA Assisted Psychotherapy Sessions

- Two person therapist team usually male and female
- Nondirective
- Safe environment
- Patient's inner healing ability
- Usually do not need to bring up trauma – it comes up
- Eyeshades
- Common initial dose 125 mg with option of 62.5 "booster dose" 2 hours later
- Blood pressure monitoring before first dose and booster dose

Models of Psychedelic Assisted Psychotherapy

- Preparatory psychotherapy (2-4 sessions ~90 minutes) – establish trust with therapy team, discuss issues of substance abuse or PTSD, prepare for psychedelic medicine
- 1-3 sessions with MDMA, psilocybin, or LSD (~8 hours)
- 3-6 sessions with Ketamine
- Integration sessions 1-3 days after the psychedelic session. May be over phone or internet link (e.g. Skype or Facetime)
- Psychotherapy sessions after or in between psychedelic sessions (~90 minutes)
- 12 week total treatment period in psilocybin and alcohol studies

MDMA Assisted Psychotherapy Manual

- Therapist Foundation
- Supporting the participants process
- Conducting Preparatory Sessions
- Conducting MDMA assisted Psychotherapy Sessions
- Conducting Integrative Follow-up sessions
- Therapist self care

A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder Michael C. Mithoefer, M.D. 2017

MDMA Assisted Psychotherapy Manual

- Non-directive method of MDMA assisted psychotherapy
- Therapeutic effect is the "interaction between the effects of the medicine, the therapeutic setting and the mindsets of the participant and the therapists"
- MDMA reduced fear allowing staying engaged and not overwhelmed by anxiety and painful emotions while revisiting traumatic experience
- Empathetic Presence and Listening
- Inner Healing Intelligence

Is MDMA Assisted Psychotherapy (MAP) for PTSD Cost Effective: Decision Analysis of MAP vs standard care for chronic, severe or extreme treatment resistant PTSD

- **COST:** $7,543 per patient who initiated the protocol.
- Therapists' compensation 91.2%.
- Cost of MDMA 4.7%;
- Test kits for pregnancy and drugs of abuse 3.7%;
- Nuclear stress tests and carotid ultrasound for patients who require them 0.4%

Marseille E, Kahn JG, Yazar-Klosinski B, Doblin R. The cost-effectiveness of MDMA-assisted psychotherapy for the treatment of chronic, treatment-resistant PTSD. PLoS One. 2020 Oct

Is MDMA Assisted Psychotherapy for PTSD Cost Effective

- BENEFITS Projected for 30 years , for cohort of 1,000 patients (MAP vs standard care)
- 42.9deaths averted (90%CI,11.1,84.1)
- 5,553discountedQALYs (90%CI,4,725,6,407)
- $103 million saved (90%CI,$71.2- $144.3million) in combined mental health and general medical care costs
- MAP is dominant(better and cheaper)unless it is assumed that benefits cease after one year following MAP,
- Using a 10-year horizon, MAP saves 2,517 QALYs, averts18.9deaths, and saves $36.7million.
- MAP breaks even in costs at3.1years when has generated 918QALYs and averts 5.9deaths.

Marseille E, Kahn JG, Yazar-Klosinski B, Doblin R. The cost-effectiveness of MDMA-assisted psychotherapy for the treatment of chronic, treatment-resistant PTSD. PLoS One. 2020 Oct 14;

Preliminary results of Phase 3 study of MDMA (MAP) for PTSD

- Independent Data Monitoring Committee reviewed the results from the first 60 out of 100 participants.
- The analysis revealed a 90% or greater probability that the trial will detect statistically significant results when all participants have been treated, and that the trial will not require additional participants beyond the first 100.
- The interim analysis was approved by the FDA as part of MAPS' Statistical Analysis Plan approved by the FDA.

https://maps.org/news/media/8154-press-release-interim-analysis-shows-at-least-90-chance-of-statistically-significant-difference-in-ptsd-symptoms-after-mdma-assisted-psychotherapy

UNM –MAPS Study of Postpartum Women with PTSD and Opioid Use Disorder

- Open label feasibility study
- Postpartum women 2-4 months after birth
- Women with opioid use disorder on buprenorphine and diagnosis of moderate or severe PTSD
- MAPS protocol of 12 weeks of psychotherapy including three MDMA medication sessions, preparation and integration
- Outcomes: PTSD, opioid use disorder and maternal infant bonding /attachment

Psilocybin

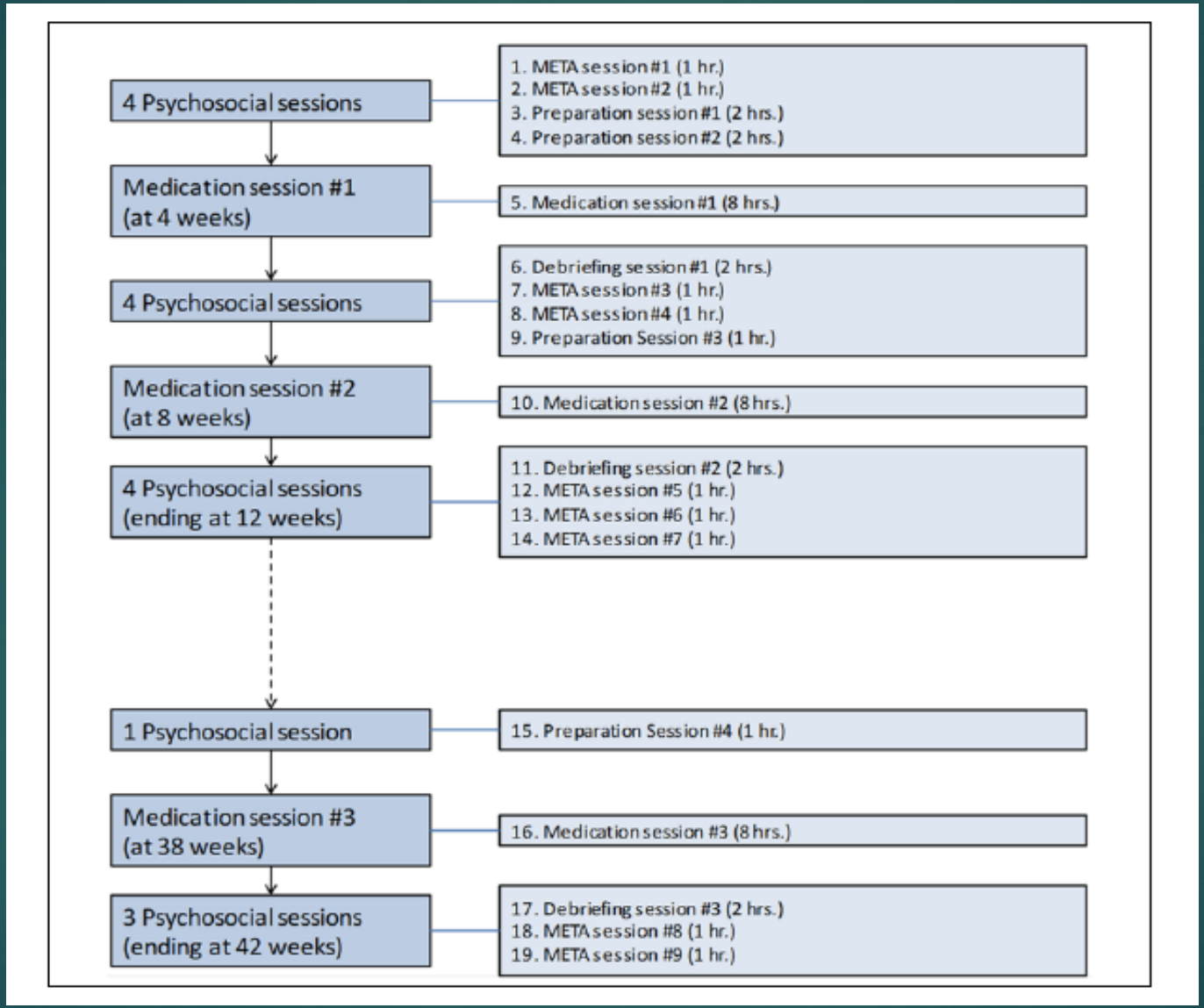
- Active ingredient in psilocybin containing mushrooms
- Metabolized to Psilocybin inside human body
- Traditionally used by Mazatecs in Mexico's Sierra Mazateca
- Stimulates *serotonin* 2A *receptors* (5-HT2ARs)

Maria Sabina
Mazatec Curandera

Psilocybin Studies

- Treatment resistant depression
- Depression and anxiety associated with cancer
- Addition: tobacco, alcohol and opioids
- A "classic" psychedelic with similar effects to LSD and mescaline but shorter time of action so easier to use in studies and for psychedelic assisted therapy
- Lacks "cultural baggage" of LSD

Psilocybin and Alcoholism Therapeutic Structure

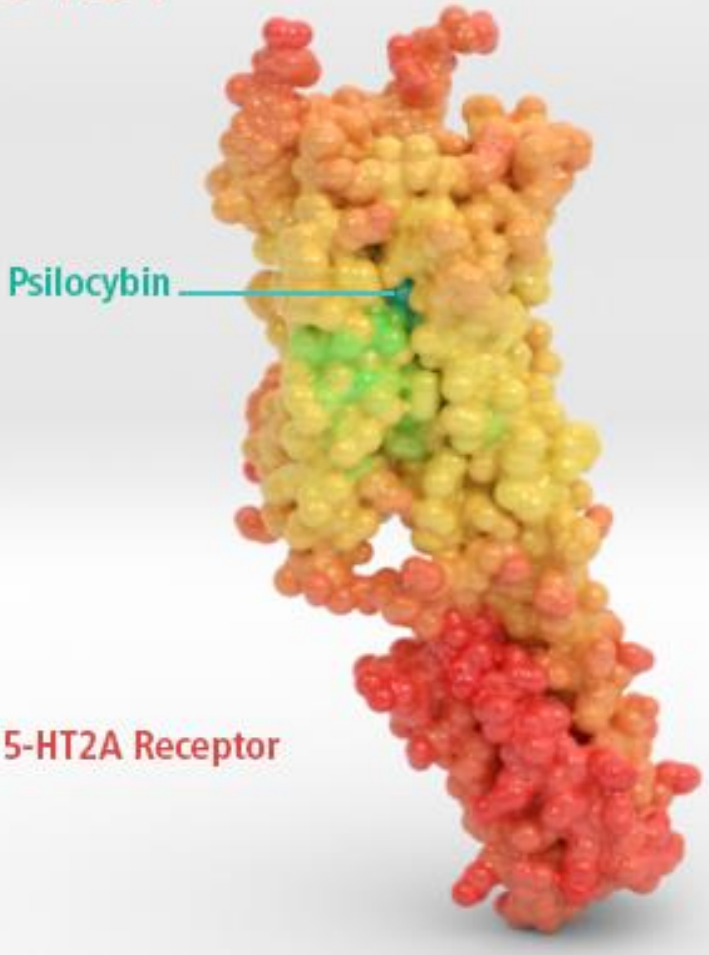


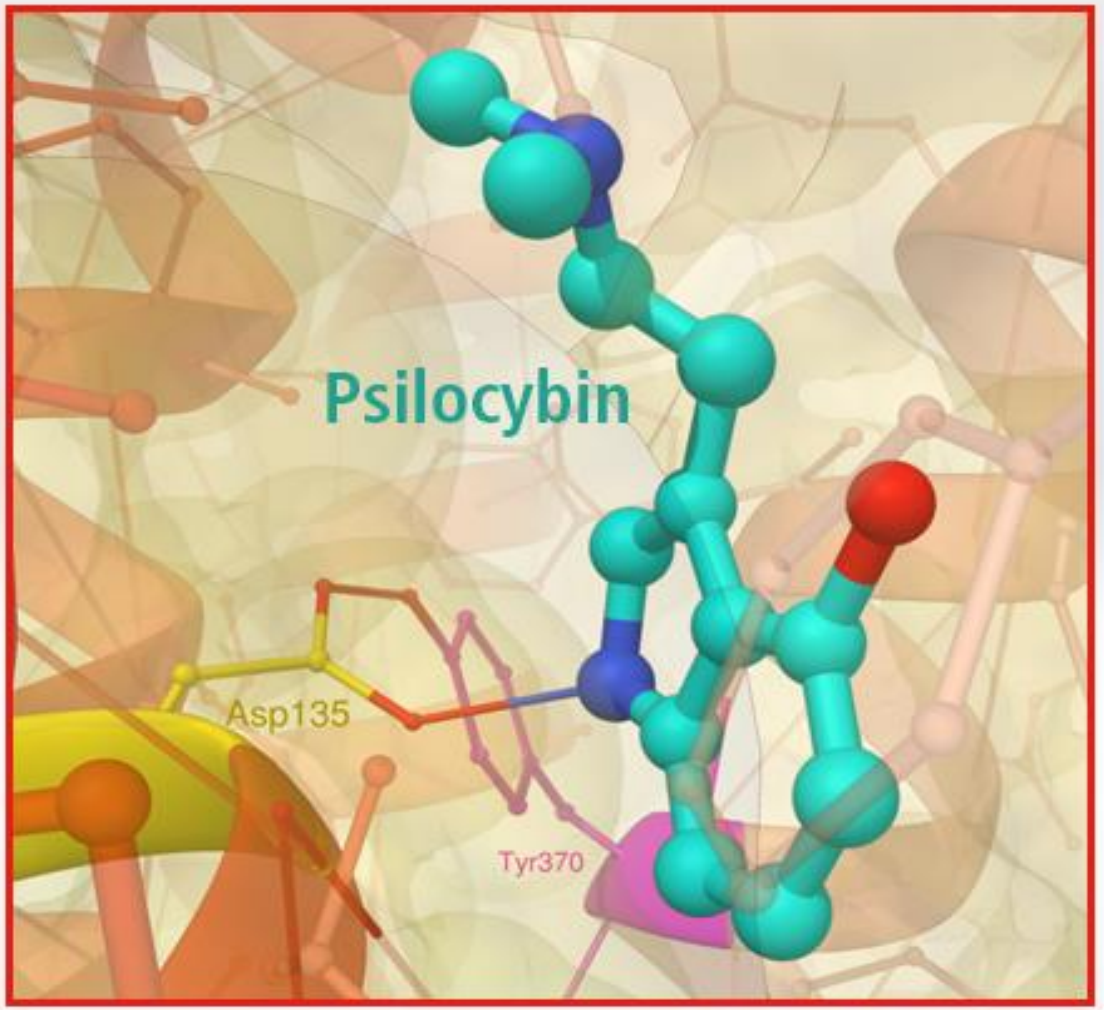
META: Motivational Enhancement and Taking Action

Bogenschutz, M. P (2017). Development of a Psychotherapeutic Model for Psilocybin-Assisted Treatment of Alcoholism. *Journal of Humanistic Psychology*,

Psilocybin bound to Serotonin (5-HT2A) Receptor

PDB ID: 4IB4

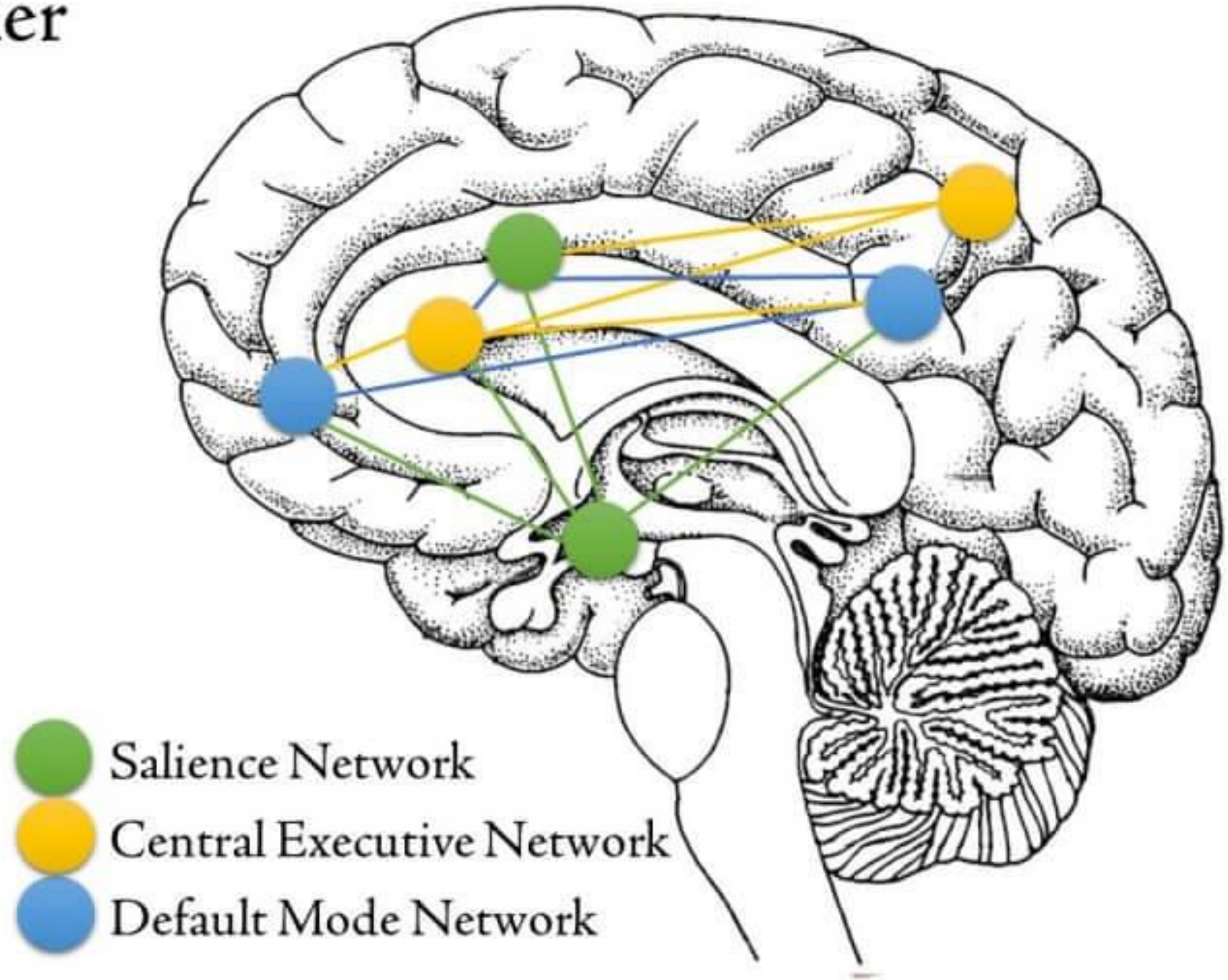




BIOLOGIC MODELS

Functioning under psychedelics

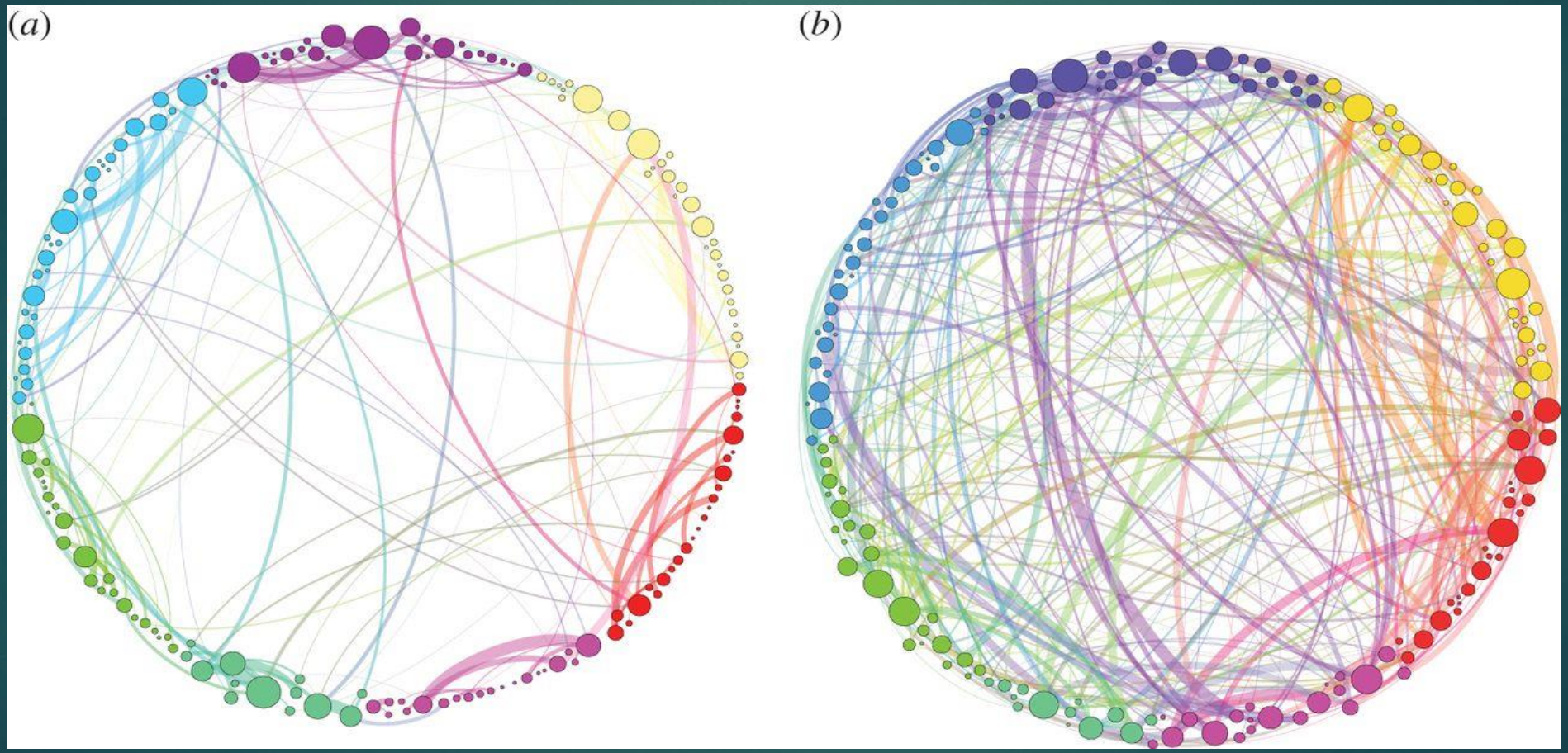
- Network regions interact more fluidly and flexibly
- Representations of the self become weaker
- The Default Mode Network in particular has been shown to exert less top-down influence over the brain; but other networks may see the same effect



Potential Effects of Decreasing Activity in the Default Mode Network (DMN)

- Psilocybin and LSD have been shown to decrease blood flow to the DMN which allows for increased connections throughout the brain
- Decrease rumination, obsessive thoughts and focus on autobiographical content that are common in severe depression
- Can explain the effects diminishing anxiety of patients with terminal cancer
- More awareness in the present moment
- Increased connectivity internally between neural networks and externally toward natural environment

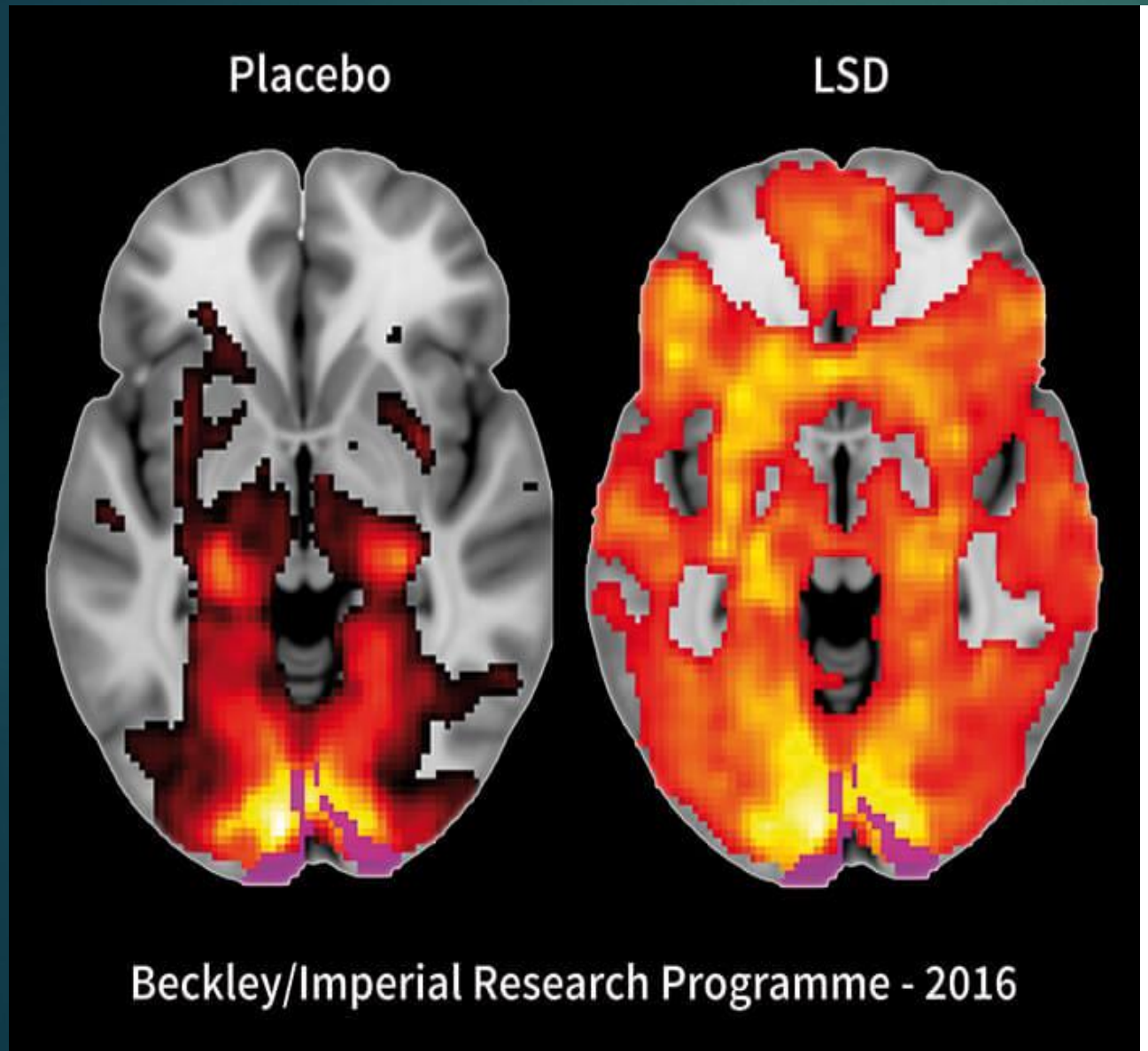
How psilocybin affects brain: increased connectivity

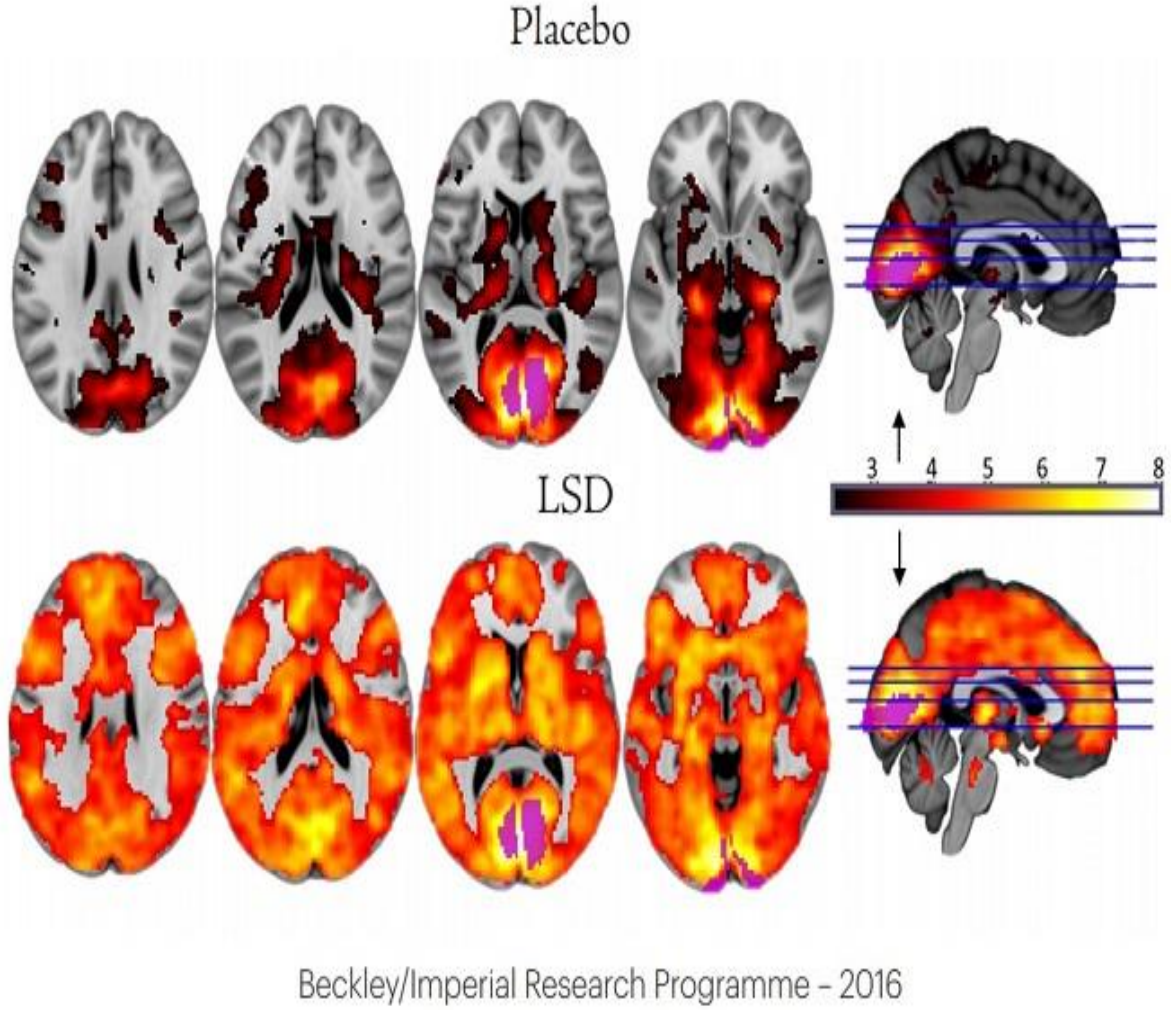


Placebo

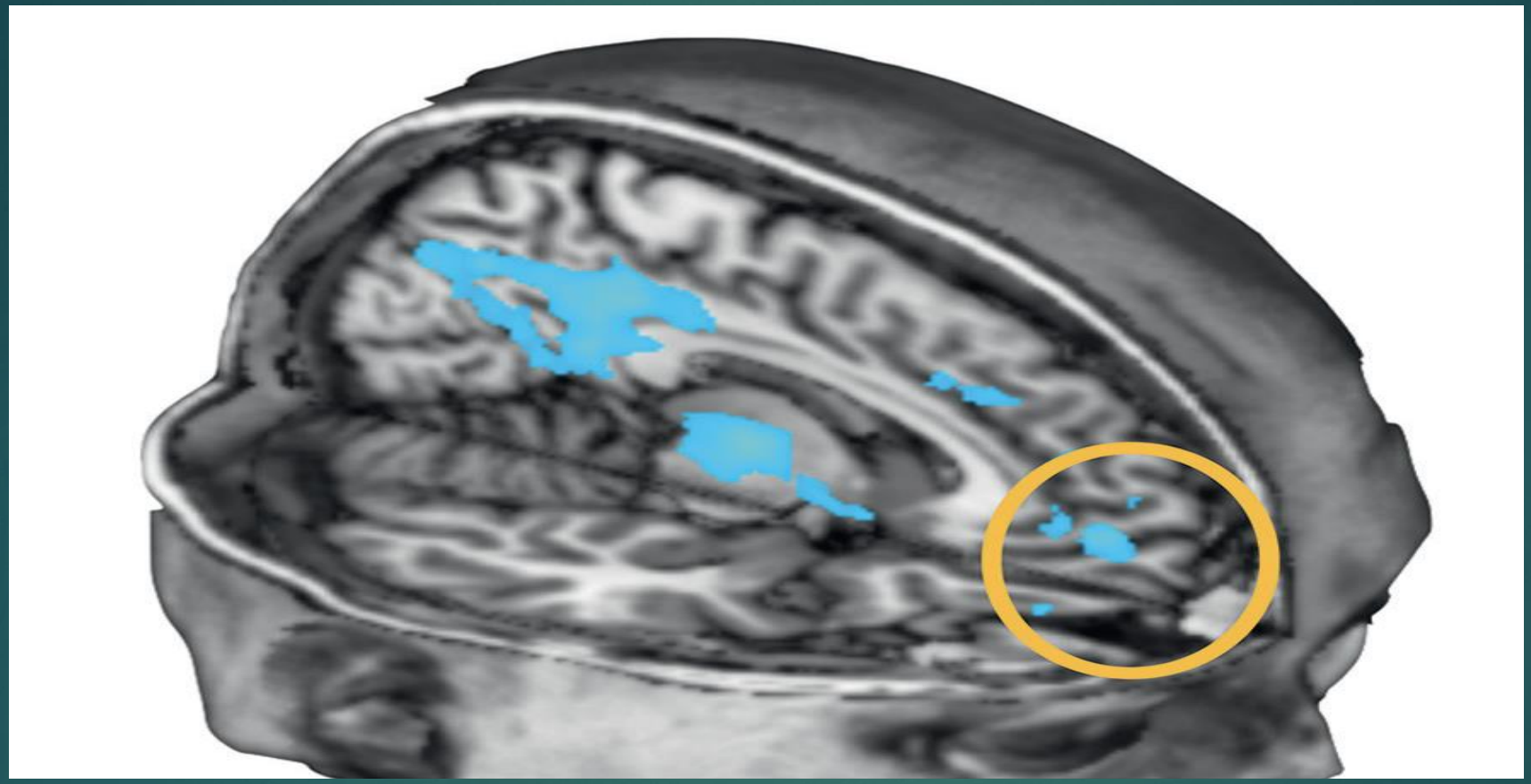
Psilocybin

LSD and Functional MRI Imaging





Psilocybin and depression



fMRI image showing psilocybin induced attenuation of brain activity in the subgenual cingulate cortex, a brain area implicated in the generation of depression

Nutt D. Psychedelic drugs-a new era in psychiatry? Dialogues Clin Neurosci. 2019;21(2):139-147

6 Month open label study of severe treatment resistant depression

- Eighteen of the 20 patients met the criteria for severe or very severe depression at baseline (QIDS-SR16 score of ≥ 16); the remaining two meeting the criteria for moderate depression (QIDS-SR16 score ≥ 11, < 16).

- The median number of (lifetime) failed previous medications was 4, The mean duration of illness of the sample was 17.7 ± 8.4 years (range = 7–30 years)

Carhart-Harris, R.L., Bolstridge, M., Day, C.M.J. et al. Psychopharmacology (2018) 235: 399.

6 Month open label study of Psilocybin for severe treatment resistant depression

- QIDS-SR16 scores were significantly reduced at all time points ($p < 0.001$), with the maximum effect size at 5 weeks. All 19 patients showed some reduction in depression severity at 1 week and these were sustained in the majority for 3–5 weeks
- Of the 9 of 16 that showed response at 5 weeks only 3 had relapses at 6 months
- Weakness: Open label (they knew they received psilocybin) and no control group
- Strength: these were severely depressed individuals with average of 17 yrs of treatment resistant depression

Carhart-Harris, R.L., Bolstridge, M., Day, C.M.J. et al. Psychopharmacology (2018) 235: 399.

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder A Randomized Clinical Trial

Alan K. Davis, PhD[1,2]; Frederick S. Barrett, PhD[1]; Darrick G. May, MD[1]; et al

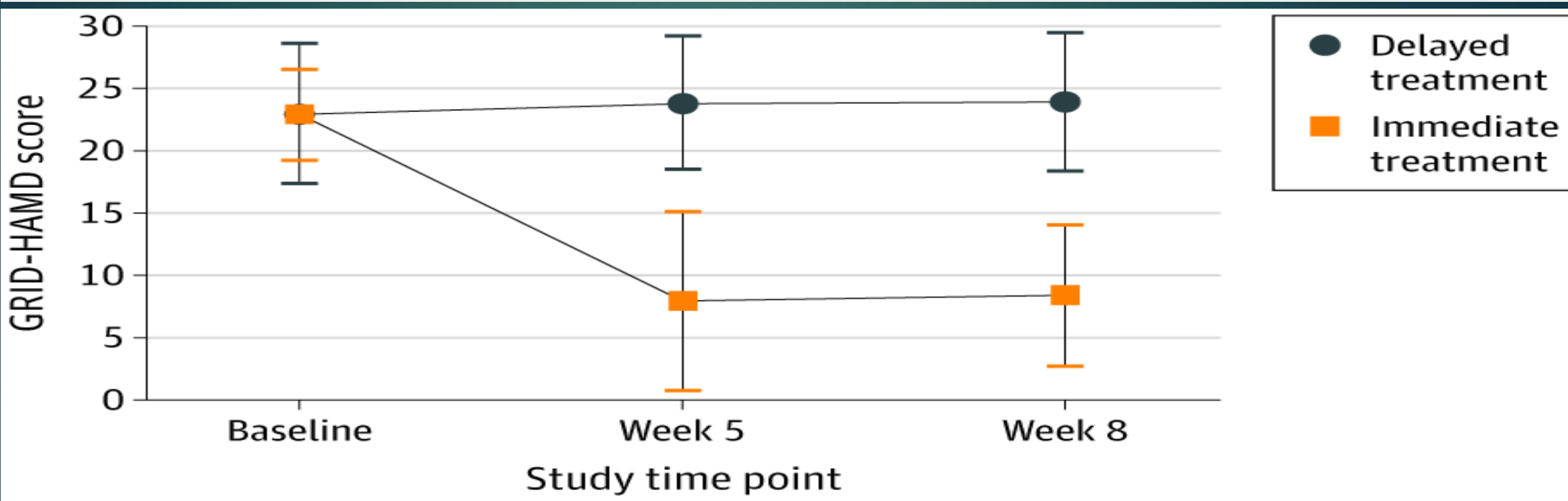
- RCT of 24 participants with major depressive disorder

- Participants who received immediate psilocybin-assisted therapy compared with delayed treatment showed improvement in blinded clinician rater–assessed depression severity and in self-reported secondary outcomes through the 1-month follow-up.

- 16 participants (67%) at week 1 and 17 (71%) at week 4 had a clinically significant response to the intervention (≥50% reduction in GRID-HAMD score), and 14 participants (58%) at week 1 and 13 participants (54%) at week 4 were in remission (≤7 GRID-HAMD score).

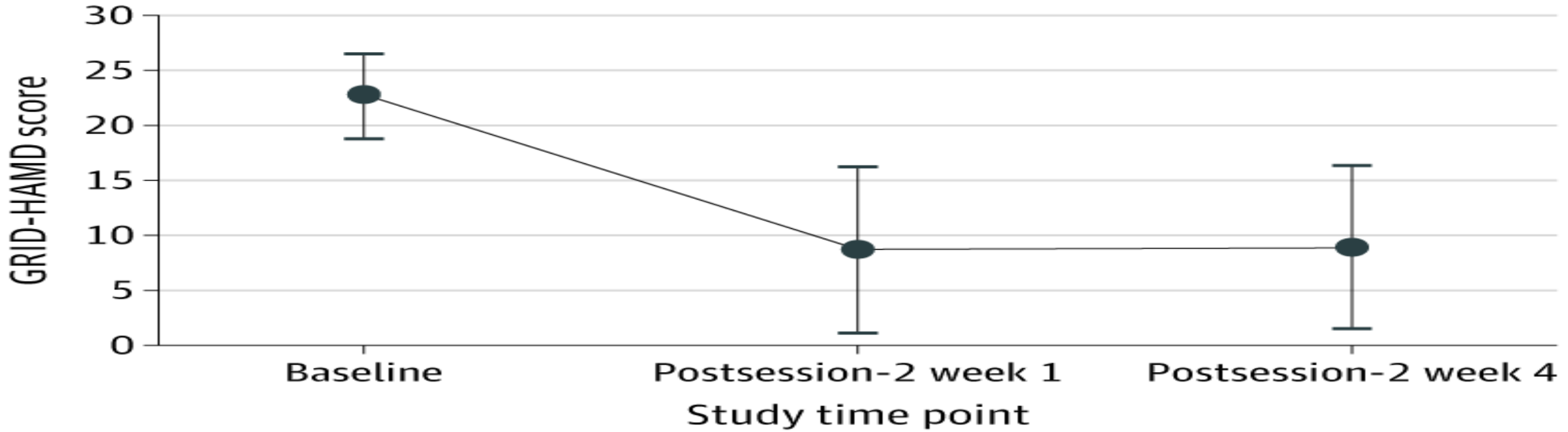
JAMA Psychiatry. Published online November 4, 2020

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial



Comparison of GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores Between the Delayed Treatment and Immediate Treatment Groups Data points are presented as mean (SD). In the immediate treatment group (n = 13), weeks 5 and 8 correspond to weeks 1 and 4 after the psilocybin session 2.In the delayed treatment group (n = 11), weeks 5 and 8 are prepsilocybin assessments obtained during the delay period. Effect sizes (Cohen d with 95% CI) and P values reflect the results of a 2-sample t test between the 2 groups at week 5 (Cohen d = 2.2; 95% CI, 1.4-3.0; P < .001) and week 8 (Cohen d = 2.6; 95% CI, 1.7-3.6; P < .001). JAMA Psychiatry. Published online November 04, 2020. doi:10.1001/jamapsychiatry.2020.3285

:Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial



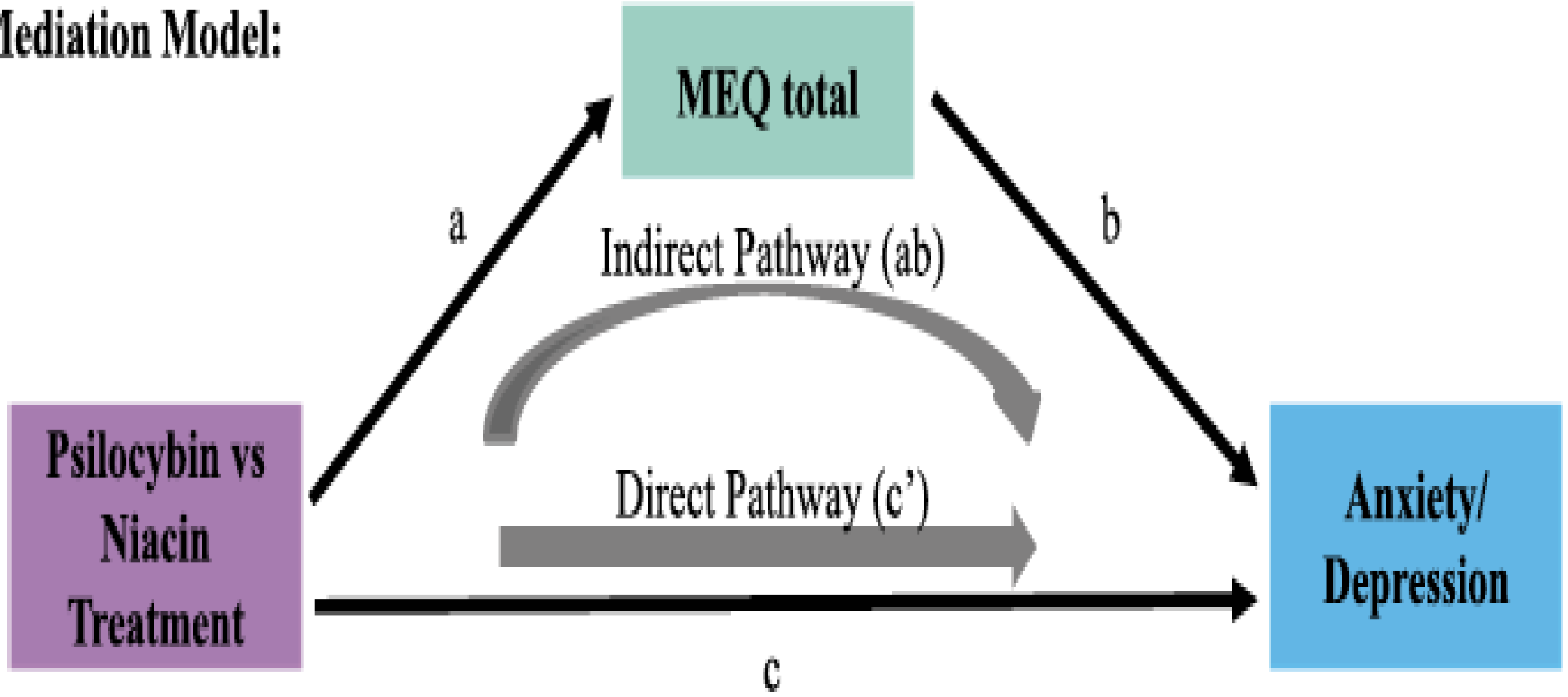
Decrease in the GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores at Week 1 and Week 4 Postsession-2 Follow-up in the Overall Treatment Sample The mean (SD) GRID-HAMD score was 22.8 (3.9) at baseline, 8.7 (7.6) at week 1, and 8.9 (7.4) at week 4. Effect sizes (Cohen d with 95% CI) and P values reflect the results of a paired sample t test that compared scores between baseline and week 1 (Cohen d = 3.6; 95% CI, 2.2-5.0; P < .001) and week 4 postsession-2 follow-up (Cohen d = 3.6; 95% CI, 2.2-4.9; P < .001).

Psilocybin and the existential anxiety of a terminal cancer diagnosis: Ross et al 29 randomized to single dose psylocibin or placebo as first drug

- 83% of participants in the psilocybin first group (vs. 14% in the niacin placebo group) met criteria for anti-depressant response and 58% for anxiolytic response compared to 14% in the niacin placebo group.
- At the 6.5-month follow-up (after both groups received psilocybin), anti-depressant or anxiolytic response rates were approximately 60–80%
- Effects appear to be mediated through Mystical Experience Questionnaire results

Ross S, randomized controlled trial. J Psychopharmacol. 2016:;30(12)

Mediation Model:



ab = Indirect effect of psilocybin on anxiety/depression *mediated by mystical experience*

c'= Direct effect of psilocybin on anxiety/depression *not mediated by mystical experience*

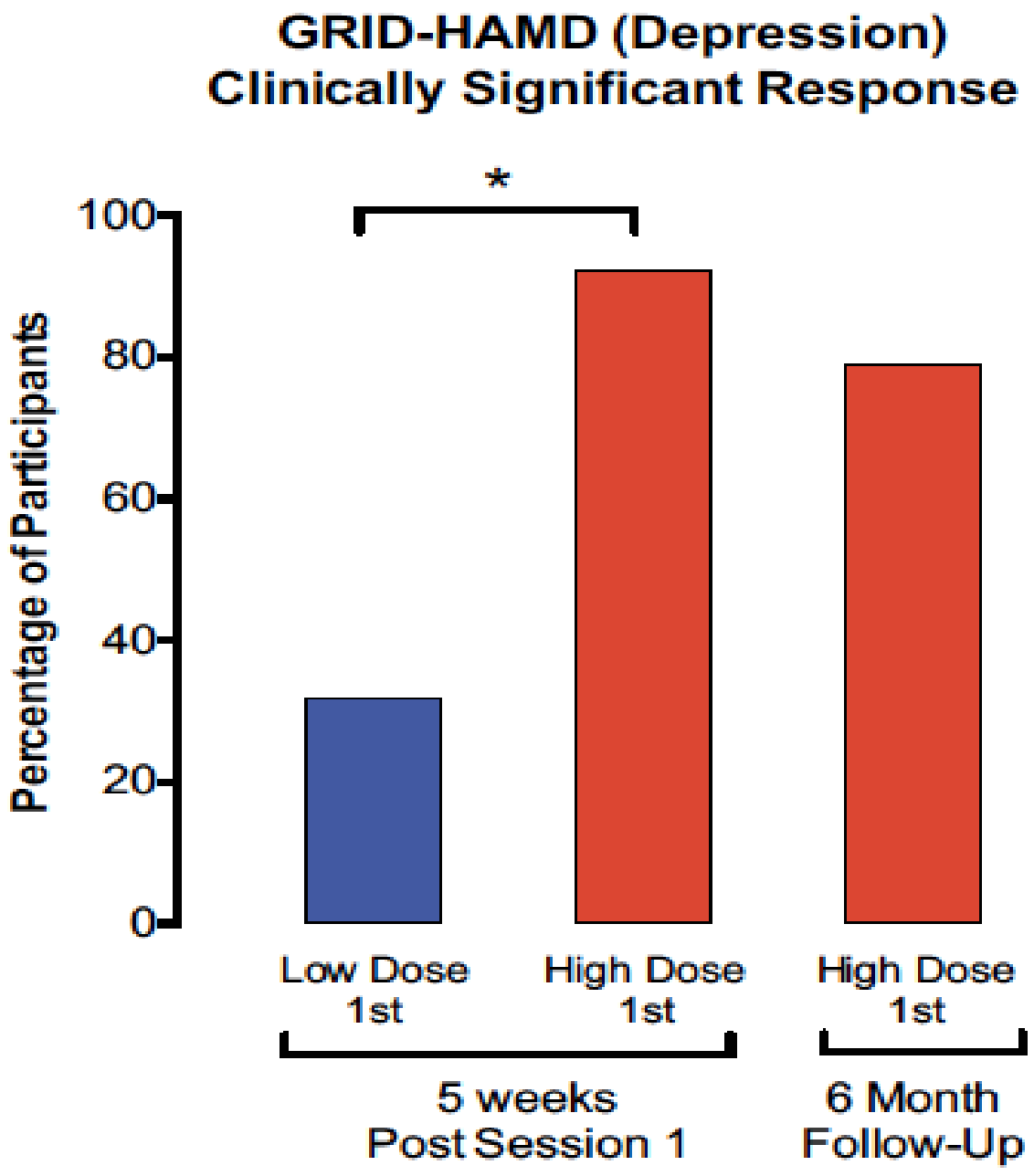
Psilocybin and the existential anxiety of a terminal cancer diagnosis: Griffiths et al Hopkins RCT of 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety

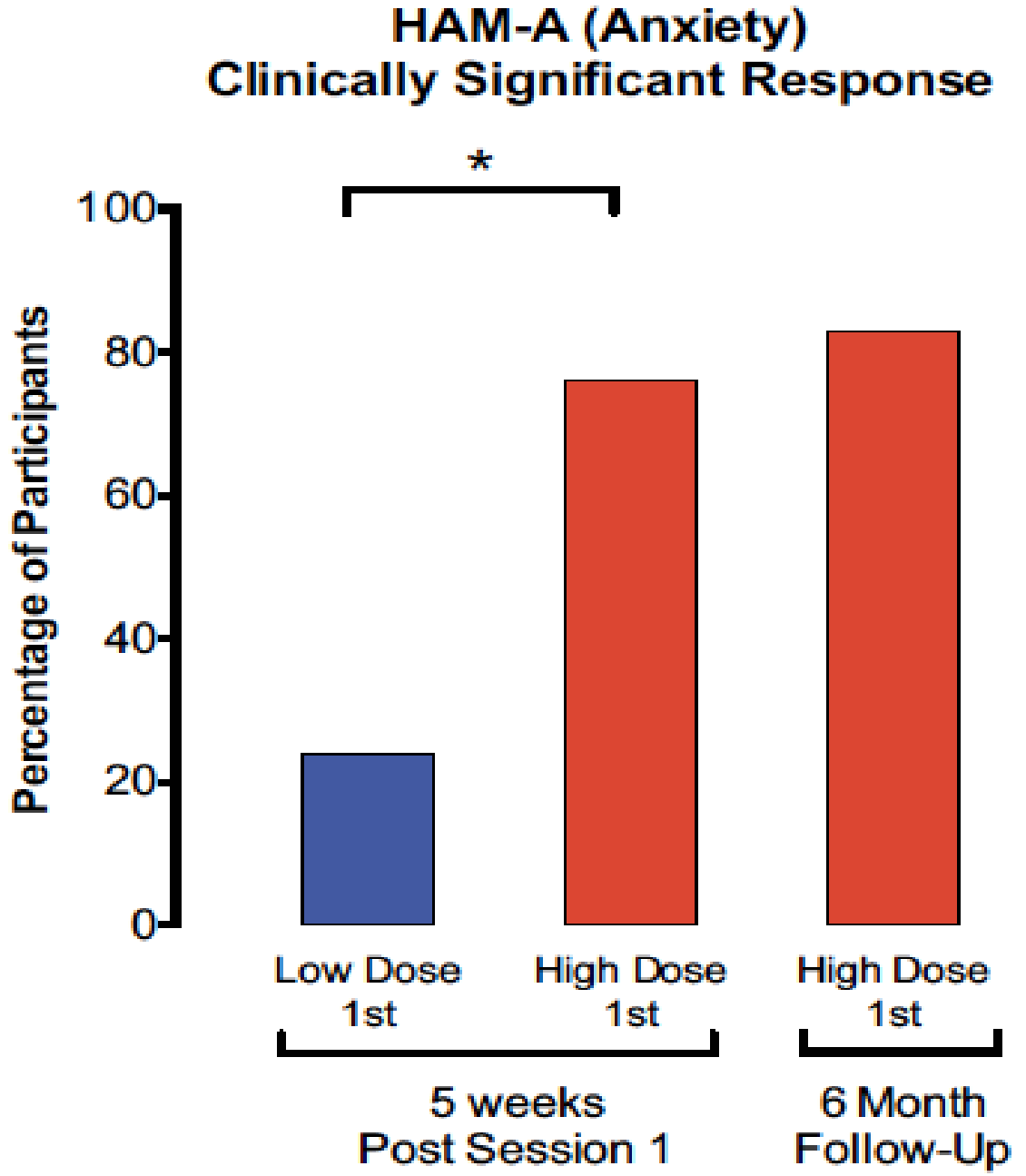
- Compared high dose psilocybin vs. very low placebo like dose of psilocybin then switched medications for second session with 5 weeks between sessions and a 6-month follow-up.

- At 6 months there were improvements on clinician-rated depression and anxiety scores for 78% and 83%, respectively.

- 6month enduring outcomes associated with score on Mystical Experience Questionnaire

Griffiths RR, et al. J Psychopharmacol. 2016;30(12)





Griffiths RR, et al. J Psychopharmacol. 2016;30(12)

Tony- Psilocybin Cancer Anxiety Study

https://vimeo.com/122267529

Multisite Phase 2 study for major depression

- 80 individuals with major depression
- 3 month study with single dose of psilocybin or placebo
- Multiple sessions of psychotherapy over 3 months including preparation and integration
- 7 sites with planned 2021 completion
- If results show benefit then moved to phase 3 with at least 300 subjects

Psilocybin and tobacco cessation

- 15 psychiatrically healthy nicotine-dependent smokers (average age 51 years), with a average of 6 previous lifetime quit attempts, and smoking average of 19 cigarettes per day for 31 year average
- Open label without a control group. 2-3 medium to high dose psilocybin sessions in conjunction with cognitive behavioral therapy
- 6 month follow : 12 of 15 to be have been abstinent from tobacco for a tleast 7 days
- 12-month follow-up, 10 participants (67%) were biologically confirmed confirmed as smoking abstinent. By urinary cotinine and breath carbon monoxide
- 12-month follow-up: 13 participants (86.7%) rated their psilocybin experiences among the five most personally meaningful and spiritually significant experiences of their lives.

Johnson MW, J Psychopharmacology. 2014

Psilocybin and Alcohol Dependence

https://www.youtube.com/watch?time_continue=11&v=uX5MrmR86mk&feature=emb_logo

1:18 to 6:10

LSD and alcoholism – Meta-analysis of six randomized controlled trials from 1960-70s

	Follow-up (months)	LSD (n/N)	Control (n/N)	Weight	Odds Ratio (95% CI)
First follow-up					
Smart *et al.*, 1966	6	[a]/10	[a]/20	7.2%	1.41 (0.36-5.60)
Hollister *et al.*, 1969	2	18/36	11/36	14.7%	2.27 (0.87-5.94)
Ludwig *et al.*, 1969	1	94/132	25/44	27.3%	1.88 (0.93-3.81)
Bowen *et al.*, 1970	12	9/22	7/22	8.9%	1.48 (0.43-5.10)
Pahnke *et al.*, 1970	6	34/73	13/44	21.6%	2.08 (0.94-4.60)
Tomsovic & Edwards, 1970	3	30/52	17/45	20.4%	2.25 (0.99-5.10)
Total		**325**	**211**	**100%**	**1.96 (1.36-2.84)**

Test for heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.65$, df = 5 ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 3.59$ ($P = 0.0003$)

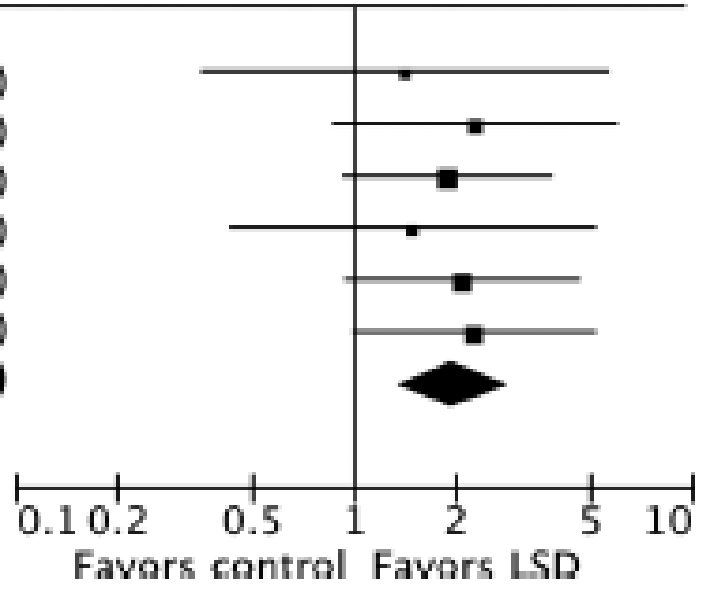


Figure 2. Improvement on alcohol misuse at the first available follow-up after LSD versus control treatments.

[a]Continuous outcome data.

Krebs TS, Johansen PØ. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol. 2012 Jul;26(7):994-1002

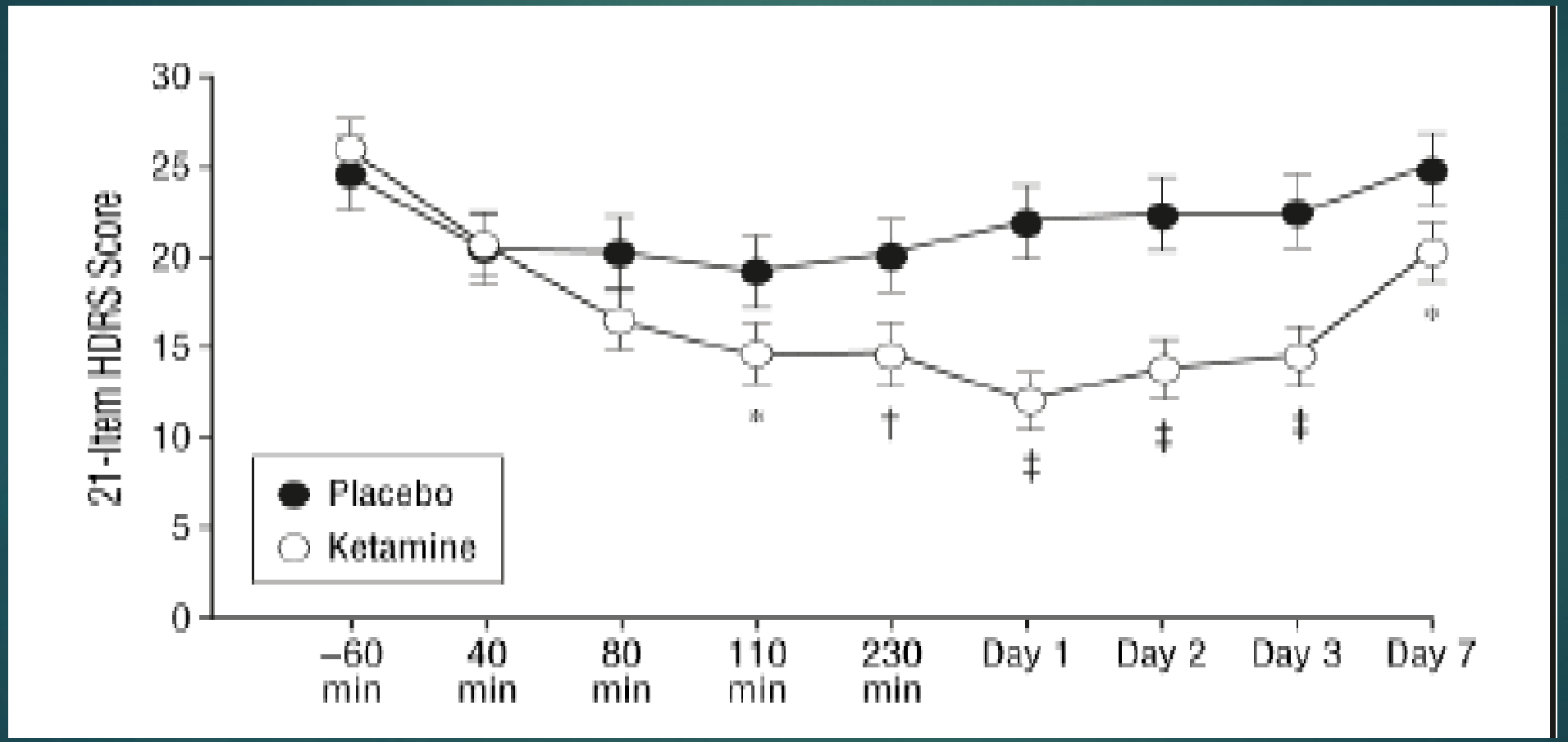
Ketamine: Psychedelic or dissociative anesthetic?

- Chemically distinct from classic psychedelics and MDMA
- Antagonist of NMDA receptor
- Rapidly acting medication for severe major depression and suicidality by IV infusion and other routes (IM/Oral/Sublingual) at different doses
- Models of care include IV ketamine at infusion center without psychotherapy or ketamine assisted psychotherapy which can occur during or after ketamine session
- Treatment resistant PTSD
- Addiction: Alcoholism

How does Ketamine work?

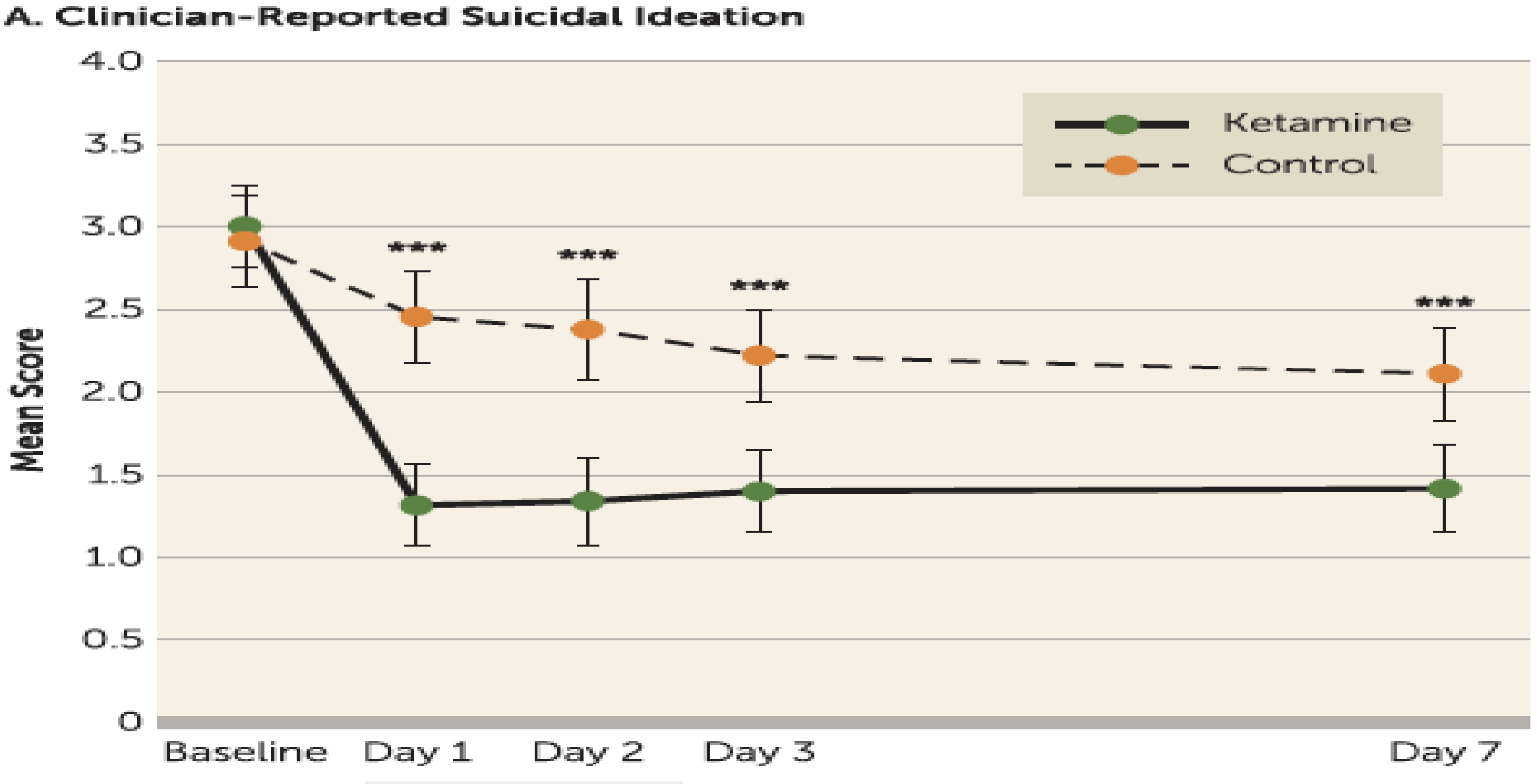
- Is psychedelic effect integral to how it works or a side effect to be eliminated?
- Neuronal plasticity/neurogenesis/synaptogenesis
- Disrupts the default mind network for at least 48 hours which can be used for delayed psychotherapy
- Music can be used with KAP model to facilitate psychedelic effects

Ketamine and treatment resistant depression

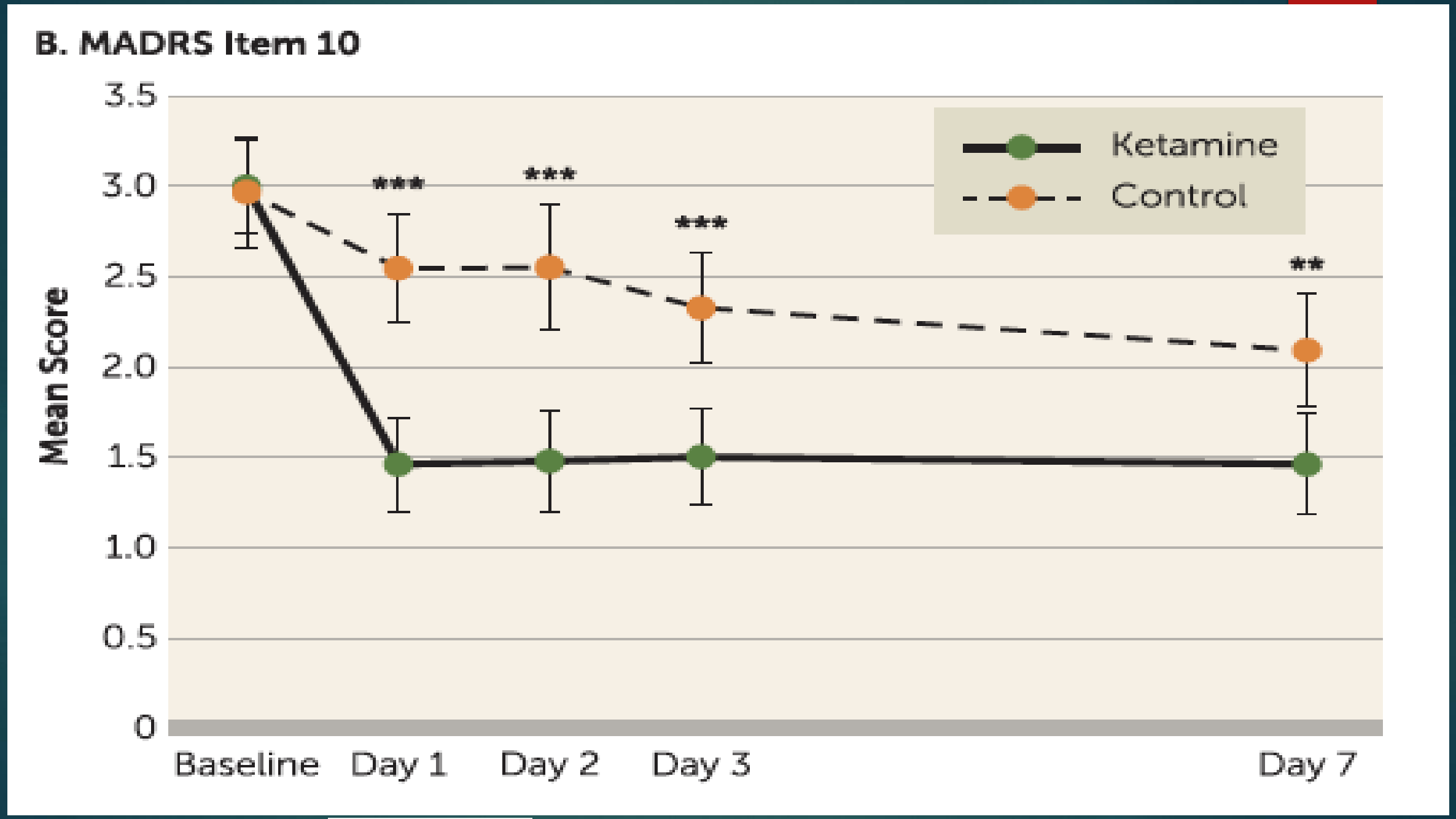


Zarate CA Jr, et al. Arch Gen Psychiatry. 2006

FIGURE 2. Effect of a Single Dose of Ketamine on Suicidal Ideation, as Indicated by Clinician-Administered Measures[a]



Wilkinson ST *Am J Psychiatry 2018; 175:150–158;*



Wilkinson ST Am J Psychiatry 2018; 175:150–158;

APA 2017 Consensus Statement : Use of Ketamine in the Treatment of Mood Disorders

- Based on 7 small placebo controlled RCTS of 147 Subject
- Not FDA reviewed or approved
- Antidepressant doseof 0.5mg/kg delivered intravenously (IV) during 40 minutes
- No significant respiratory effects but can raise blood pressure and heart rate
- Twice weekly for up to 4 weeks. No clear data for frequency or repeated infusions
- Recommended against home use of ketamine

Sanacora G, et al American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry. April 2017

Ketamine Assisted Psychotherapy

- Expanded indications beyond treatment resistant depression
- Psychedelic effects considered part of treatment not an unwanted side effect
- Intramuscular ro sublingual are common modalities of administration
- IV not needed

KAP experience: Trance and transformation

Trance State – SL with dose ranges 25–400 mg varying with individual–slower onset 8–20 min

- *Promotes communication, access to difficult states of mind with less fear of those encounters, and a relief from obsessive and depressive concerns.*
- *Conscious awareness and an ability to communicate with attending therapists and involved relatives is maintained throughout the experience, often with a reduction in direct verbal output.*
- *Integrate a sense of newness and healing, this occurring as the main experience diminishes.*
- *Usually a multiple session process that can last anywhere from two weeks to many months.*

Dore J, et al . Ketamine Assisted Psychotherapy (KAP): Patient Demographics, Clinical Data and Outcomes in Three Large Practices Administering Ketamine with Psychotherapy. J Psychoactive Drugs. 2019

KAP experience: Trance and transformation

Transformational State – IM with dose ranges of 25–130 mg

varying with the individual–fast onset 2–4 min, patients with less

sensitivity may receive higher doses

- Reduction of body and sensory awareness of an ego reductive, spiritual and liberatory nature—from our usual sense of our constitution.

- While the full out-of body experience is primarily reached with an IM injection, it may also be accessed with the sublingual lozenge, depending on individual sensitivity and dose.

- With diminution of tactile and visual sensation, and alteration of auditory receptivity, the internal visual realm is activated. Verbal,ntellectual description is limited.

Dore J, et al . Ketamine Assisted Psychotherapy (KAP): Patient Demographics, Clinical Data and Outcomes in Three Large Practices Administering Ketamine with Psychotherapy. J Psychoactive Drugs. 2019

Ketamine Assisted Psychotherapy

- Conceptual model is that psychedelic effects are beneficial not an unwanted side effect
- Broader applications than treatment resistant depression – may include addiction, PTSD, anxiety disorders, bipolar as well as depression
- Sublingual used in office

Jennifer Dore, et al (2019) Ketamine Assisted Psychotherapy (KAP): Patient Demographics, Clinical Data and Outcomes in Three Large Practices Administering Ketamine with Psychotherapy, Journal of Psychoactive Drugs, 51:2

Ketamine and PTSD

- Individuals with chronic PTSD (N=30) for an average of 15 yeasrs were randomized to receive six infusions of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) (psychoactive placebo control) over 2 consecutive weeks
- PTSD assessed using golf standard CAPS-5 assessment
- At week 2, the mean CAPS-5 total score was 11.88 points lower in the ketamine group than in the midazolam group and 67% of participants in the ketamine group were treatment responders, compared with 20% in the midazolam group.
- Among ketamine responders, the median time to loss of response was 27.5 days
- Did not include standardized psychotherapy. Advocates of Ketamine assisted psychotherapy believe the dissociative psychedelic state may be helpful for processing trauma

Feder A, et al Am J Psychiatry. 2021 Feb

How about use of psychedelics in "well" people?

- MDMA and couples therapy
- Increase connectedness with other people
- Connection with natural environment and climate change

MDMA therapy for individuals or couples without PTSD, addiction, or depression

- Prior to the criminalization of MDMA it was being used in California, Massachusetts and other areas by a network of psychotherapists including George Greer, Leo Zeff and Ralph Metzner. Outcomes described in books and articles but there were no RCTS or rigorous cohort studies
- Effects of decreasing fear and allowing for processing may aid psychotherapy for issues other than PTSD, addiction or depression
- FDA less interested in supporting research into use for subjects without diagnosis of psychopathology
- If and when MDMA has approved use for PTSD and is removed from schedule one classification then off label use or studies will likely be easier to perform

Greer GR, Tolbert R. A method of conducting therapeutic sessions with MDMA. J Psychoactive Drugs. 1998 30(4).
Secret Chief Revealed Myron J Stolaroff 2004
Through the Gateway of the Heart, Adamson, Metzner , Catell 2013

Psilocybin and Mystical type experiences

- Johns Hopkins study of 36 hallucinogen-naïve adults reporting regular participation in religious/ spiritual activities were then given high dose psilocybin
- Volunteers were encouraged to close their eyes and direct their attention inward.
- At the 14-month follow-up, 58% and 67%, respectively, of volunteers rated the psilocybin experience as among the five most personally meaningful and among the five most spiritually significant experiences of their lives;
- 64% indicated that the experience increased well-being or life satisfaction
- 58% met criteria for having had a 'complete' mystical experience.

Griffiths R, Richards W, Johnson M, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin J Psychopharmacol. 2008 Aug;22(6):621-32.

Psychedelics and connection with nature

- Psychedelic narratives and the Mystical Experience Questionnaire commonly describe profound mystical feelings of unity and connection with universe

- Carhart: psychedelics were found to decrease integrity within brain networks while simultaneously increasing functional connectivity between different brain networks, which correlate with self-reported experiences of ego-dissolution

Carhart-Harris RL et al Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci U S A. 2012 Feb 7;109(6):2138-43

Studies of psychedelics and nature connectedness

- Study demonstrated significant association of increased lifetime use of classic psychedelics and measures of nature relatedness (Forstmann 2017; N=1487)
- Nature relatedness: stable personality trait that captures people's ecological self-construal or perceived connectedness with the natural world and can be measured (Nisbet 2009)
- Small RCT showed psilocybin for treatment resistant depression showed nature relatedness significantly increased (,p=0.003) and authoritarianism significantly decreased (p=0.04) 1 week after the dosing sessions. At 7-12 months post-dosing, nature relatedness remained significantly increased (Lyons 2018)

Forstmann M, Sagioglou C.) J Psychopharmacol. 2017
Nisbet E. The nature relatedness scale. Environ. Behav. 2009
Lyons T, Carhart-Harris RL.. J Psychopharmacol. 2018

What is current state of research and ability to use psychedelic medicines outside of research?

Status of MDMA for PTSD

- In phase three studies and if confirm phase 2 study results confirmed could be approved by FDA for use by 2022
- Multidisciplinary Association for Psychedelic Studies Public Benefit Pharmaceutical model
- FDA Grants Breakthrough Therapy Designation for MDMA-Assisted Psychotherapy for PTSD Aug 2017
- FDA approves MAPS plan for Expanded Access December 2019: Initially 50 patient in up to 10 sites with MAPS PBC planning to apply to expand after 35 patient

Status of Psilocybin for depression and addiction

- FDA Breakthrough status for treatment resistant depression
- Usona Institute (Wisconsin based nonprofit) manufacturing psilocybin and sponsoring the phase 2 placebo controlled with 9 centers in the United States results expected in early 2021 and plan to rapidly move to a larger phase 3 study in United States with nine research site
- Compass Pathways (for profit) has Phase II trial in 216 patients with treatment-resistant depression across sites in North America and Europe. Results expected by early 2021. Not placebo controlled.
- Heffter Research Institute(Santa Fe based nonprofit) supporting research on psilocybin and addiction (alcohol, tobacco, cocaine and opioids)
- FDA break through status: Compass received in October 2018 for treatment resistant depression and Usona in November 2019 for major depressive disorder

Johns Hopkins Launches Center For Psychedelic Research

- The Center for Psychedelic and Consciousness Research will focus on how psychedelics affect behavior, brain function, learning and memory, the brain's biology and mood.

- A group of private donors has given $17 million to start the Center for Psychedelic and Consciousness Research at Johns Hopkins Medicine

Roland Griffiths (left) and Matthew Johnson (right)

https://www.hopkinsmedicine.org/news/newsroom/news-releases/johns-hopkins-launches-center-for-psychedelic-research

How about the postpartum women with opioid use disorder ?

- Potential role for MDMA with large group of women with PTSD who have completed breastfeeding
- Await studies of Psilocybin for Opioid Use Disorder
- Treatment resistant postpartum depression- Ketamine appropriate

California Institute of Integral Studies (CIIS) Center and Certificate in Psychedelic Therapies and Research

- Training of skilled therapist researchers who will ideally seek advanced training for future
- FDA-approved psychedelic-assisted and entactogen-assisted psychotherapy research.
- Enrollees are professionals in specific licensed mental health and medical professions, as well as eligible ordained or commissioned clergy and chaplains.

https://www.ciis.edu/research-centers/center-for-psychedelic-therapies-and-research

How to support research into psychedelic medicines?

https://maps.org

MAPS

MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES

Summary

- Therapeutic approach is using psychedelic medication to assist psychotherapy
- One to three experiences for psilocybin or MDMA rather than as a chronic medication Need for therapists trained in psychedelic assisted psychotherapy
- Some patients with treatment resistant severe depression may need intermittent ketamine for long term
- Awaiting Phase 3 studies of MDMA for PTSD and Psilocybin for major depression
- Additional research into use of MDMA and Psilocybin for addiction is needed

Thank you!