PSYCHEDELIC-ASSISTED MENTAL HEALTH TREATMENT

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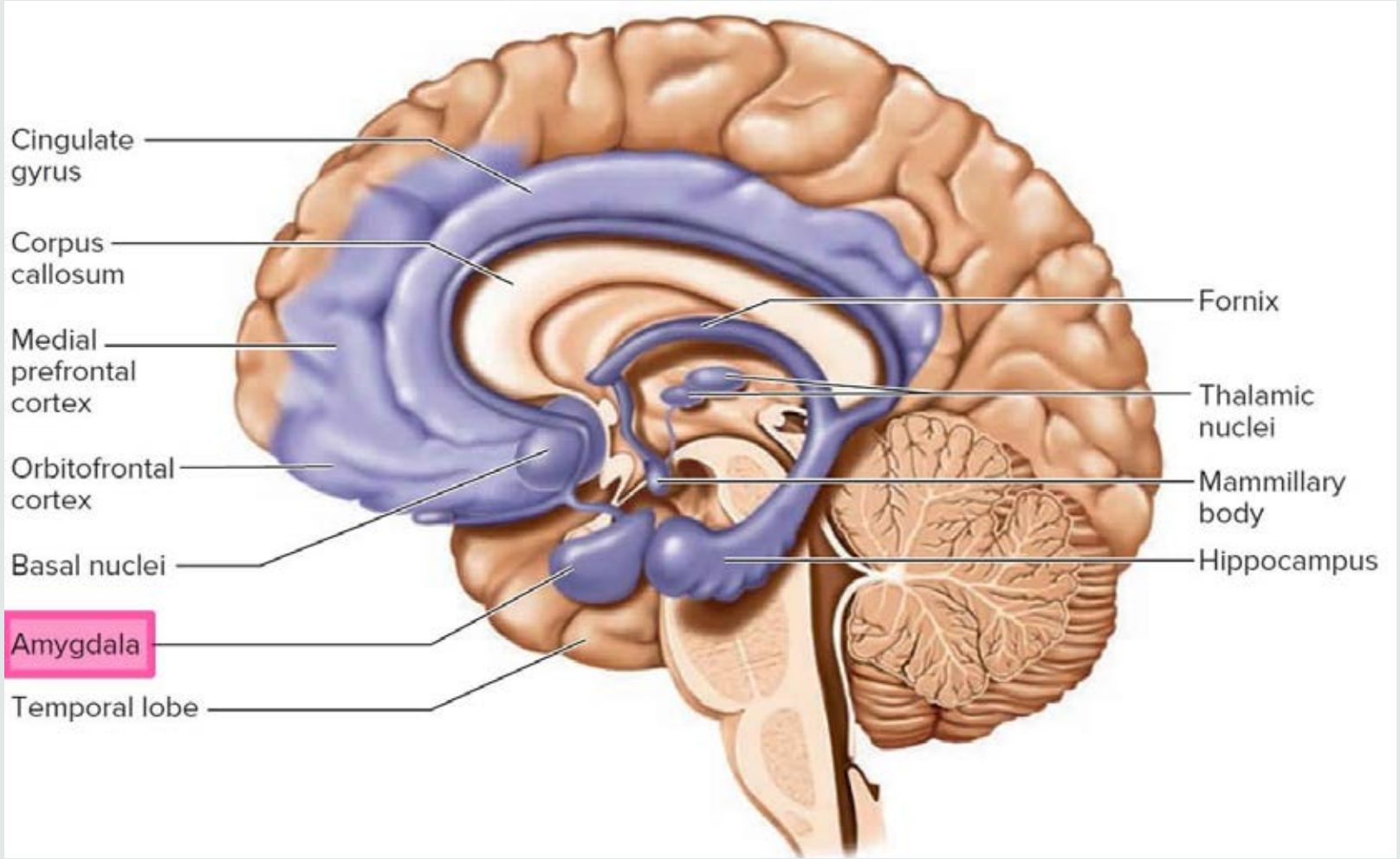
OBJECTIVES

At the conclusion of this lecture, the successful learner will be able to:

1. Describe the similarities of common mental health disorders and the mechanisms of action for current pharmacologic treatment options and psychedelics.
2. Describe the pooled impact of psychedelics on mental health disorders and the strength of evidence for benefit.
3. Describe the potential implications for treating patients with psychedelics for mental health disorders and what are the risks (including risks of self-medicating with illicit products)?

AMYGDALA – A KEY BRAIN AREA

- In depression or anxiety, amygdala neural activity and blood flow is increased
- Mind is fixated on stressors or disappointments
- Mind is trapped in positive feedback loop
- Traditional antidepressant drugs don’t fix this



PSYCHEDELIC MECHANISMS OF ACTION

- Dissociative therapy: Ketamine, Esketamine
  - *N-methyl-D-aspartate (NMDA) and glutamate receptor antagonist*
  - *Like ECT, turn it off and turn it back on again*
- Classical psychedelics: LSD, psilocybin, Ayahuasca, DMT
  - *Amygdala reset caused by psychedelic hallucination via serotonin 2A agonism*
- MDMA + psychotherapy: Increase oxytocin (bonding), burst of serotonin and norepinephrine release, synesthesia/surreal feeling (not a hallucination)
  - *Create environment where insight into trauma can occur*
- THC: Stimulate CB1 receptors

WHAT IS AN MDMA SESSION LIKE?

Before the session, patients are walked through what to expect during the MDMA session and the hopes for that session

They stay at the center for 8 hours to ensure that they are not exercising, not drinking too much water, not overcome by grief, and to work with a counselor to intensively identify the traumatic events or life events that underlie their mental health issues and help initially process them

- *They get their initial dose of MDMA and then a couple hours later, get a supplemental dose to extend the duration of effect*
- *The room and comfortable, the music is pleasant, the vibe is calming*

They come back for other psychotherapy sessions without the drug to work through the issues

If needed, they have up to two other MDMA sessions interspersed with psychotherapy alone sessions

WHAT PATIENTS EXPERIENCE DURING AN MDMA SESSION

- Increased mood (serotonin release)
- Increase energy (amphetamine effect)
- Surreal feeling – no hallucinations but sounds may be linked to colors (synesthesia) and the feelings are different (mescaline like effect)
- Intense feeling of bonding (oxytocin release)
- When directed to go into “dark places” where traumatic memories are, some patients can finally access them, but they are not as overwhelming to experience
- Once they are out in the open, they can be worked through when the drug effects are lower or in other sessions

WHAT IS A CLASSICAL PSYCHEDELIC SESSION LIKE?

The patient is checked in a secure room, comfortable furniture, and pleasant music to create a calming atmosphere

What will happen is discussed to set the stage for a "good trip"

- *Removing patient anxiety or paranoia is key before the drug is given*

There is either a psychotherapist or a "guide" to help the patient process their hallucination and prevent the "trip" from becoming a bad one

The session continues for several hours until the effects of the drug are out of the body to prevent a "reactivation" of a hallucination when they leave

Patients should not drive until the following day

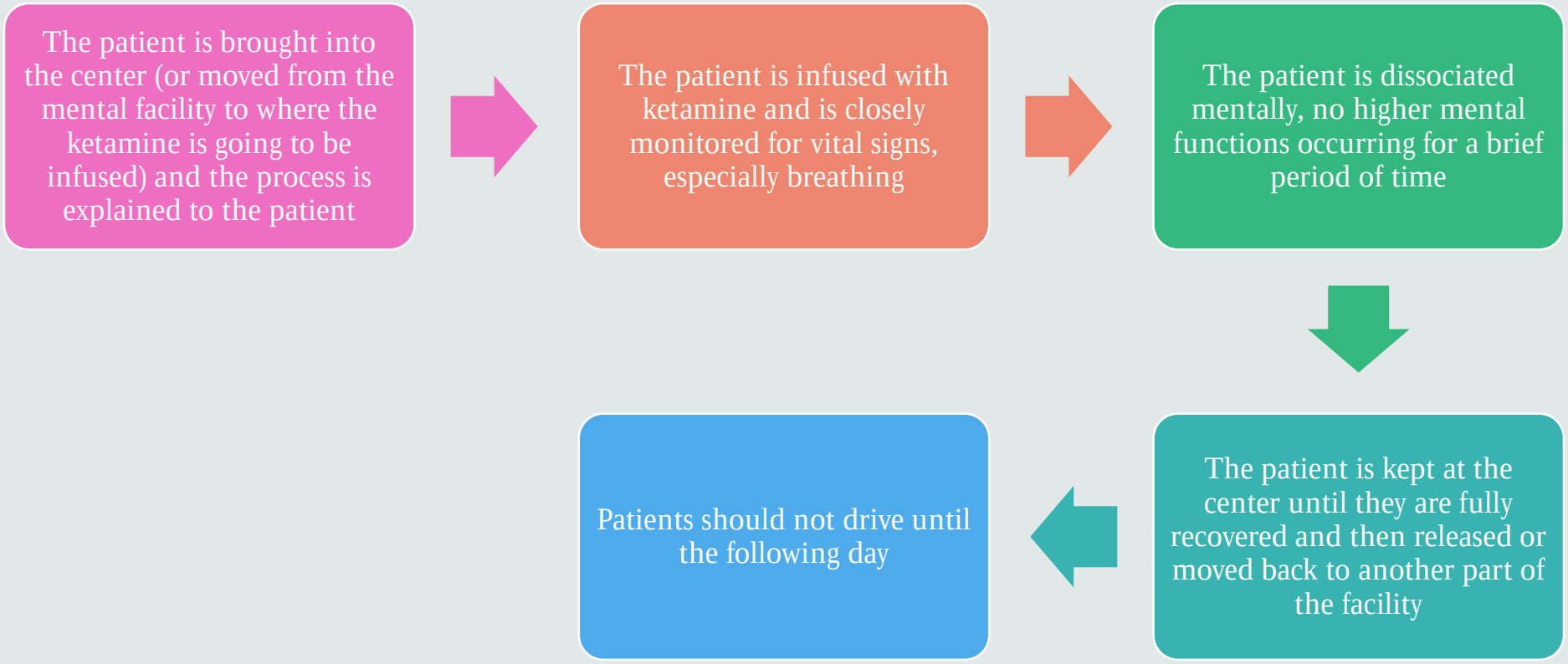
WHAT PATIENTS EXPERIENCE IN A CLASSICAL PSYCHEDELIC EXPERIENCE

- Can hear voices, see visions, see floating colors, animals who can speak, talk with deity
  - *If you can imagine it, you can experience it during one of these sessions*
  - *The hallucinations can suddenly shift and change*
- A “good trip”
  - *You can come out of yourself and look at your life or your mental health issue more objectively*
  - *You appreciate the bonds that tie things in the universe together and depersonalize your negative experiences*
  - *You understand human frailties and forgive those who failed you (family, friends, society, your body)*
- A “bad trip”
  - *Someone or something haunting you*
  - *Life or death situations where you are panicked*
  - *You feel you can read the mind or intentions of others and imagine they wish you ill or want to do you harm*

CLASSICAL PSYCHEDELICS

- Patients felt that they suppressed memories and emotions after learning they had cancer to be strong for others, to deny their own mortality, to deny it was really happening to them
  - *They were angry with the world and with their bodies but kept it in, suppressed it*
  - *They finally grieved for their loss, fully grieved and could move to the next stage of grieve on their way to acceptance*
  - *They better understood that mortality is a part of living*
- Patients with major depression or anxiety felt they couldn't escape from these negative thoughts, they couldn't reach their reasoning centers, they were stuck in a feedback loop of negativity
  - *The hallucination lit up the entire brain and took away the focus on a small subset of thoughts and emotions in the amygdala to better appreciate the totality of the human experience or put the thoughts into perspective*

WHAT IS A KETAMINE SESSION LIKE



WHAT IS AN ESKETAMINE SESSION LIKE?

Esketamine is administered intranasally

This occurs in the presence of a REMS program healthcare professional who monitors the patient for up to 2 hours for elevations in blood pressure, dizziness, vertigo, and breathing in an office or clinic

The patient is instructed not to drive until the next day

WHAT PATIENTS EXPERIENCE WHILE ON KETAMINE OR ESKETAMINE

- A whole or partial detachment from their surroundings, emotions, and memories for a period of time
  - *A feeling of bliss*
- Less obsessed or inundated with negative thoughts or emotions once higher cognition returns (for a period of time)
  - *A lessening of the small cage of negative thoughts and emotions*

RATING SCALES FOR MENTAL HEALTH DISORDERS

- PTSD: CAPS
- Depression: HAM-D, HADS-D, QIDS-SR-16, BDI
- Anxiety: STAI-S, STAI-T, HAM-A, HADS-A

HUGE ISSUES WITH ALL PSYCHEDELIC STUDIES

- Can you really blind them?
  - *Unblinding biases the participants and evaluators*
    - If you are a patient and believe in psychedelics as a promising therapy, the placebo effect can occur
    - If you are an evaluator that believes in psychedelics, you might assess patient in the psychedelic group differently
  - *Some investigators are also users of illicit psychedelics*
    - Could personally benefit from psychedelics being found effective
  - *Patients with history of psychedelic or cannabis use rarely excluded*
    - People with positive past-experience may be more likely to participate
- Some trials are really old
  - *Trials from 1960s and 1970s, do they reflect current patients?*
- Many newer studies funded by companies making them or drug legalization advocacy organizations (MAPS)
  - *Safeguards to prevent interference/influence not fully transparent*

MDMA IN PTSD

- Psychotherapy session (PS), then PS + MDMA (80mg + 40mg) or Placebo, then PS, then PS + MDMA or placebo, then PS, then PS or PS + MDMA or Placebo, then PS

Source	MDMA Mean	MDMA SD	MDMA Total	Control Mean	Control SD	Control Total	MD [95%-CI]	Weight
Mithoefer 2011	-53.70	7.2000	12	-20.50	8.8000	8	-33.20 [-40.53; -25.87]	24.3%
Mitchell 2021	-24.40	11.6000	42	-13.90	11.5000	37	-10.50 [-15.60; -5.40]	25.5%
Mithoefer 2018	-49.50	24.2000	19	-11.40	12.7000	7	-38.10 [-52.48; -23.72]	19.4%
Ot'Alora 2018	-24.40	24.2000	21	-11.50	21.2000	6	-12.90 [-32.77; 6.97]	15.5%
Oehen 2013	-15.60	18.1000	7	-3.20	15.3000	4	-12.40 [-32.51; 7.71]	15.3%
Random effects model			**101**			**62**	**-22.03 [-38.53; -5.52]**	**100.0%**

Heterogeneity: I^2 = 88%, τ^2 = 141.3706, p < 0.01

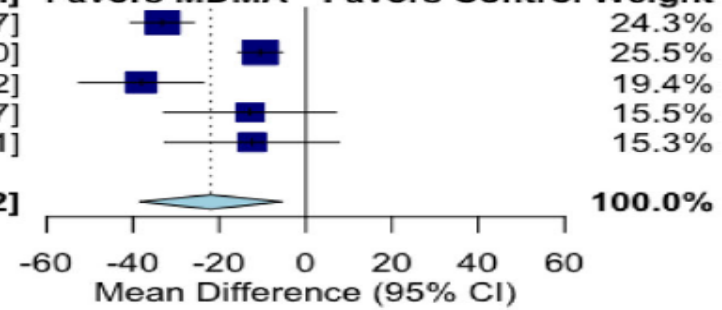


Figure 2. Pooled comparison of differences of CAPS scores from baseline for MDMA-assisted psychotherapy versus control. CAPS, Clinician-Administered PTSD Scale; MD, mean difference; MDMA, 3,4-methylenedioxymethamphetamine.

Source	MDMA Events	MDMA Total	Control Events	Control Total	RR [95%CI]	Weight
Mithoefer 2011	10	12	2	8	3.33 [0.98; 11.37]	11.4%
Mitchell 2021	28	42	12	37	2.06 [1.23; 3.43]	65.6%
Mithoefer 2018	13	19	2	7	2.39 [0.71; 8.03]	11.7%
Ot'Alora 2018	9	21	2	6	1.29 [0.37; 4.42]	11.3%
Random effects model	**60**	**94**	**18**	**58**	**2.10 [1.37; 3.21]**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.75

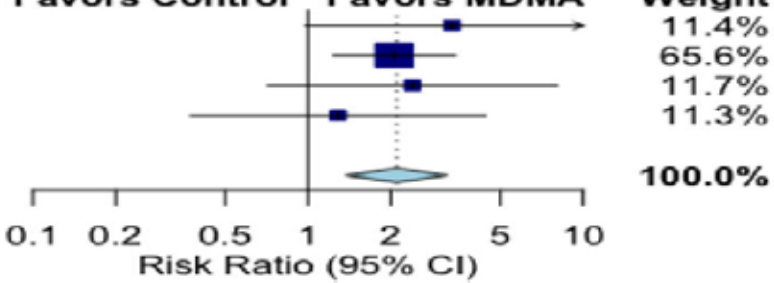


Figure 4. Pooled comparison of the percentage of patients no longer meeting CAPS score criteria for PTSD with MDMA-assisted psychotherapy versus control. CAPS, Clinician-Administered PTSD Scale; MDMA, 3,4-methylenedioxymethamphetamine; RR, relative risk.

The Journal of Clinical Pharmacology 2022, 62(4) 463–471.

MDMA IN PTSD

- Took several weeks for the effects to occur (like regular antidepressants)
  - *Need to access repressed or panic inducing memories and experience them to deal with them in psychotherapy*
- Sessions can be emotionally taxing (catharsis)
- Magnitude of effect is 2-3x greater for MDMA vs. placebo than SSRI or SNRI vs. placebo
- Effects maintained for 6-mo to 1-year
- No one with schizophrenia/psychosis studied
- Raised BP and HR
- One counselor took advantage of participant (oxytocin effect)?

The Journal of Clinical Pharmacology 2022, 62(4) 463–471.

ADVERSE EVENTS

- Patients not allowed to exercise, room controlled and kept environmentally comfortable
- Patients kept until drug effects completely wore off (8 hours)
- Reliving the trauma or the amphetamine effects can induce anxiety and panic attack, reduced appetite, jittery, irritability and boost blood pressure and heart rate
- Amphetamine effects cause jaw clenching and irritability

Adverse Event	Placebo or Low-Dose MDMA, %	Moderate or High-Dose MDMA, %
Aggregate of phase II trials		
Anxiety	48	72
Jaw clenching	19	64
Reduced appetite	23	49
Dizziness	19	40
Nausea	19	40
Depressed mood	3	8
Irritability	0	6
Panic attack	0	6
Mitchell et al 2021 (phase III)		
Muscle tightness	11	63
Reduced appetite	11	52
Nausea/Vomiting	11/0	30/9
Excessive sweating	2	20
Restlessness	0	15
Jaw clenching	2	13
Dizziness	5	13
Jittery	0	11
Pyrexia	2	7
Anxiety	0	7
Blurred vision	2	9

KETAMINE IN PTSD

- Ketamine or control (midazolam or saline) given to patients with severe PTSD
- Two to three times weekly for 2-4 weeks
- Results at the end of the last dose
- Beneficial effects began as early as 24-hours after first dose
- A bridge to other therapy

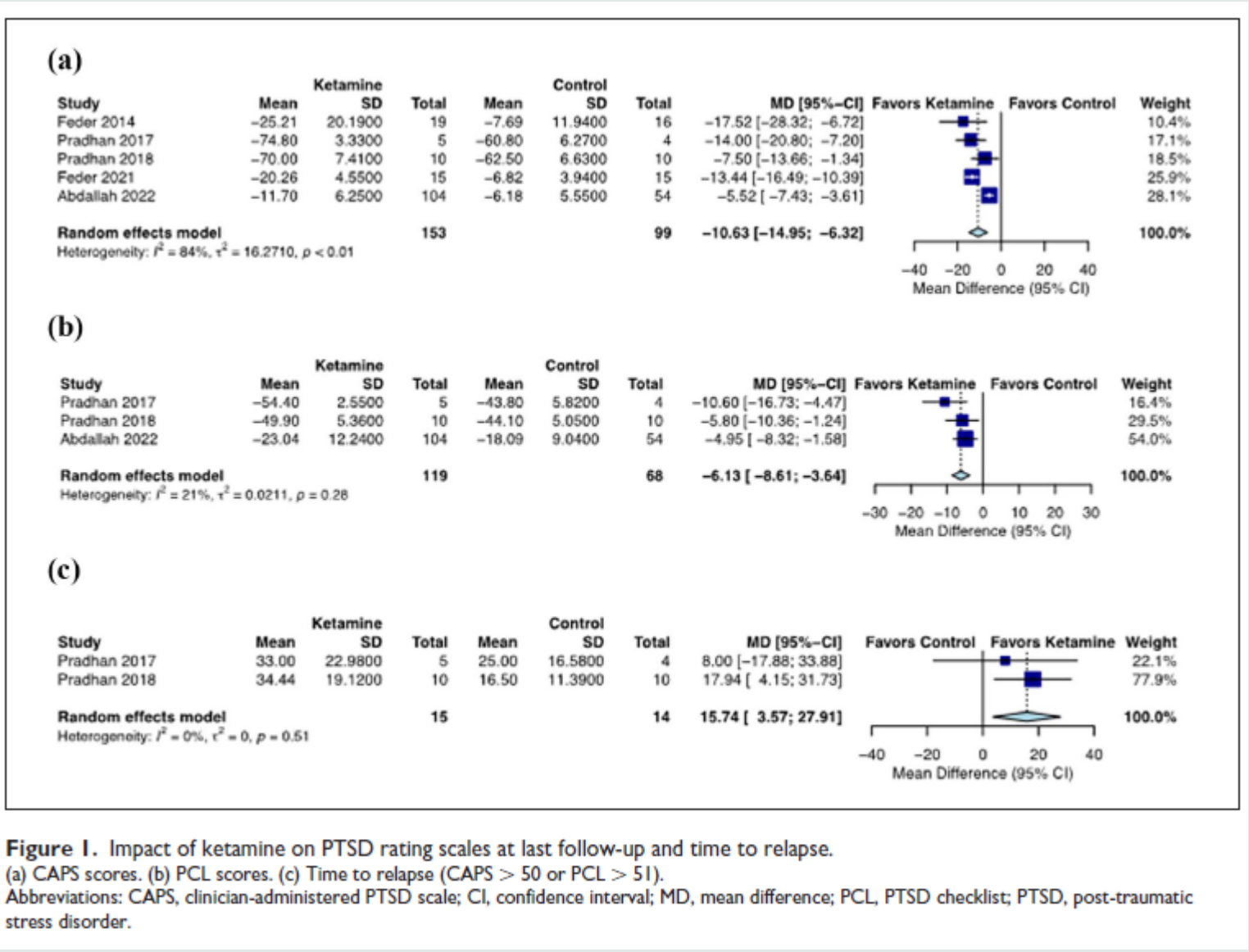


Figure 1. Impact of ketamine on PTSD rating scales at last follow-up and time to relapse.
(a) CAPS scores. (b) PCL scores. (c) Time to relapse (CAPS > 50 or PCL > 51).
Abbreviations: CAPS, clinician-administered PTSD scale; CI, confidence interval; MD, mean difference; PCL, PTSD checklist; PTSD, post-traumatic stress disorder.

KETAMINE ADVERSE EVENTS

Table 2. Adverse Events in the Ketamine Versus Control Group at Different Time Periods.

Study name	Time period	Adverse event	% Ketamine (n/total n)	% Control (n/total n)	OR [95% CI]
Feder 2014	Infusion Day	Dry Mouth	40.9% (9/22)	10.5% (2/19)	5.88 [1.08 to 32.01]
Feder 2021	Week 1 After 3 Infusions		0.0% (0/15)	0.0% (0/15)	1.00 [0.02 to 53.66]
Feder 2021	Week 2 After 6 Infusions		13.3% (2/15)	0.0% (0/15)	5.74 [0.25 to 130.38]
Feder 2014	Infusion Day	Nausea or Vomiting	36.4% (8/22)	0.0% (0/19)	22.86 [1.22 to 429.04]
Feder 2021	Week 1 After 3 Infusions		20% (3/15)	6.7% (1/15)	3.50 [0.32 to 38.23]
Feder 2021	Week 2 After 6 Infusions		13.3% (2/15)	0.0% (0/15)	5.74 [0.25 to 130.38]
Abdallah 2022	Week 4 After 16 Infusions		23.1% (24/104)	18.5% (10/54)	1.32 [0.58 to 3.01]
Feder 2014	Infusion Day	Cardiac	45.5% (10/22)	15.8% (3/19)	4.44 [1.00 to 19.75]
Feder 2021	Week 1 After 3 Infusions		6.7% (1/15)	13.3% (2/15)	0.46 [0.04 to 5.75]
Feder 2021	Week 2 After 6 Infusions		0.0% (0/15)	6.7% (1/15)	0.31 [0.01 to 8.29]
Feder 2014	Infusion Day	Headache	27.3% (6/22)	10.5% (2/19)	3.19 [0.55 to 18.16]
Feder 2021	Week 1 After 3 Infusions		26.7% (4/15)	13.3% (2/15)	2.36 [0.36 to 15.46]
Feder 2021	Week 2 After 6 Infusions		20.0% (3/15)	13.3% (2/15)	1.63 [0.23 to 11.46]
Abdallah 2022	Week 4 After 16 Infusions		19.2% (20/104)	13.0% (7/54)	1.60 [0.63 to 4.06]
Feder 2014	Infusion Day	Dizziness	63.6% (14/22)	26.3% (5/19)	4.90 [1.28 to 18.73]
Feder 2021	Week 1 After 3 Infusions		33.3% (5/15)	6.7% (1/15)	7.00 [0.75 to 69.49]
Feder 2021	Week 2 After 6 Infusions		26.7% (4/15)	13.3% (2/15)	2.36 [0.36 to 15.46]
Feder 2014	Infusion Day	Blurred Vision	63.6% (14/22)	31.6% (6/19)	3.79 [1.03 to 13.91]
Feder 2021	Week 1 After 3 Infusions		40.0% (6/15)	0.0% (0/15)	21.21 [1.06 to 420.82]
Feder 2021	Week 2 After 6 Infusions		53.3% (8/15)	0.0% (0/15)	35.13 [1.78 to 693.42]
Feder 2014	Infusion Day	Fatigue	40.9% (9/22)	26.3% (5/19)	1.94 [0.51 to 7.32]
Feder 2021	Week 1 After 3 Infusions		26.7% (4/15)	73.3% (11/15)	0.13 [0.02 to 0.67]
Feder 2021	Week 2 After 6 Infusions		33.3% (5/15)	86.7% (13/15)	0.08 [0.01 to 0.48]
Abdallah 2022	Week 4 After 16 Infusions		6.7% (7/104)	3.7% (2/54)	1.88 [0.38 to 9.36]

Abbreviations: CI, confidence interval; OR, odds ratio.

Annals of Pharmacotherapy. 2024;58(7):669-677.
doi:10.1177/10600280231199666

PSYCHEDELICS VS. SSRIS IN DEPRESSION

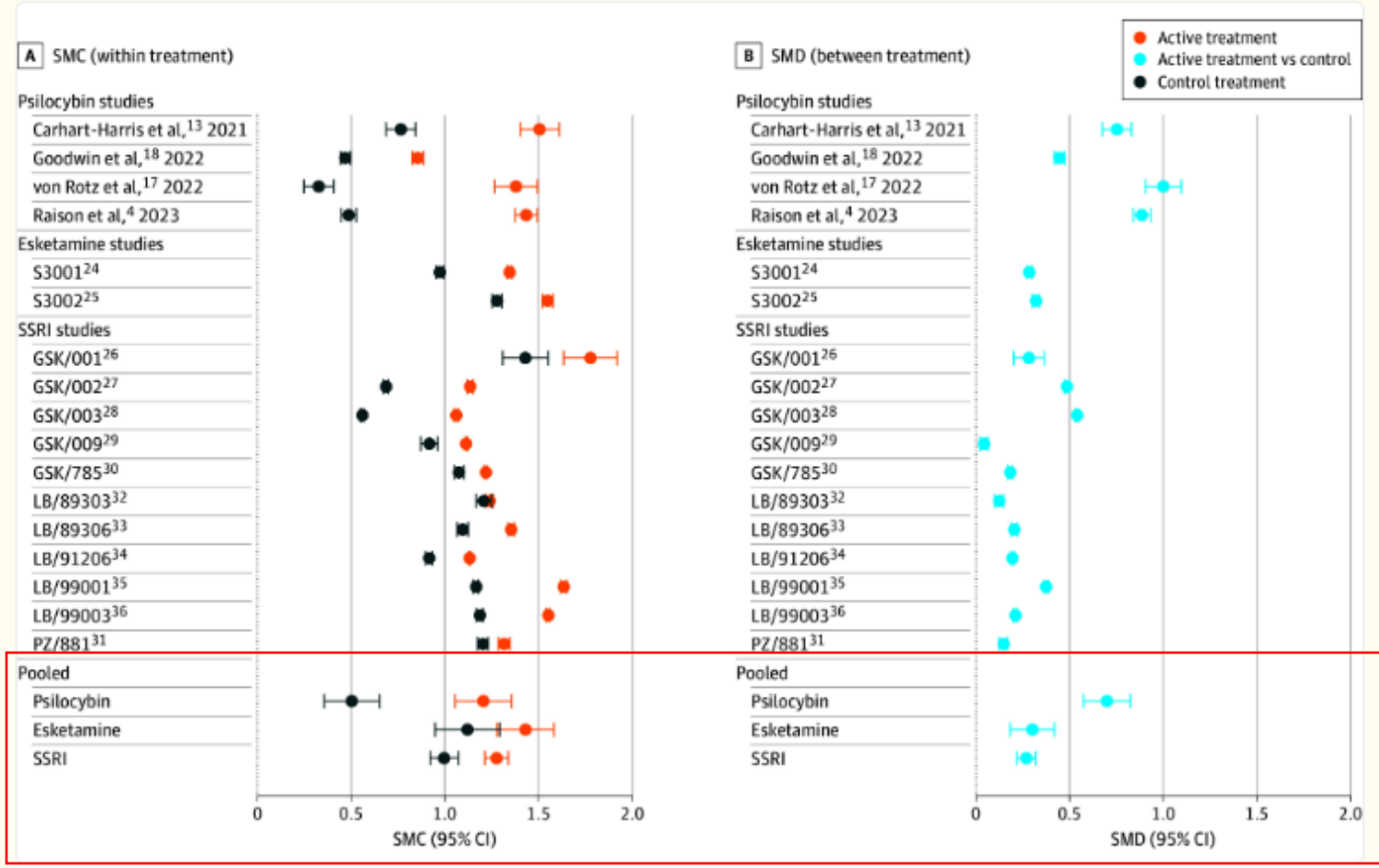
Left: Psilocybin changes from baseline align with esketamine and SSRIs (red whisker plots) but placebo effect is much less (black whisker plot)

This suggests bias/confounding was introduced

This means the benefits of psilocybin are likely aligned with other options (blue whisker plots).

https://pmc.ncbi.nlm.nih.gov/articles/PMC12311713/

Figure 2. Within- and Between-Group Effect Sizes for Psilocybin, Selective Serotonin Reuptake Inhibitors (SSRIs), and Esketamine.



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Error bars indicate plus or minus 1 SE. SMC indicates standardized mean change; SMD, standardized mean difference.

PSILOCYBIN VS. ESCITALOPRAM IN DEPRESSION

- R, DB, PC trial
- Patients received 25 mg of psilocybin once in weeks 1 and 4 (active) or 1mg in weeks 1 and 4 + escitalopram 10-20mg daily for 6 weeks
- Results at 6-weeks were assessed

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

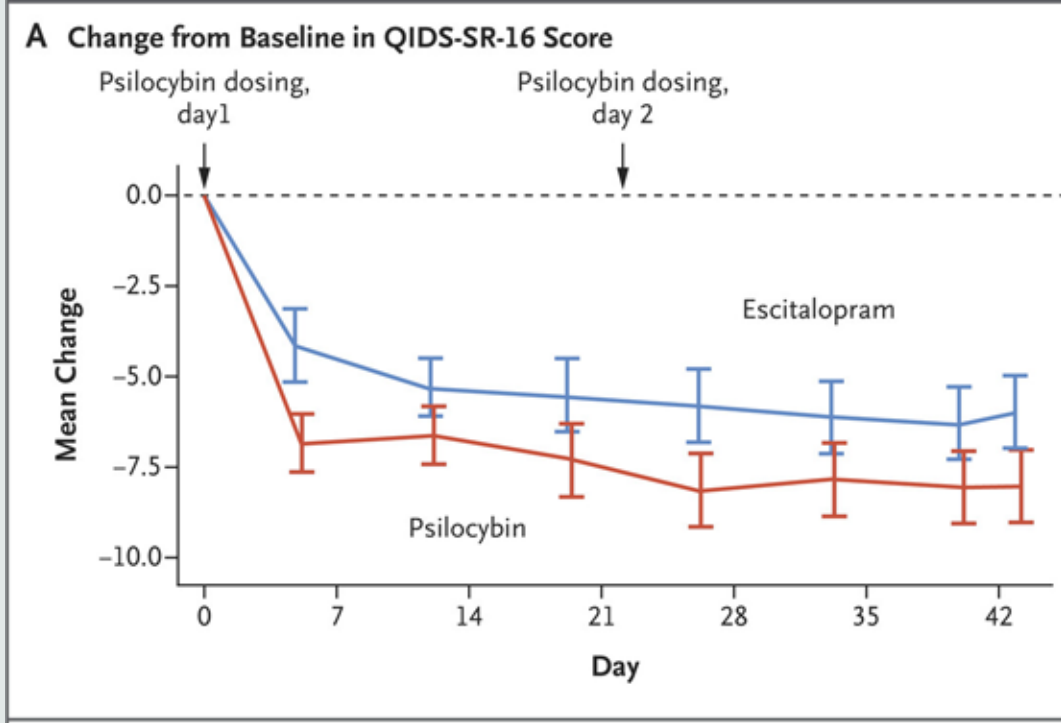
Characteristic	Psilocybin (N=30)	Escitalopram (N=29)
Demographic		
Age (range) — yr	43.3±11.7 (21–64)	39.1±9.7 (22–60)
Female sex — no. (%)	11 (37)	9 (31)
White race — no. (%)†	28 (93)	24 (83)
Employment status — no. (%)		
Employed	21 (70)	21 (72)
Student	2 (7)	3 (10)
Unemployed	7 (23)	5 (17)
University level education — no. (%)	22 (73)	23 (79)
No previous psilocybin use — no. (%)	22 (73)	21 (72)
Weekly alcohol use (range) — g‡	36.8±43.1 (0–160)	67.7±66.6 (0–240)
Discontinued psychiatric medication for trial — no. (%)	11 (37)	12 (41)
Clinical		
Duration of illness (range) — yr	22.1±10.7 (3–44)	15.1±11.0 (2–46)
No. of psychiatric medications previously used (range)	2.2±1.6 (0–6)	1.8±1.5 (0–5)
Previous use of psychotherapy — no. (%)	28 (93)	26 (90)
QIDS-SR-16 score at pretreatment baseline (range)§	14.5±3.9 (7–23)	16.4±4.1 (6–22)
HAM-D-17 score at pretreatment baseline (range)¶	19.2±2.3 (16–23)	18.4±3.4 (11–26)
BDI-1A score at pretreatment baseline (range)‖	29.1±6.8 (16–41)	28.7±7.0 (10–44)

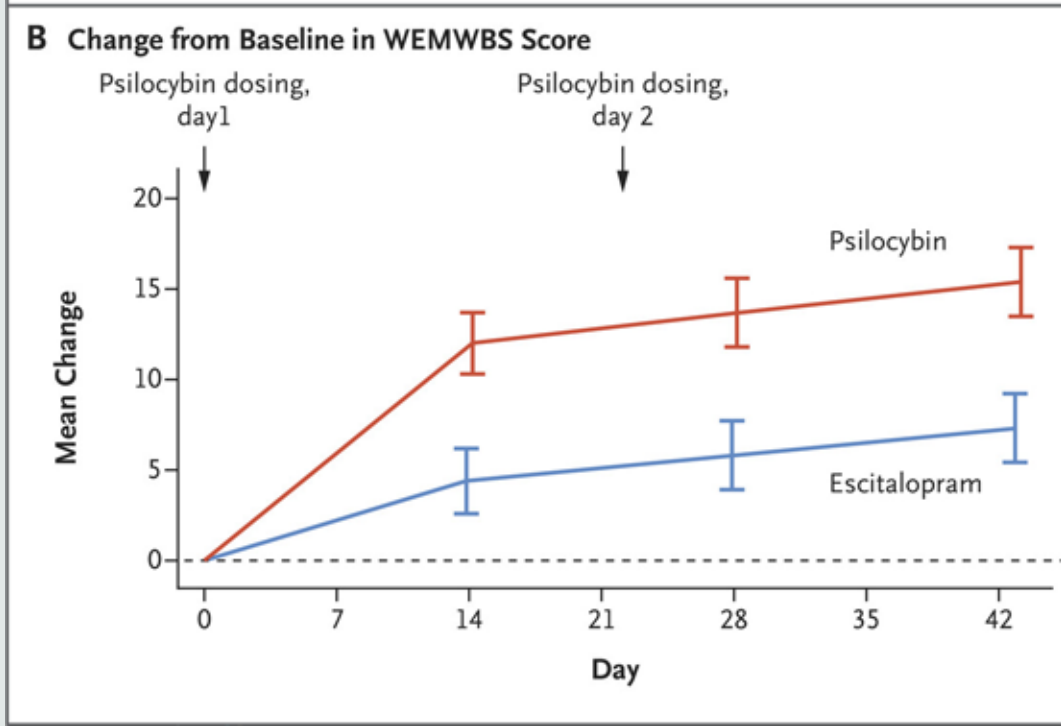
* Plus–minus values are means ±SD. Pretreatment baseline was 7 to 10 days before dosing-day 1.
† Race was reported by the patients.
‡ To convert grams to U.K. units, divide by 8.
§ The scores on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) range from 0 to 27, with higher scores indicating greater depression.
¶ The scores on the 17-item Hamilton Depression Rating Scale (HAM-D-17) range from 0 to 50, with higher scores indicating greater depression. At screening, which was typically a few weeks before pretreatment baseline, all the patients had a score of at least 17 on the HAM-D-17. The depression scores reported in this table are from pretreatment baseline and not screening.
‖ The scores on the Beck Depression Inventory 1A (BDI-1A) range from 0 to 63, with higher scores indicating greater depression.

N Engl J Med 2021;384:1402-1411
DOI: 10.1056/NEJMoa2032994

PSILOCYBIN VS. ESCITALOPRAM

- Psilocybin, given twice (0 and 21 days), was as effective as daily escitalopram at alleviating depression symptoms and patients expressed significantly higher feelings of well-being





N Engl J Med 2021;384:1402-1411
DOI: 10.1056/NEJMoa2032994

PSILOCYBIN ADVERSE EVENTS

- Environment carefully controlled to prevent “bad trips”
- Peaceful music, someone to assist/guide the “trip”
- Patient kept until drug effects fully wore off

Table 3. Adverse Events Reported during the 6-Week Trial Period and on Dosing-Day 1.*

Event	6-Wk Trial Period		Dosing-Day 1	
	Psilocybin (N=30)	Escitalopram (N=29)	Psilocybin (N=30)	Escitalopram (N=29)
	number of patients (percent)			
Any adverse event	26 (87)	24 (83)	15 (50)	8 (28)
Serious adverse event	0	0	0	0
Related adverse event†	22 (73)	23 (79)	15 (50)	6 (21)
Adverse event reported in ≥3 patients during the full trial period				
Headache	20 (67)	15 (52)	13 (43)	5 (17)
Nausea	8 (27)	9 (31)	4 (13)	0
Fatigue	2 (7)	7 (24)	0	0
Anxiety	0	4 (14)	0	0
Dry mouth	0	4 (14)	0	0
Migraine	3 (10)	1 (3)	0	0
Palpitations	1 (3)	3 (10)	0	0
Sleep disorder	1 (3)	3 (10)	0	0
Diarrhea	1 (3)	2 (7)	0	0
Feeling abnormal	0	3 (10)	0	0
Feeling jittery	2 (7)	1 (3)	0	0
Vomiting	2 (7)	1 (3)	0	0

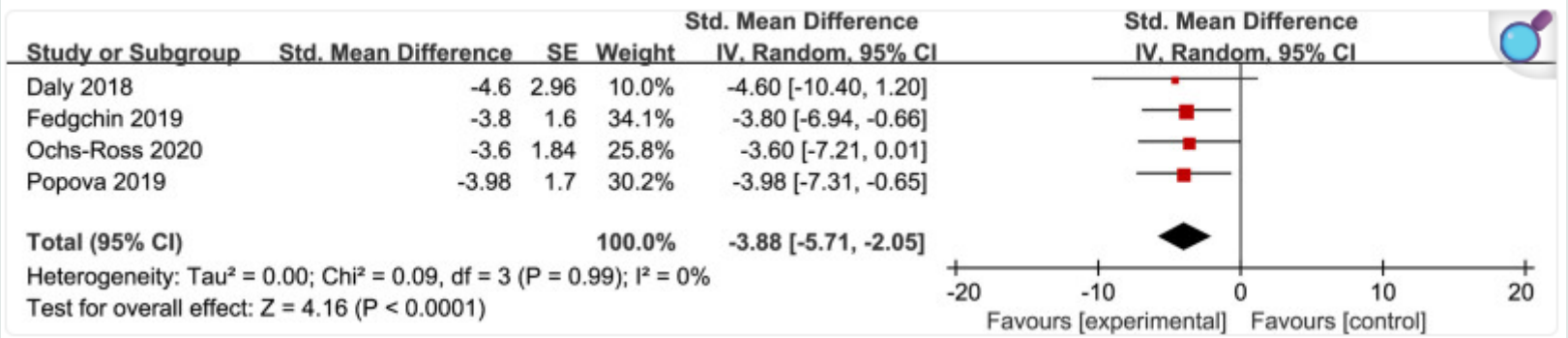
* These were the most prevalent adverse events that were reported during the trial.
† Whether an adverse event was related to the therapeutic intervention was determined by the study clinician through dialogue with each patient. Events deemed “probably” or “definitely” related were counted.

N Engl J Med 2021;384:1402-1411
DOI: 10.1056/NEJMoa2032994

CHRONIC ESKETAMINE SEVERE DEPRESSION VS. PLACEBO

- MADRS score reduced 3.88 points, $p<0.05$

- More than twice as likely to have clinical response

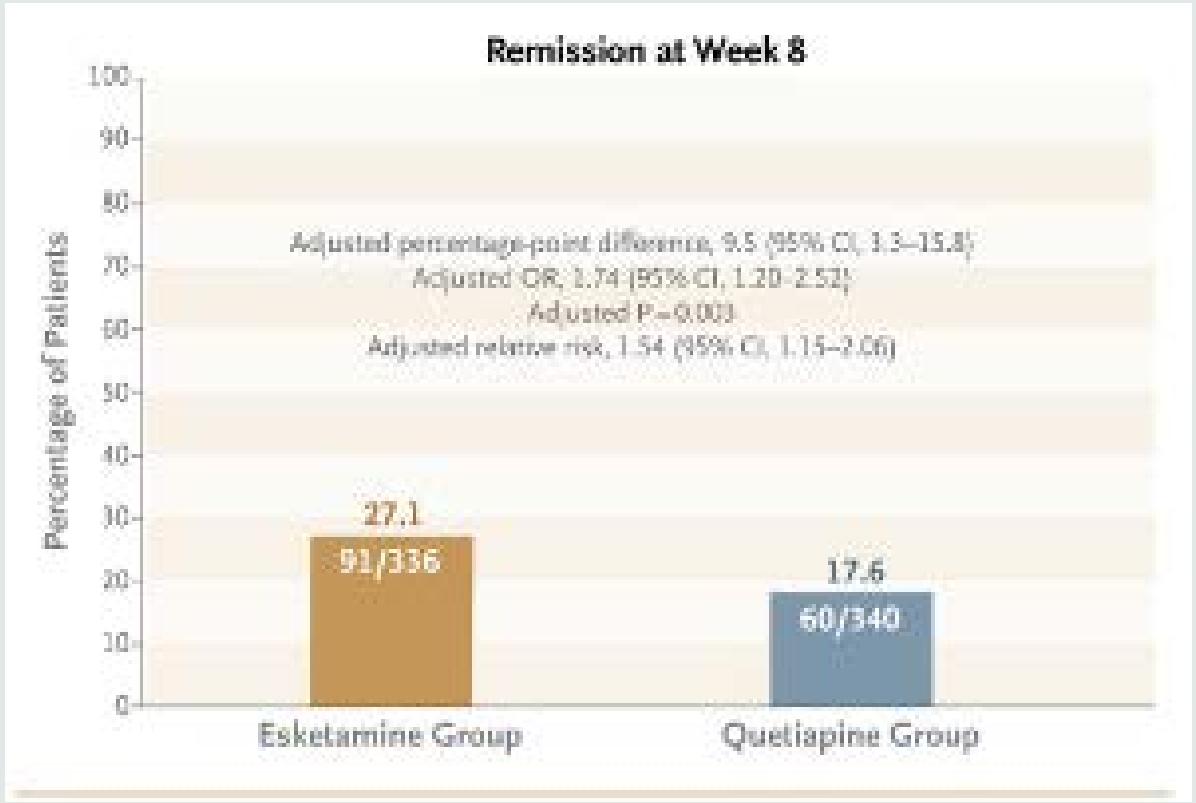


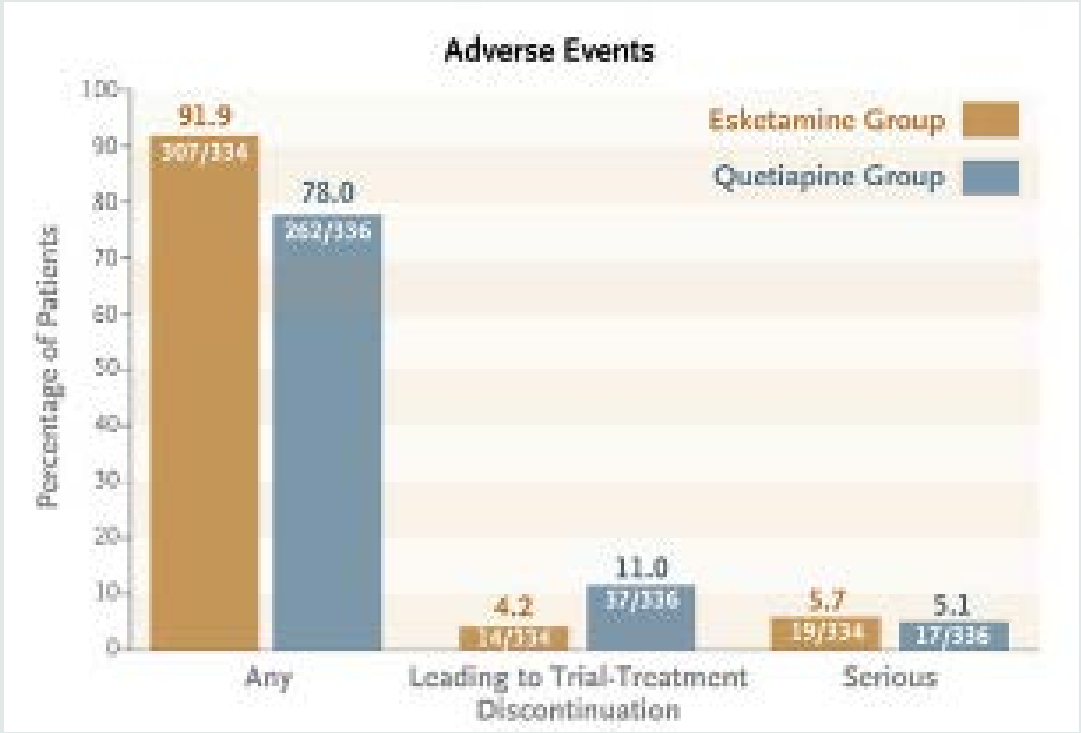
https://pmc.ncbi.nlm.nih.gov/articles/PMC11875627/

CHRONIC ESKETAMINE VS. QUETIAPINE DOSING

- Patients randomly assigned to receive esketamine nasal spray plus an SSRI or SNRI (esketamine group) or extended-release quetiapine plus an SSRI or SNRI (quetiapine group)
- The starting dose of esketamine was dependent on age and ancestry, then flexibly dosed (18–

CHRONIC ESKETAMINE VS. QUETIAPINE IN RESISTANT DEPRESSION





N Engl J Med 2023;389:1298-1309
DOI: 10.1056/NEJMoa230414

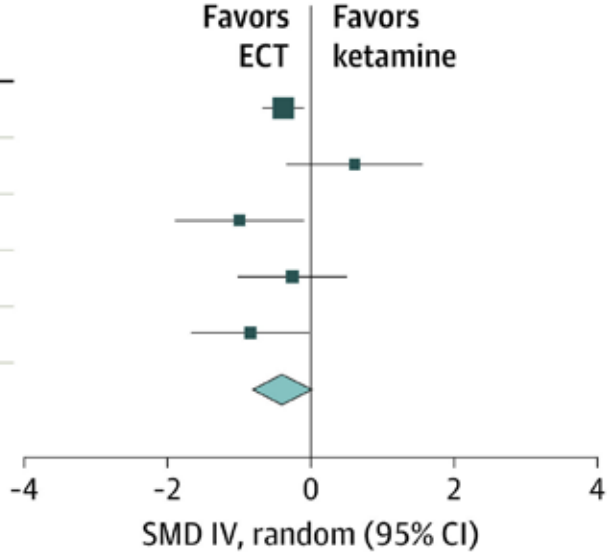
KETAMINE VS. ECT FOR TREATMENT RESISTANT DEPRESSION

JAMA Psychiatry. 2023 Jun 1;80(6):639-642. doi: 10.1001/jamapsychiatry.2023.0562.

- All studies (Multiple sessions of ECT vs. ketamine, end of treatment results on depression scales)

Study	ECT Mean (SD)	ECT Total No.	Ketamine Mean (SD)	Ketamine Total No.	SMD IV, random (95% CI)	Weight, %
Ekstrand et al,[4] 2022	12.2 (11.1)	91	16.9 (13.1)	95	-0.38 (-0.68 to -0.09)	37.8
Ghasemi et al,[9] 2014	15.7 (7.5)	9	10.9 (7.5)	9	0.61 (-0.34 to 1.56)	13.4
Kheirabadi et al,[7] 2019	13.6 (3.1)	12	16.9 (3.3)	10	-0.99 (-1.89 to -0.09)	14.5
Kheirabadi et al,[8] 2020	9.5 (5.4)	12	10.9 (5.1)	15	-0.26 (-1.02 to 0.50)	18.0
Sharma et al,[5] 2020	3.9 (3.2)	13	8.8 (7.4)	12	-0.84 (-1.67 to -0.02)	16.3
Total (95% CI)		137		141	-0.39 (-0.81 to 0.02)	100.0

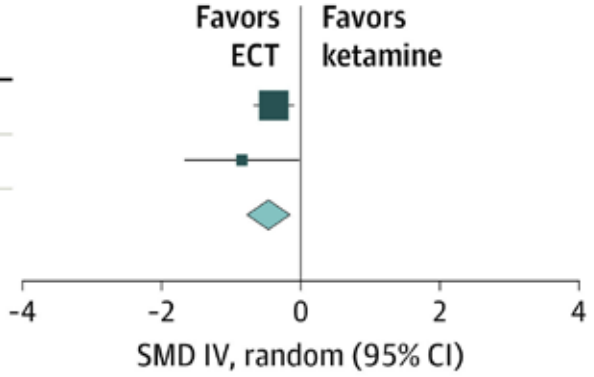
Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 7.26$; $df = 4$; $P = .12$; $I^2 = 45\%$
Test for overall effect: $z = 1.86$ ($P = .06$)



- Lowest RoB studies (ECT vs. ketamine, end of treatment results on depression scales)

Study	ECT Mean (SD)	ECT Total No.	Ketamine Mean (SD)	Ketamine Total No.	SMD IV, random (95% CI)	Weight, %
Ekstrand et al,[4] 2022	12.2 (11.1)	91	16.9 (13.1)	95	-0.38 (-0.68 to -0.09)	86.8
Sharma et al,[5] 2020	3.9 (3.2)	13	8.8 (7.4)	12	-0.84 (-1.67 to -0.02)	13.2
Total (95% CI)		104		107	-0.45 (-0.75 to -0.14)	100.0

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 1.06$; $df = 1$; $P = .30$; $I^2 = 6\%$
Test for overall effect: $z = 2.87$ ($P = .004$)



KETAMINE + ECT VS. ECT IN DEPRESSION

	MD -2.26 (95%CI: -6.52 to 2.00), I^2=85%, N=5	MD -5.61 (95%CI: -14.96 to 3.75), I^2=92%, N=2
	MD -0.89 (95%CI: -5.58 to 3.79), I^2=95%, N=6	MD -4.39 (95%CI: -10.75 to 1.97), I^2=79%, N=2
	MD -2.65 (95%CI: -4.01 to -1.29), I^2=42%, N=4	MD -4.42 (95%CI: -7.66 to -1.19), I^2=46%, N=3
	MD -2.95 (95%CI: -5.32 to -0.59), I^2=73%, N=7	MD -1.23 (95%CI: -7.35 to 4.89), I^2=86%, N=3
	MD -2.96 (95%CI: -4.02 to -1.90), I^2=0%, N=3	MD -6.45 (95%CI: -19.60 to 6.70), I^2=90%, N=3
	MD -2.60 (95%CI: -5.16 to -0.03), I^2=82%, N=7	MD -3.88 (95%CI: -9.47 to 1.71), I^2=87%, N=3
	MD -2.34 (95%CI: -3.74 to -0.95), I^2=29%, N=3	MD -1.23 (95%CI: -14.14 to 11.68), I^2=90%, N=2

Ketamine use with ECT significantly increased fear with hallucinations (OR: 1.99, [95% CI: 1.11-3.58], I2 = 0%, N = 7) than with nonketamine anesthesia.

	OR 1.31 (95%CI: 0.85 to 2.02), I^2=23%, N=8
	OR 1.99 (95%CI: 1.11 to 3.58), I^2=0%, N=7
	OR 1.67 (95%CI: 0.96 to 2.88), I^2=2%, N=6
	OR 1.93 (95%CI: 0.97 to 3.84), I^2=0%, N=5
	OR 1.38 (95%CI: 0.45 to 4.21), I^2=9%, N=3
	OR 0.27 (95%CI: 0.05 to 1.36), I^2=69%, N=3

Ann Pharmacother 2024:

PSYCHEDELICS IN ANXIETY

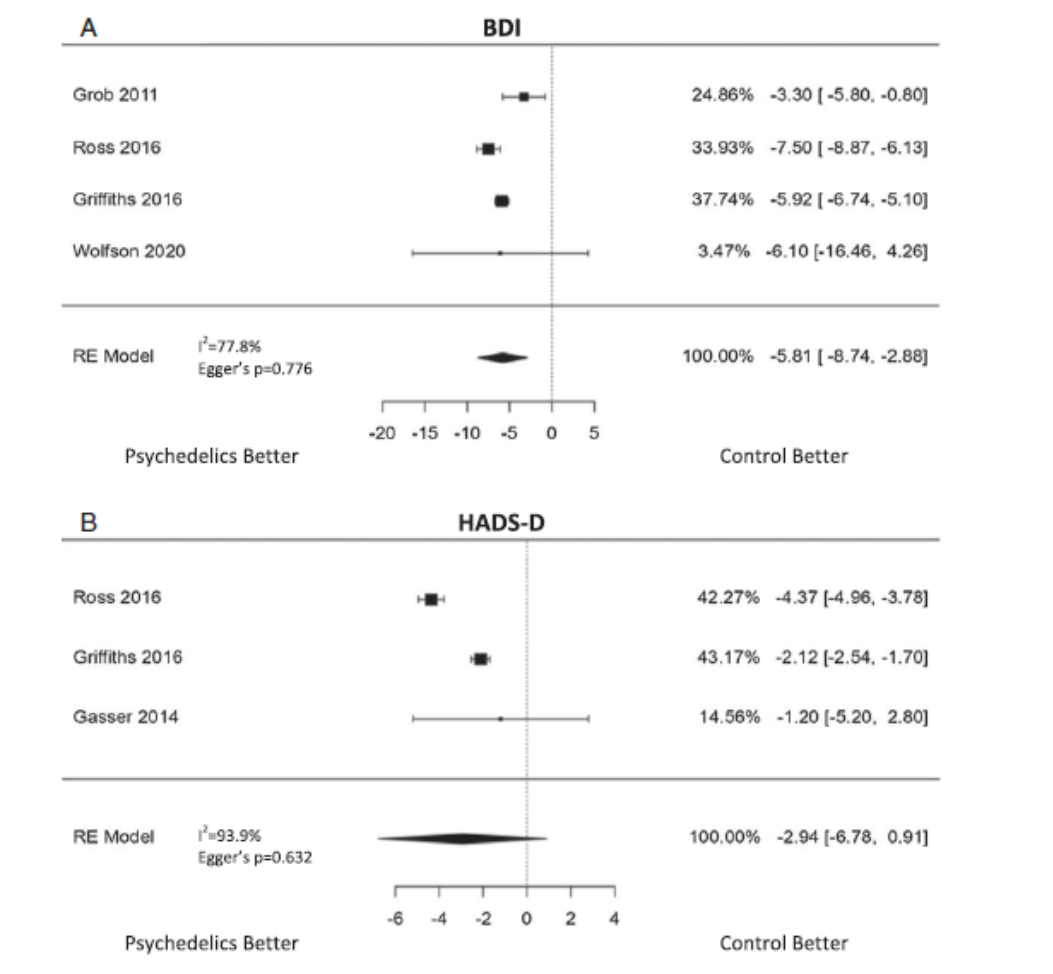
- MM-120 is a purified form of LSD (Phase IIb)
  - *MM120 100 µg demonstrated a 7.7-point improvement in HAM-A over placebo at Week 12 (-21.9 MM120 vs. -14.2 placebo; p<0.003 Cohen's d=0.81)*
  - *MM120 provided a 65% clinical response rate and a 48% clinical remission rate in HAM-A sustained to Week 12*
  - *This clinical activity was observed as early as study day 2*
- Psilocybin (Phase IIb)
  - *Psilocybin reduced HAM-A scores from 29.5 at baseline to 16.8 on the Hamilton Anxiety Rating Scale (HAM-A)–a validated tool used to measure the severity of anxiety symptoms–versus 29.5 points at baseline*
  - *The 12.8-point decrease in HAM-A score after psilocybin treatment was significantly greater than the 3.6-point reduction in the placebo group, with a p-value less than 0.0001*
  - *With psilocybin, 44% of patients demonstrated a clinically meaningful improvement in anxiety symptoms, quantified by a 50% drop in HAM-A scores. Moreover, 27% of patients achieved full disease remission, a rate five times higher than that in the placebo group*

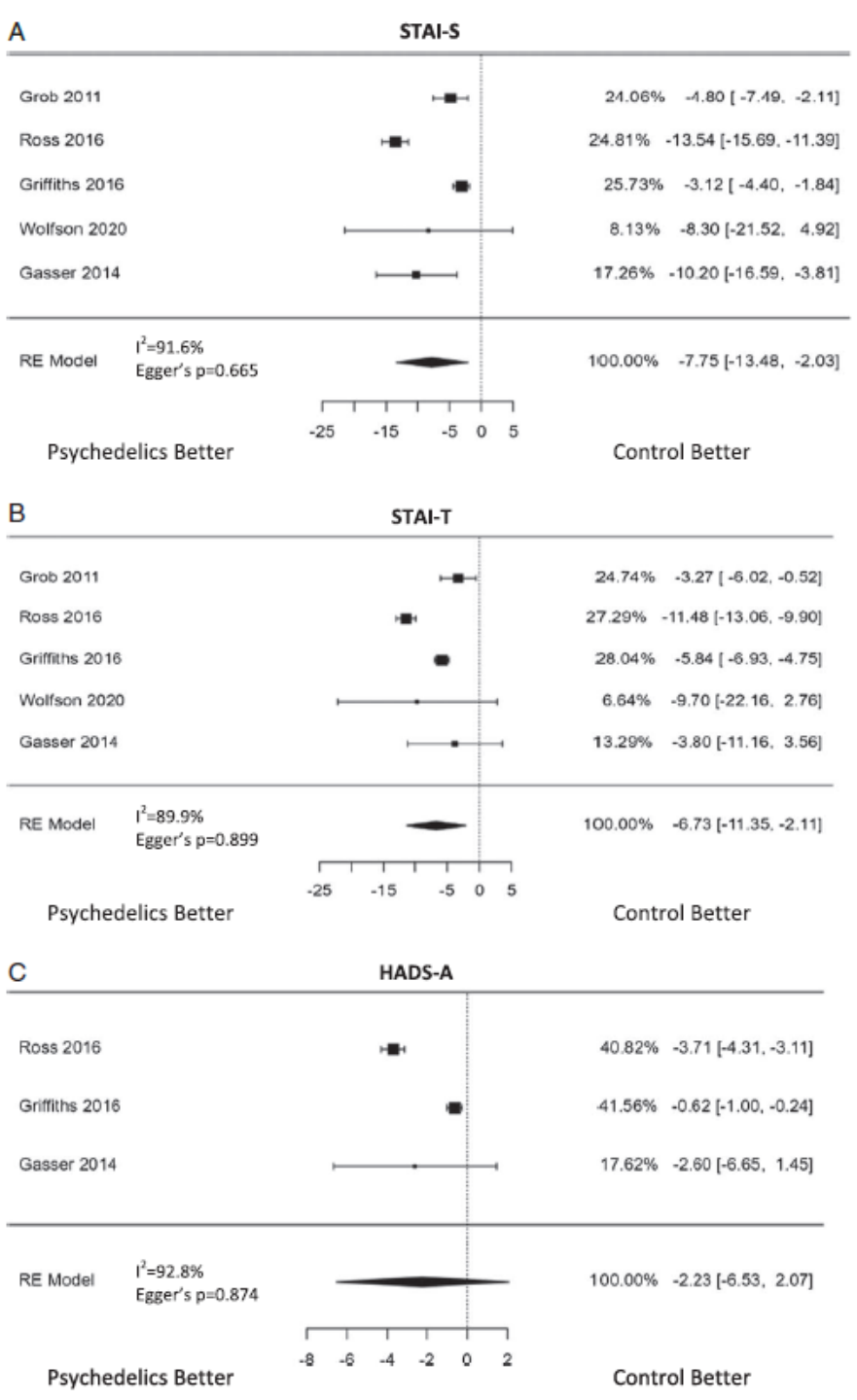
https://ir.mindmed.co/news-events/press-releases/detail/137/mindmed-receives-fda-breakthrough-therapy-designation-and-announces-positive-12-week-durability-data-from-phase-2b-study-of-mm120-for-generalized-anxiety-disorder

https://www.biospace.com/article/incannex-s-psilocybin-clears-phase-ii-trial-in-generalized-anxiety-disorder/#:~:text=Following%20treatment%20with%20psilocybin%2C%2044%25%20of%20patients%20demonstrated,times%20higher%20than%20that%20in%20the%20placebo%20group.

PSYCHEDELICS IN CANCER

- Cancer is a form of trauma, and can lead to anxiety and depression
- Psilocybin, MDMA & LSD vs. control

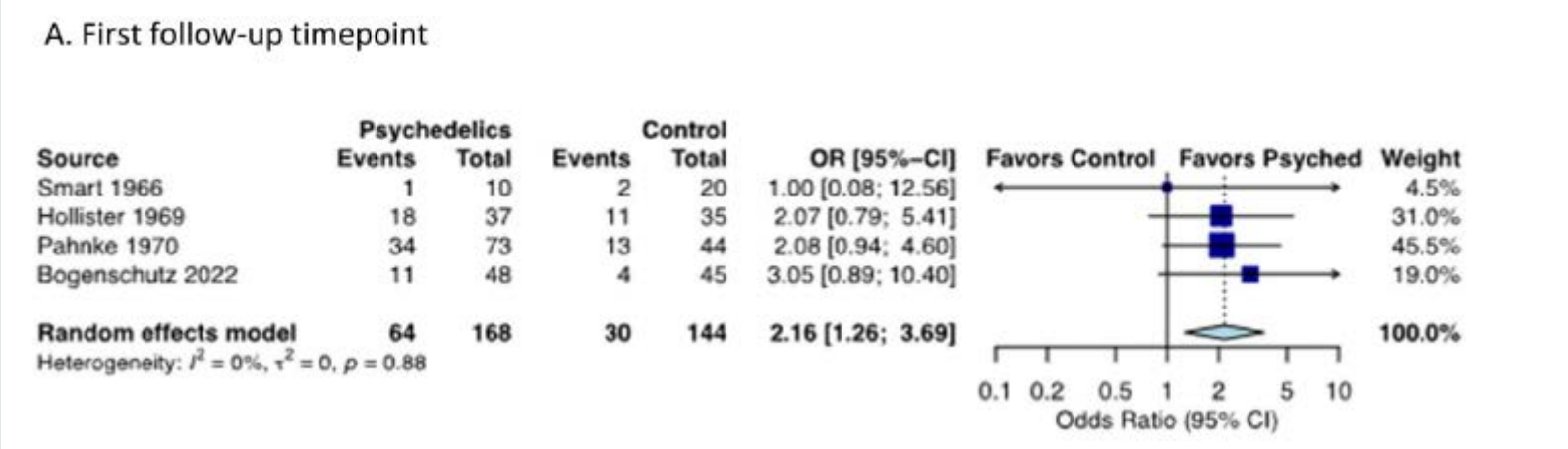


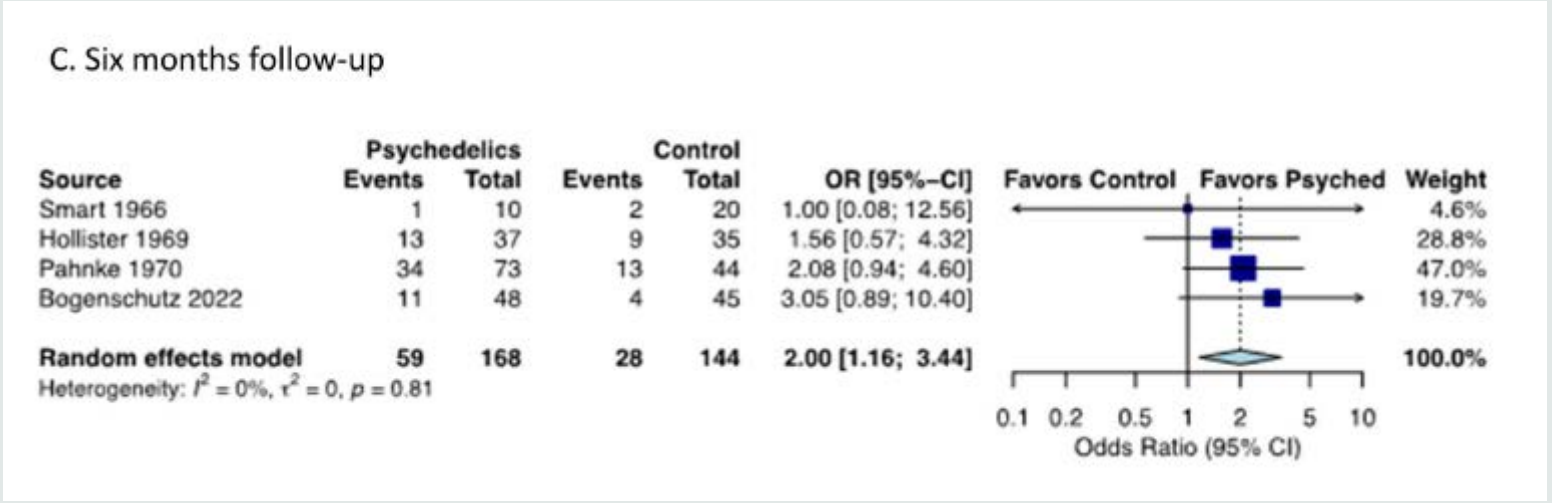


American Journal of Clinical Oncology 2023;46(6):236-245. |
DOI: 10.1097/COC.0000000000000998

PSYCHEDELICS FOR ALCOHOL USE DISORDER

- All studies but Bogenschutz used LSD
- Bogenschutz used psilocybin, only study to assess adverse events
  - *BP increase 21/12 mmHg, HR increase 8-12bpm*
  - *One psilocybin patient had a mild 15-minute episode of suicidal ideation while receiving psilocybin*
- No benefits if patients had schizophrenia/psychosis hx





CANNABIS FOR MENTAL HEALTH?

- Ninety-nine studies (221,097 participants) assessing high dose delta-9 THC products
- Randomized trials (42%), observational studies (47%), and other interventional study designs (11%)
  - *More than 95% had moderate or high risk of bias.*
- Among therapeutic studies, 47% of studies found anxiety lessened while 24% found it worsened
- Among therapeutic studies, 48% of studies found depression lessened while 30% found it worsened
- 70-75% of recreational user studies found unfavorable associations with psychosis or schizophrenia and cannabis use disorder
  - *No studies reported favorable results for these outcomes*
- It is difficult to support delta-9 THC use for mental health disorders based on current dataset

https://pubmed.ncbi.nlm.nih.gov/40854216/

CONCLUSIONS

- Ketamine is FDA approved for anesthesia but offers patients a drug option for rapid improvement of depression symptoms or PTSD symptoms
  - *If ECT alone is ineffective, adding ketamine can enhance its effectiveness*
  - *Ketamine is a bridge to psychotherapy and SSRI or SNRI therapy, not a viable long-term therapy*
- Esketamine can be used chronically, but only for those not responding to the best current therapies
  - *In the future, psilocybin or MDMA + psychotherapy might be better options for long term depression relief*
  - *Fewer doses needed, possibly lower risk of addiction*
- MDMA + psychotherapy (not FDA approved) can be used when psychotherapy is ineffective for PTSD patients or when depression or anxiety are induced by trauma
- Classical psychedelics (LSD, psilocybin) offer valuable alternatives for patients not responding to traditional therapy with psychotherapy, SSRIs, or SNRIs