Psychedelic-Assisted Psychotherapy: An Overview of Empirical Utility, Rationale, and Future Clinical Considerations

March 10, 2023

Sandeep Nayak, MD
Assistant Professor
Johns Hopkins Center for Psychedelic and Consciousness Research

THE ROSSCENTER

JOHNS HOPKINS
Center for Psychedelic & Consciousness Research

Washington DC • Northern VA • New York NY

THE ROSS CENTER IS APPROVED BY THE AMERICAN PSYCHOLOGICAL ASSOCIATION TO SPONSOR CONTINUING EDUCATION FOR PSYCHOLOGISTS. THE ROSS CENTER MAINTAINS RESPONSIBILITY FOR THIS PROGRAM AND ITS CONTENT.

The Ross Center for Anxiety and Related Disorders LLC is recognized by the New York State Education Department's State Board for Psychology as an approved provider of continuing education for licensed psychologists #PSY-0105. Ross Management Services, LLC is recognized by the New York State Education Department's State Board for Social Work as an approved provider of continuing education for licensed social workers #SW-0701

DISCLOSURES

NEITHER SANDEEP NAYAK, PHD NOR MARY SALCEDO, MD HAVE ANY FINANCIAL RELATIONSHIPS WITH COMMERCIAL INTERESTS TO DISCLOSE.

ACKNOWLEDGEMENTS

THERE ARE MANY INDIVIDUALS WHO HAVE WORKED BEHIND THE SCENES TO HELP PUT THIS TRAINING TOGETHER. A SPECIAL THANKS TO OUR CONTINUING EDUCATION COMMITTEE: DR. GRETA HIRSCH, DR. ABIGAIL ROMIROWSKY, DR. BETH SALCEDO, DR. AVY STOCK, DR. SHARON THOMAS, DR. CHRISTINA TRIPODI MITCHELL AND BARBRA WALDFOGEL FOR THEIR COLLABORATION TO REVIEW TRAININGS AND TO ENSURE A HIGH LEVEL OF QUALITY OF EACH TRAINING WE PROVIDE. EACH TRAINING REQUIRES A TREMENDOUS AMOUNT OF PLANNING AND PREPARATION. MUCH APPRECIATION AND THANKS IS EXTENDED TO OUR PROFESSIONAL DEVELOPMENT PROGRAM ADMINISTRATIVE TEAM FOR ALL THE HARD WORK AND ATTENTION TO DETAIL THEY PUT INTO MAKING SURE EACH TRAINING RUNS SMOOTHLY.

COMMITMENT TO INCLUSIVITY

The Ross Center is an equal opportunity organization, and does not discriminate on the basis of race, age, ethnicity, ancestry, national origin, disability, color, size, religion, gender, sexual orientation, marital status, or socioeconomic background. We are committed to providing an inclusive and welcoming environment for all patients and members of our staff. For any questions, or to report any concerns, please contact us at info@rosscenter.com.

OVERVIEW

1. **Background / history/ models of use**
2. **Empirical evidence**
    a) depression
    b) tobacco smoking
    c) palliative
3. **Psychedelic therapy delivery**
4. **Psychedelic therapy as psychotherapy**
        a) common factors
        b) representative cases
5. **Clinical issues and future studies**

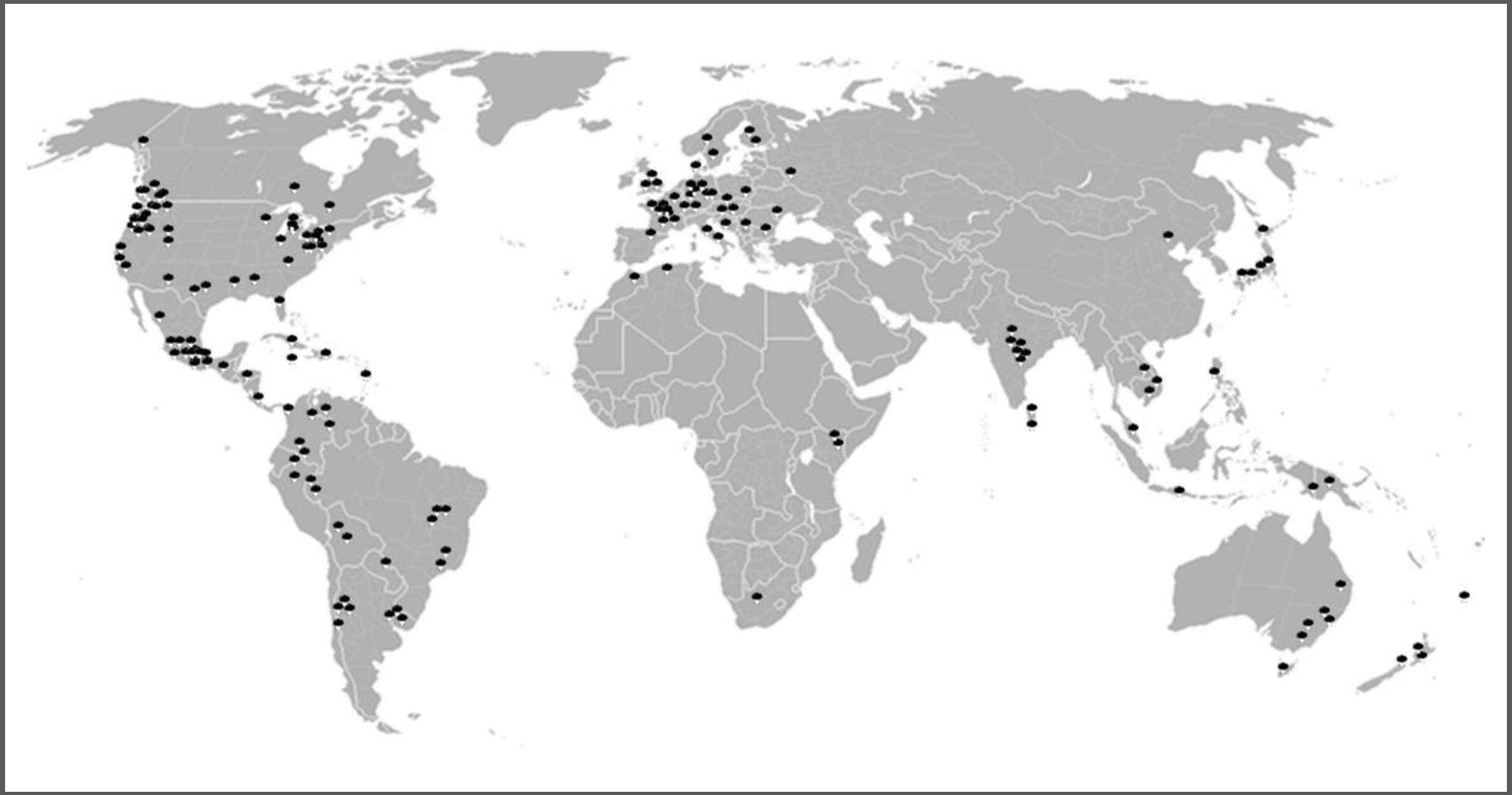
1. **Background / history/ models of use**

a. What is a psychedelic?
b. History
c. Models of use

“Classic Psychedelics”

- “Classic psychedelic”
  - Psilocybin
  - LSD
  - Mescaline (peyote, san pedro)
  - Bufotenine
  - DMT
  - 5-MeO-DMT

- Psilocybin in >200 mushroom species

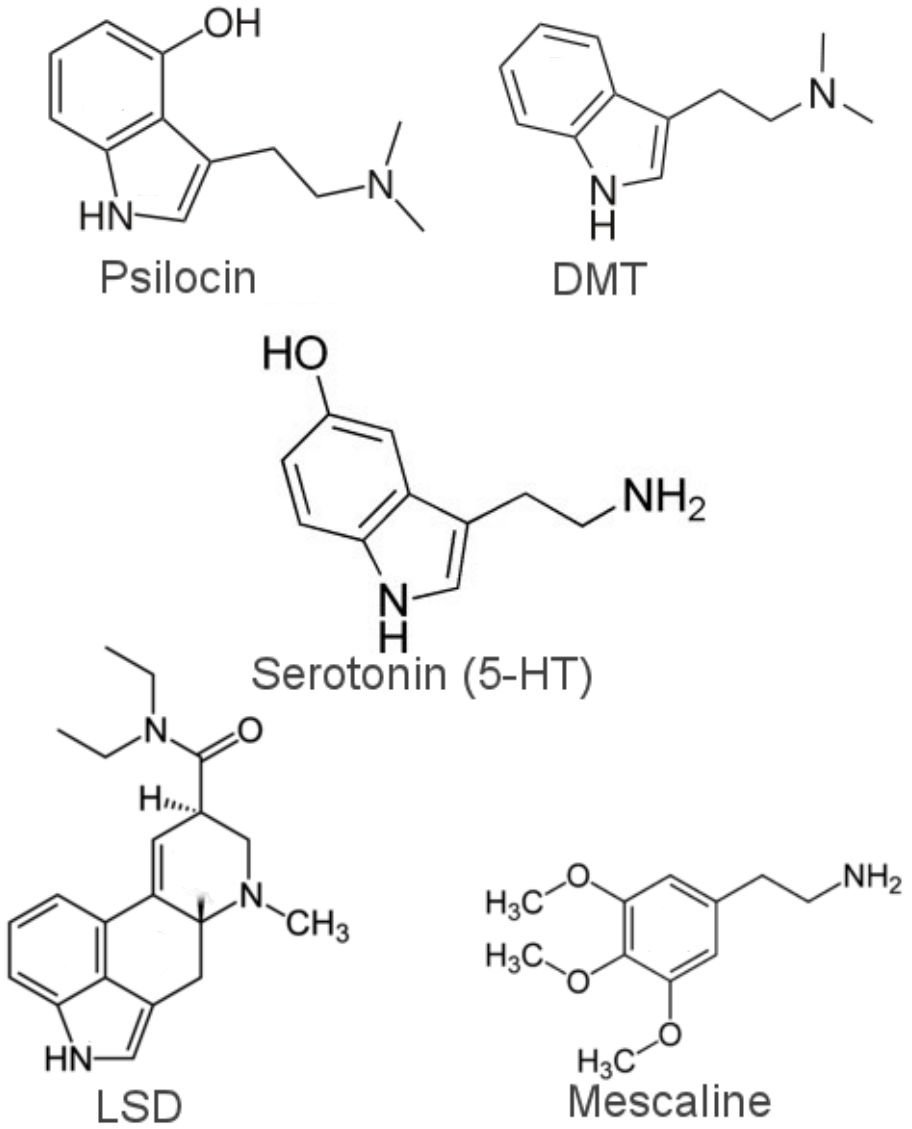


“Classic Psychedelics”

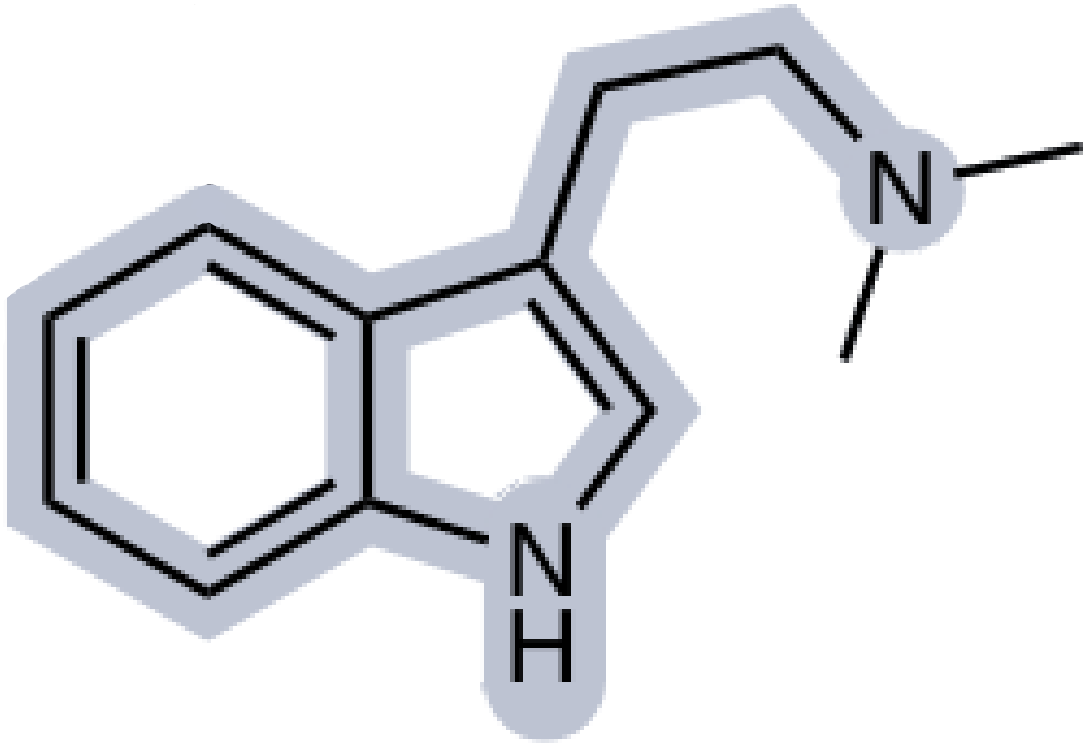
- “Classic psychedelic”
  - Psilocybin
  - LSD
  - Mescaline (peyote, san pedro)
  - Bufotenine
  - DMT
  - 5-MeO-DMT

- Psilocybin in >200 mushroom species

All psychedelics mimic serotonin



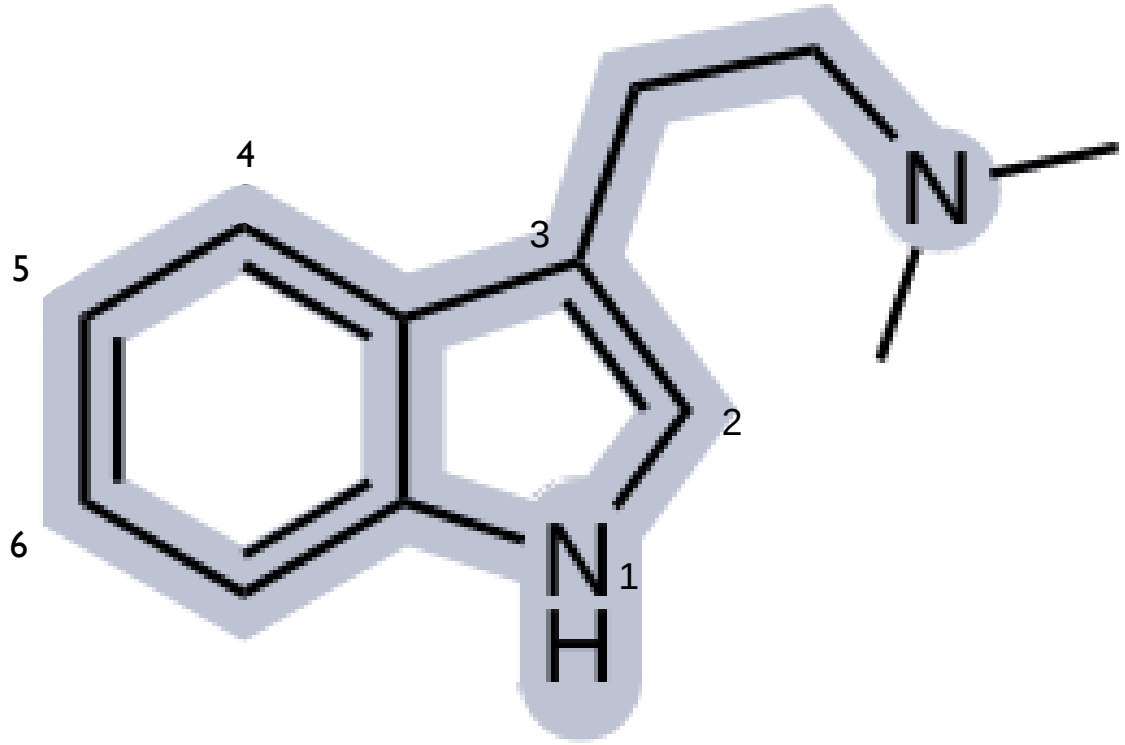
DMT



Dimethyltryptamine

Kwan et al. (2022)

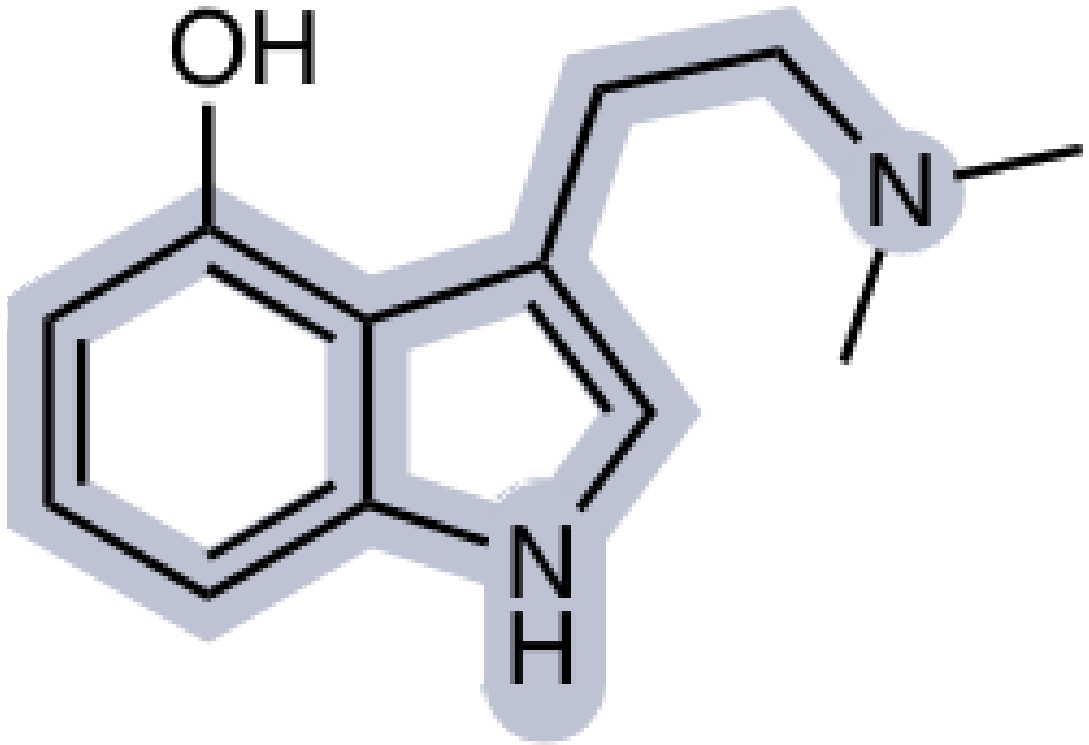
DMT



Dimethyltryptamine

Kwan et al. (2022)

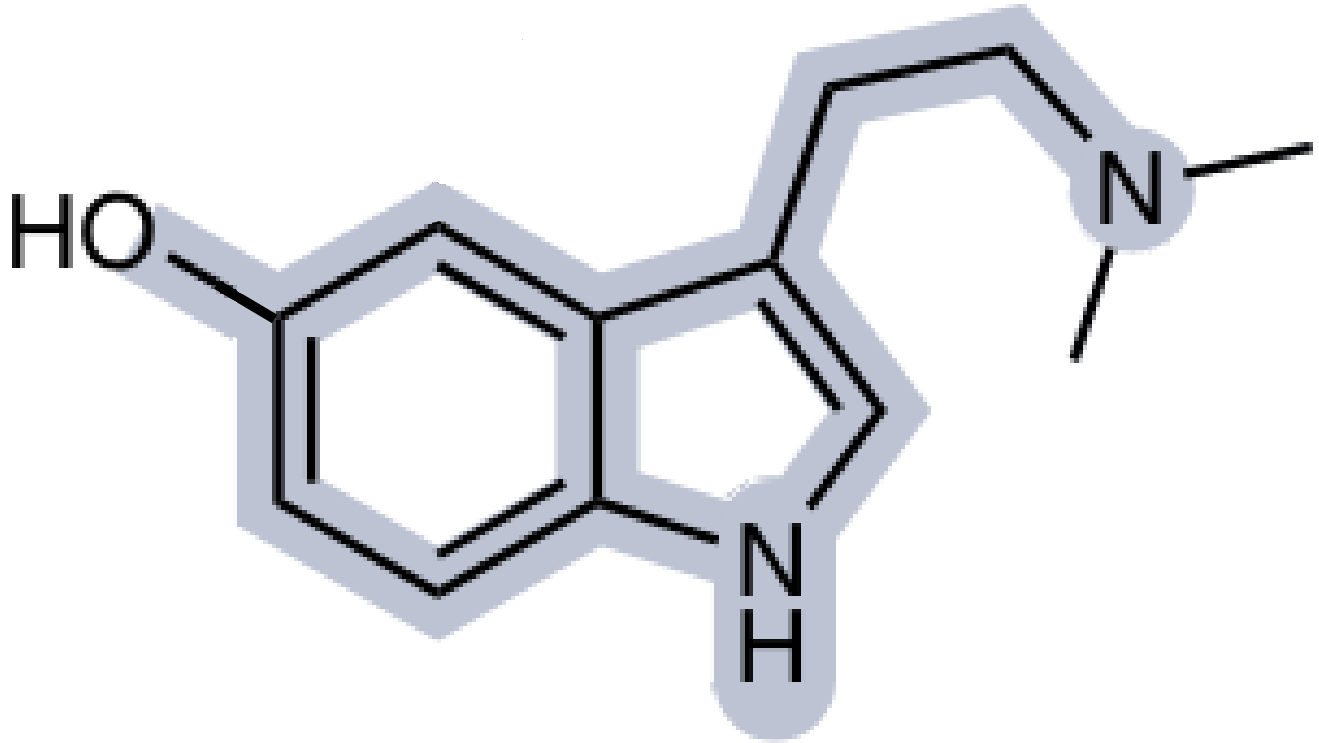
Psilocin



4-hydroxy-DMT

Kwan et al. (2022)

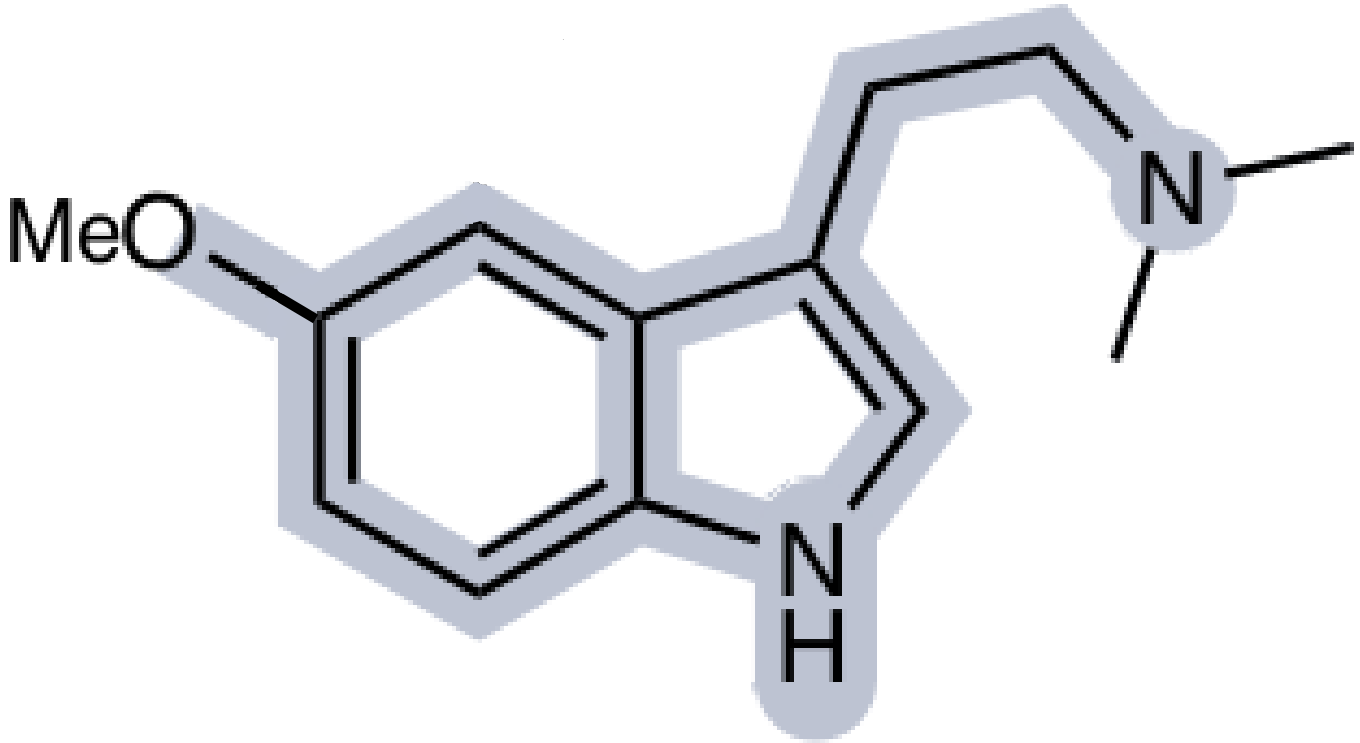
Bufotenine



5-hydroxy-DMT

Kwan et al. (2022)

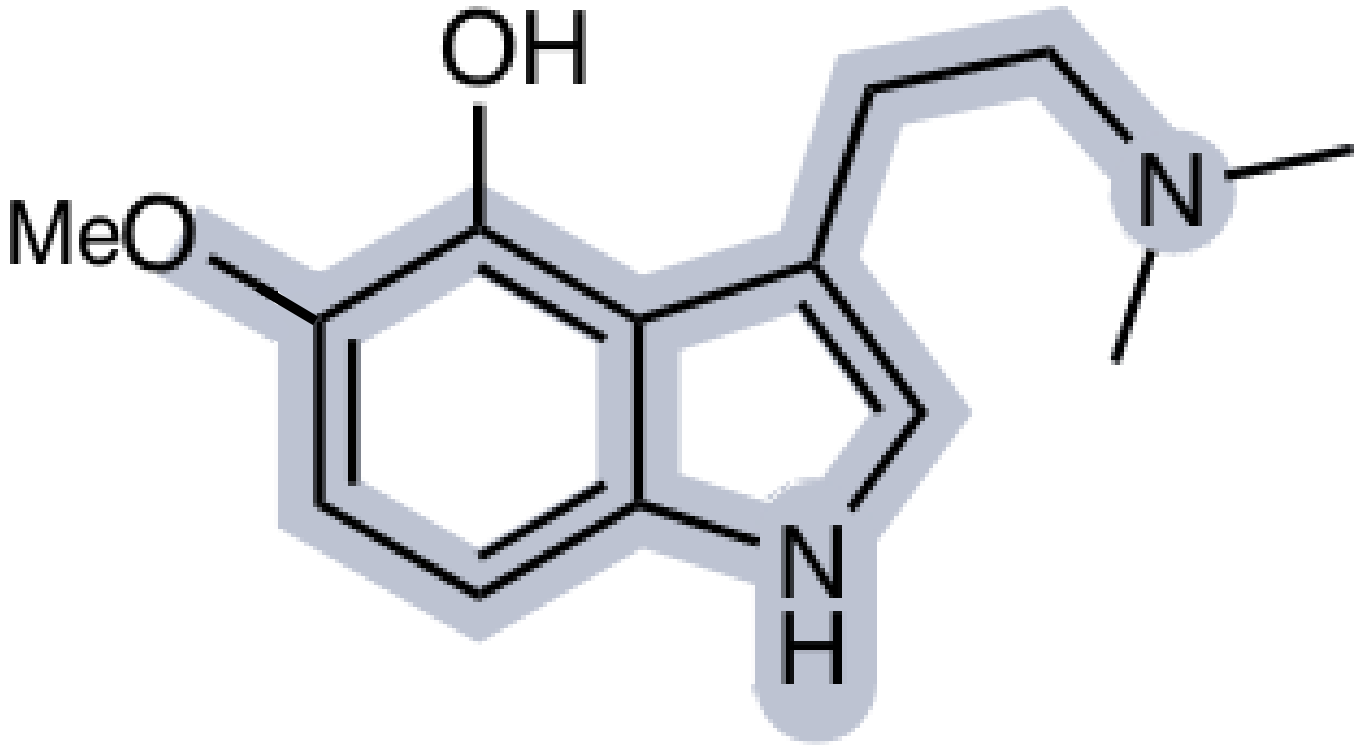
5-MeO-DMT



5-methoxy-DMT

Kwan et al. (2022)

Psilomethoxin



4-hydroxy-5-methoxy-DMT

Kwan et al. (2022)

Psilomethoxin

4-hydroxy-5-methoxy-DMT

What effects do psychedelics have?

- Visual
- Synesthesia
- Meaning enhancing
- Broadening of emotional range
- Altered sense of self
- Cognitive
- Mystical-type experiences

What effects do psychedelics have?

"A psychedelic drug is one which has small likelihood of causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, produces thought, mood, and perceptual changes otherwise rarely experienced except perhaps in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory and acute psychoses."

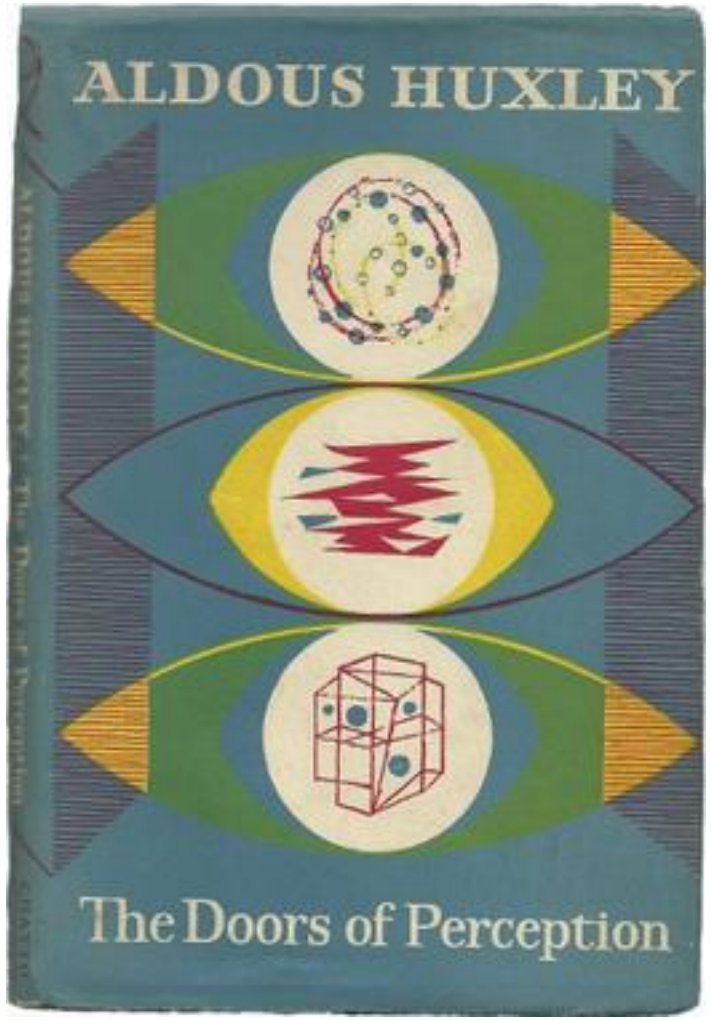
- Dr. Lester Grinspoon

Mystical Experiences

- Sense of unity
- Sense of sacredness
- Transcendence of time and space
- Positive mood
- Ineffability
- Noetic quality
- Selflessness

What effects do psychedelics have?

"I was now a Not-self, simultaneously perceiving and being the Not-self of the things around me. To this new-born Not-self, the behavior, the appearance, the very thought of the self it had momentarily ceased to be… seemed… enormously irrelevant."



Adverse effects

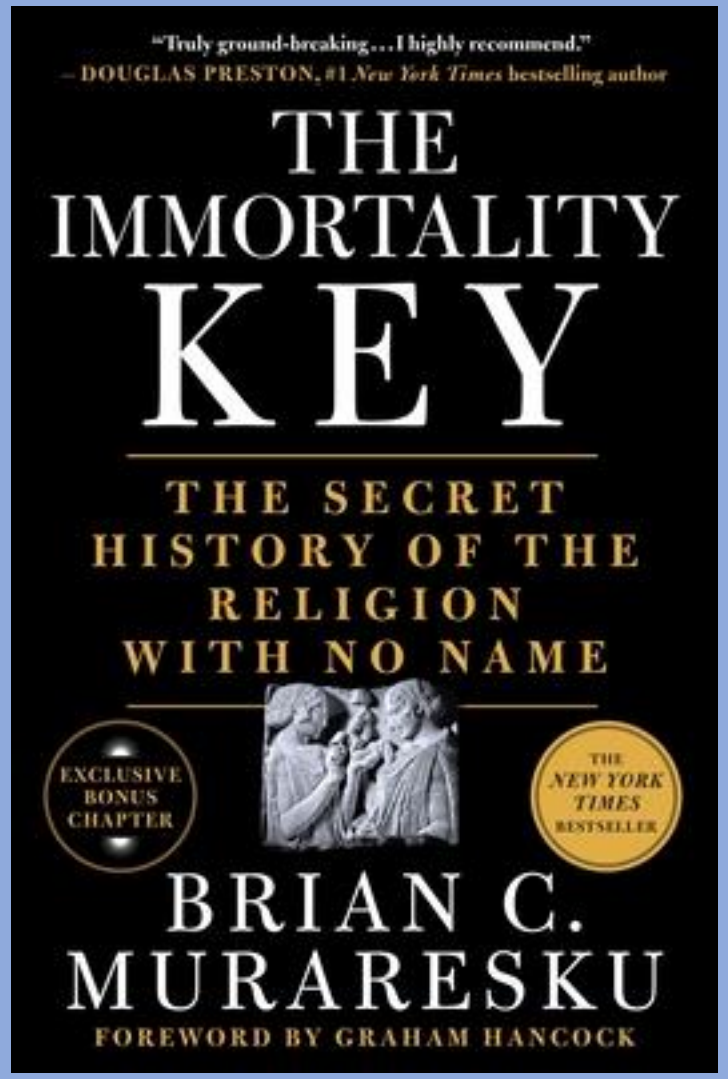
- Cardiovascular
- Headaches
- Nausea/vomiting
- Valvulopathy?

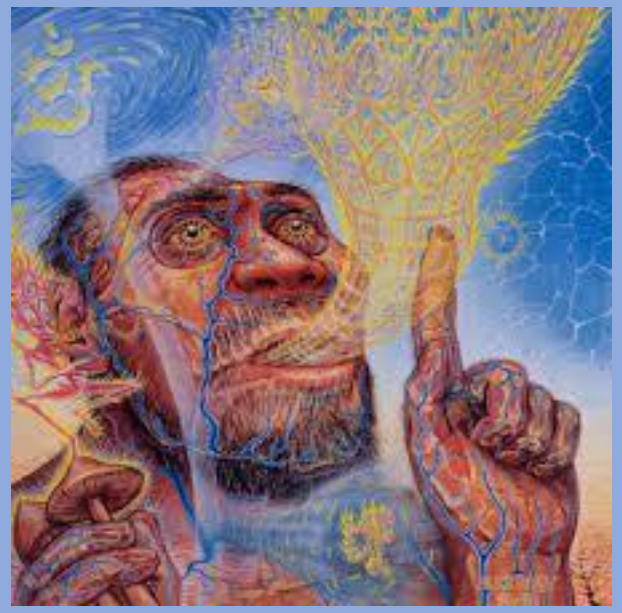
- ~~Disordered use~~

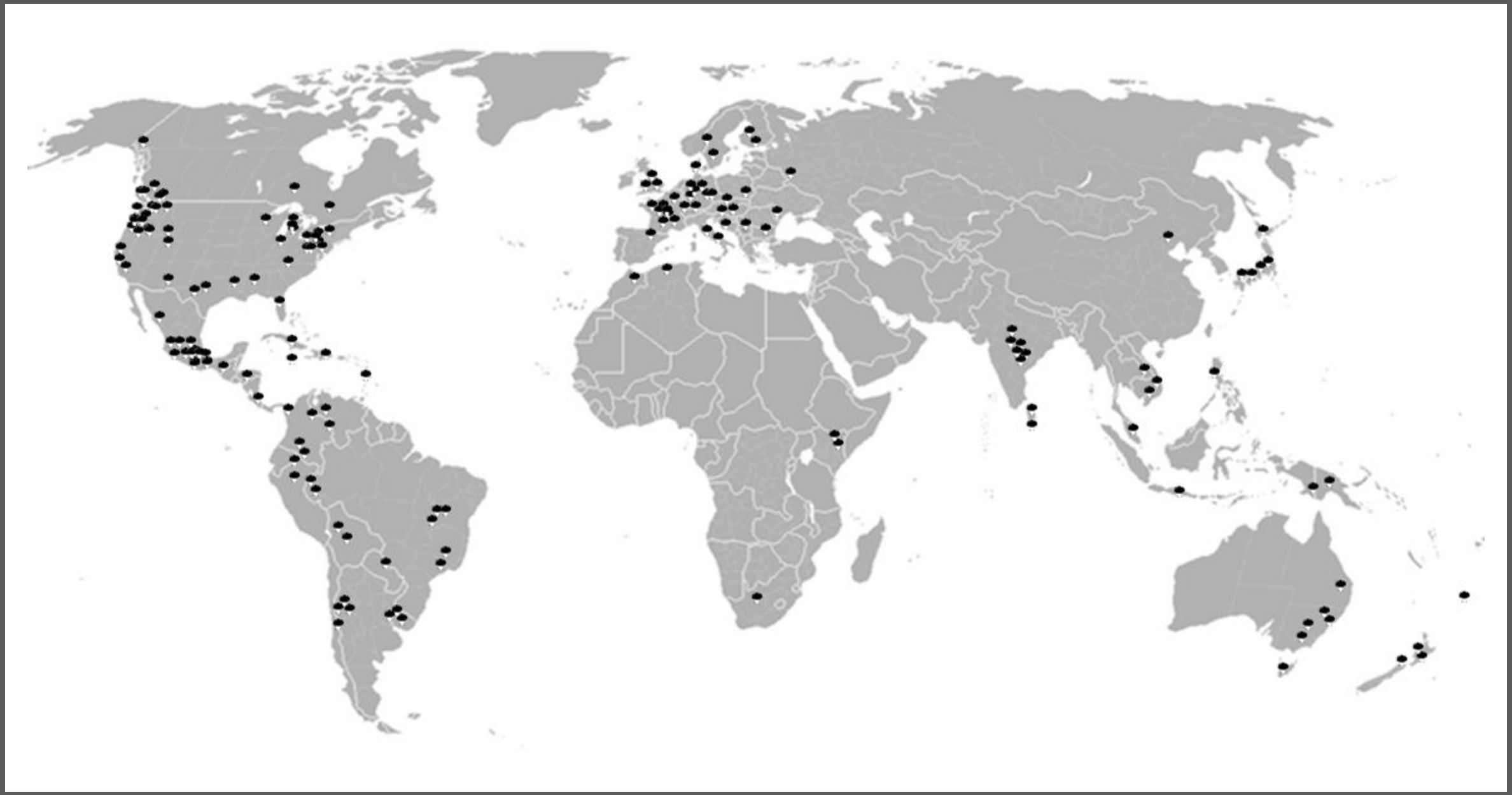
- Psychosis/Bipolar
- Psychological distress
- Behavioral consequences

Ancient use

- Psilocybin mushrooms used in Central America, for at least hundreds of years
- *Anedenanthera* (yopo or cebil) for millennia in various parts of S America
- Ayahuasca for at least hundreds of years in the Amazon basin
- Peyote for ?thousands of years


"Truly ground-breaking…I highly recommend."
– DOUGLAS PRESTON, #1 New York Times bestselling author
THE IMMORTALITY KEY
THE SECRET HISTORY OF THE RELIGION WITH NO NAME
EXCLUSIVE BONUS CHAPTER
THE NEW YORK TIMES BESTSELLER
BRIAN C. MURARESKU
FOREWORD BY GRAHAM HANCOCK





Diversity of indigenous use

- “Psychedelics are taken only in ceremony under the guidance and supervision of the shaman, or the spiritual leader of the community. The shaman would administer these compounds only for very clear circumscribed reasons, such as an initiation rite or a healing ceremony to address individuals with severe medical or psychological problems. In the shamanic world, these compounds are never taken for frivolous reasons. That would be absolutely taboo. It would be a heresy to misuse these compounds for hedonic reasons.”

  - Charles Grob MD on Goop

Diversity of indigenous use

- Shamanic use
  - Healing ceremonies
  - Witchcraft/divination
- Knowledge cultivation
- Recreational

- Group use

Previous waves of research

- Peyote/mescaline (Late 1800s - ?)
- Second Wave: LSD (1950s-1970s)
- Psychedelic renaissance (2000s)

Previous waves of research

- Peyote/mescaline (Late 1800s - ?)
- Second Wave: LSD (1950s-1970s)
- Psychedelic renaissance (2000s)

Modern models in research (Second Wave on)

- CIA research
- Gay conversion therapy

- Psychotomimetic
- Chemotherapeutic

- Psychedelic

Lessons learned from Second Wave

- “Set and Setting” / context dependency

Context dependency

- "The responses described in clinical experiments on Whites are so different from the responses described by Indian Peyotists… as to fall into completely different categories. They do not seem to be talking about the same thing" (Slotkin, 1956)

Slotkin J. The peyote religion. Glencoe, Ill.: Free Press; 1956.
Wallace A. Cultural Determinants of Response to Hallucinatory Experience Archives of General Psychiatry. 1959;1(1):58.

Context dependency

- In this era, white participants who took peyote in a research setting had experiences characterized by suspiciousness, feelings of meaninglessness and distress, “hallucinations largely idiosyncratic in content”, and a general lack of therapeutic benefits.

Slotkin J. The peyote religion. Glencoe, Ill.: Free Press; 1956.
Wallace A. Cultural Determinants of Response to Hallucinatory Experience
Archives of General Psychiatry. 1959;1(1):58.

Context dependency

- In contrast, American Indian peyotists generally took the cactus in a ceremonial setting, with a presumption of a meaningful, beneficial experience and had therapeutic benefits and "welcome feelings of contact with a new, more meaningful… reality prefigured in doctrinal knowledge" (Wallace, 1959)

Slotkin J. The peyote religion. Glencoe, Ill.: Free Press; 1956.
Wallace A. Cultural Determinants of Response to Hallucinatory Experience Archives of General Psychiatry. 1959;1(1):58.

Lessons learned from Second Wave

- “Set and Setting” / context dependency
- Extensive psychological support

Osmond Saskatchewan alcohol trials

- Initial rationale:
  - Psychotomimetic
  - Mimic Delirium Tremens
  - “hit rock bottom”

Lessons learned from Second Wave

- “Set and Setting” / context dependency
- Extensive psychological support
- Music
- Basic clinical ethics (what not to do)

- Attitude of experiential acceptance (“Trust, let go, be open”)

1. Empirical studies

a. Effect sizes
b. Depression
c. Tobacco smoking
d. Palliative

Effect sizes

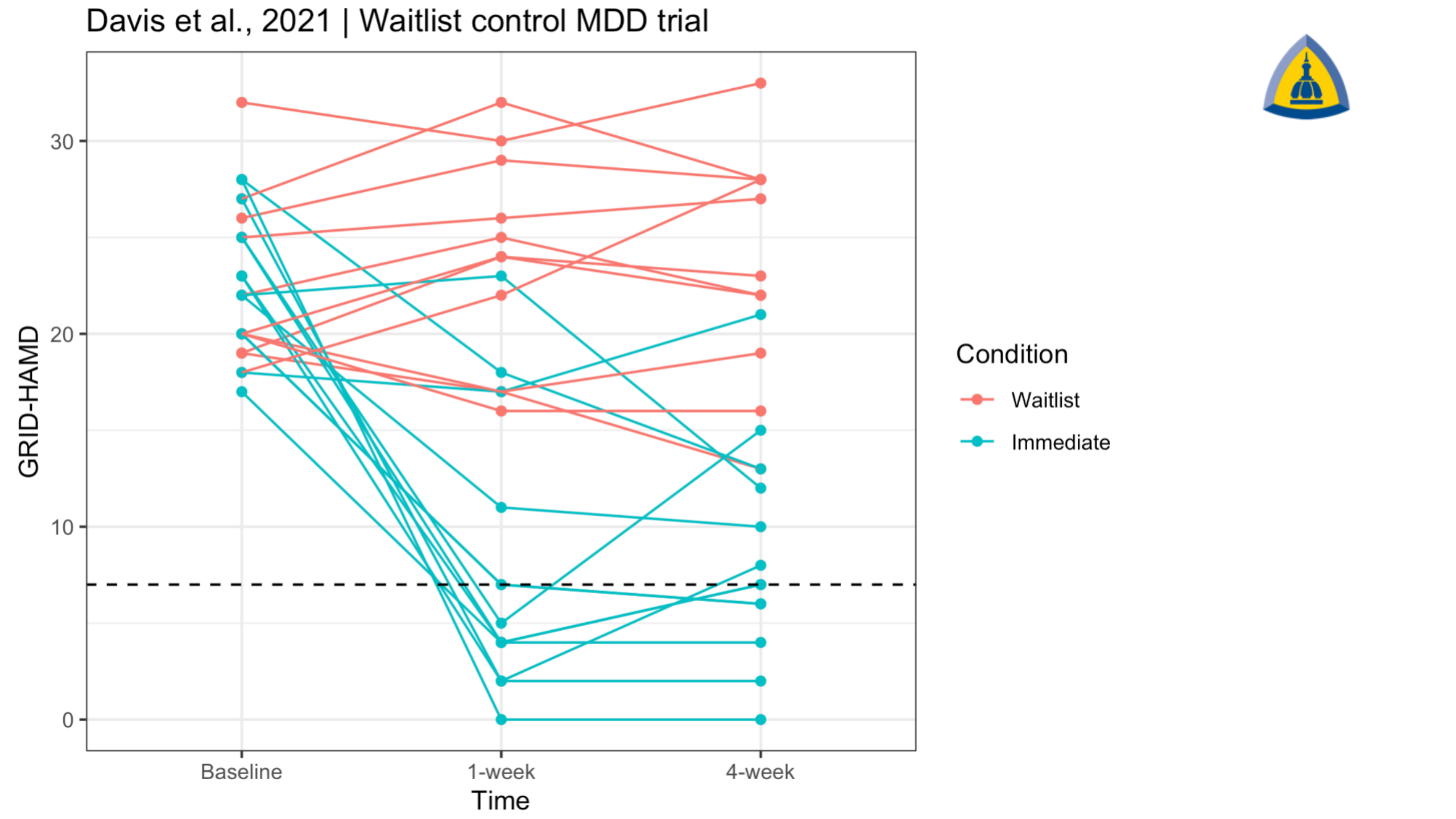
- Within group (psilocybin)
- Between group (psilocybin vs placebo)

Effect size in placebo groups in MDD trials (within-group)

- Meta-analysis (n = 96) of placebo effect size in MDD = 1.6 (Rieff et al., 2009)
  - TRD = 1.1 (Jones et al., 2021)

RCT of psychedelic for MDD

- Johns Hopkins open-label waitlist control (Davis et al., 2021)
- Brazilian ayahuasca for TRD (Palhano-Fontes et al., 2019)
- Imperial college psilocybin vs escitalopram (Carhart-Harris et al., 2021)
- Compass Phase 2 TRD trial (Goodwin et al., 2022)
- U of Zurich psilocybin vs placebo for MDD


Davis et al., 2021 | Waitlist control MDD trial
GRID-HAMD
30
20
10
0
Baseline
1-week
4-week
Time
Condition
Waitlist
Immediate

Davis et al. (2021) - Remission

Drug	**Remission (%)**
Psilocybin	45%
Waitlist	0%

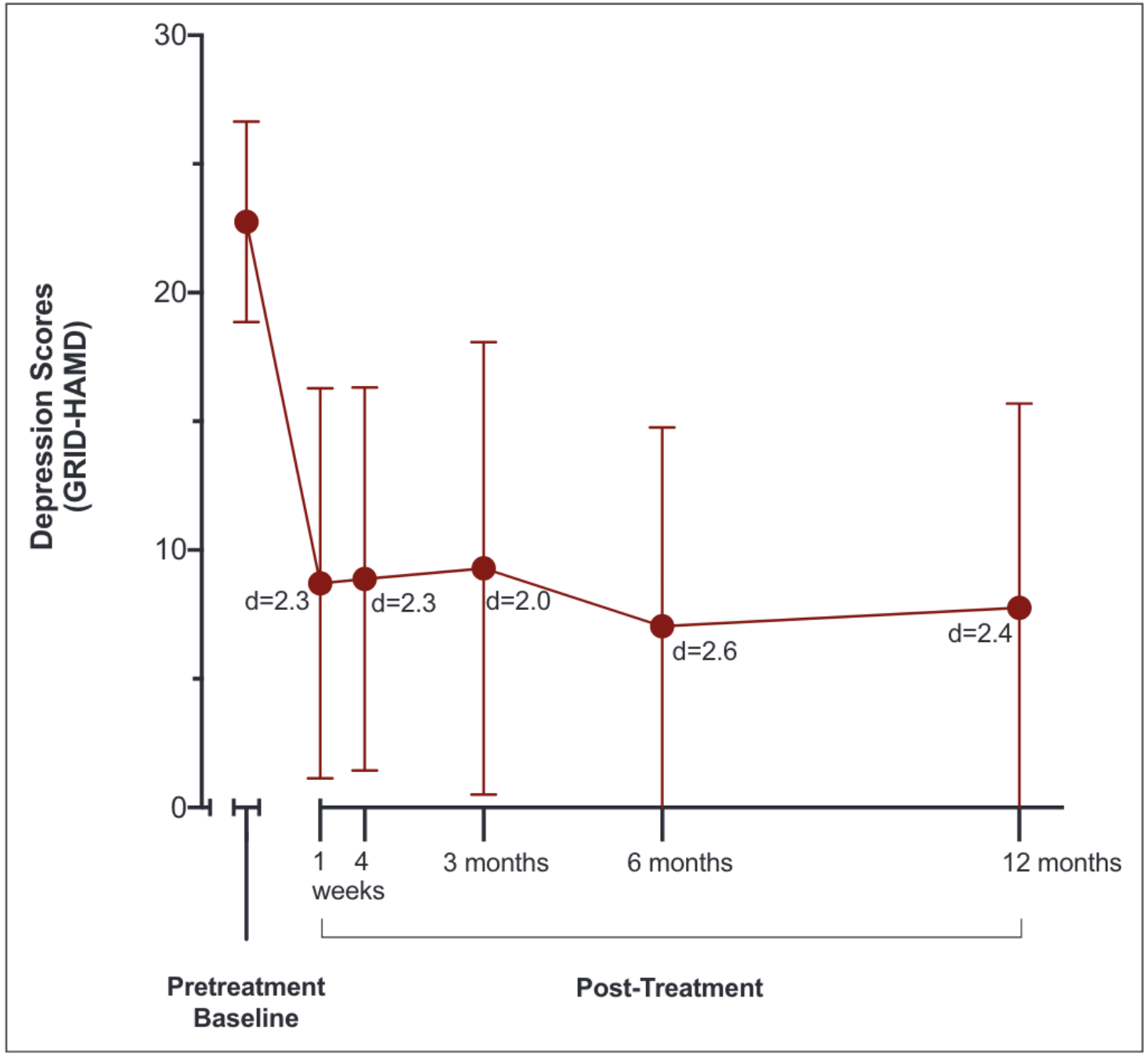
Davis et al., (2021)

- Between group effect size: d = 2.6 at 4 weeks post 2nd session
- Within group effect size
  - Waitlist: d = -0.2

Davis et al., (2021)

- Between group effect size: d = 2.6 at 4 weeks post 2nd session
- Within group effect size
  - Waitlist: d = -0.2

- Remember: average placebo group effect size in MDD = 1.6 (Rieff et al., 2009)

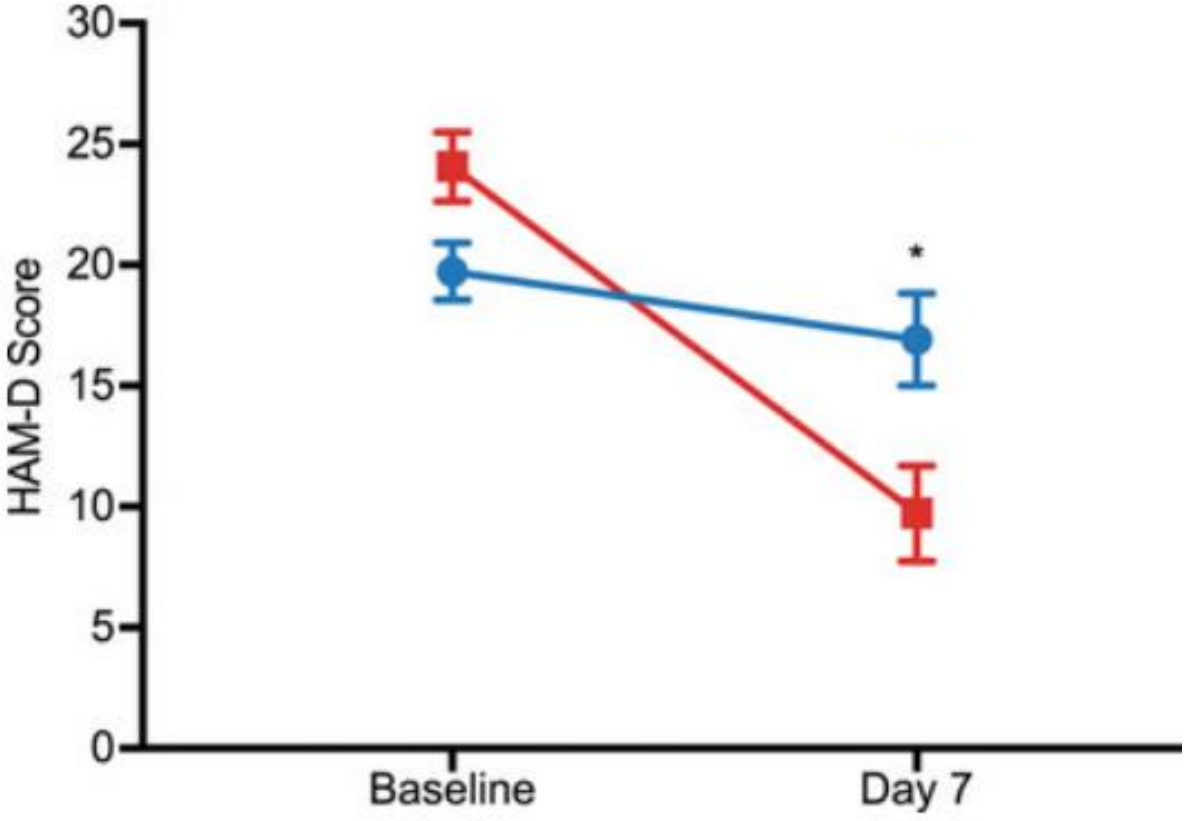

Depression Scores
(GRID-HAMD)
30
20
10
0
d=2.3
d=2.3
d=2.0
d=2.6
d=2.4
1
4
weeks
3 months
6 months
12 months
Pretreatment
Baseline
Post-Treatment

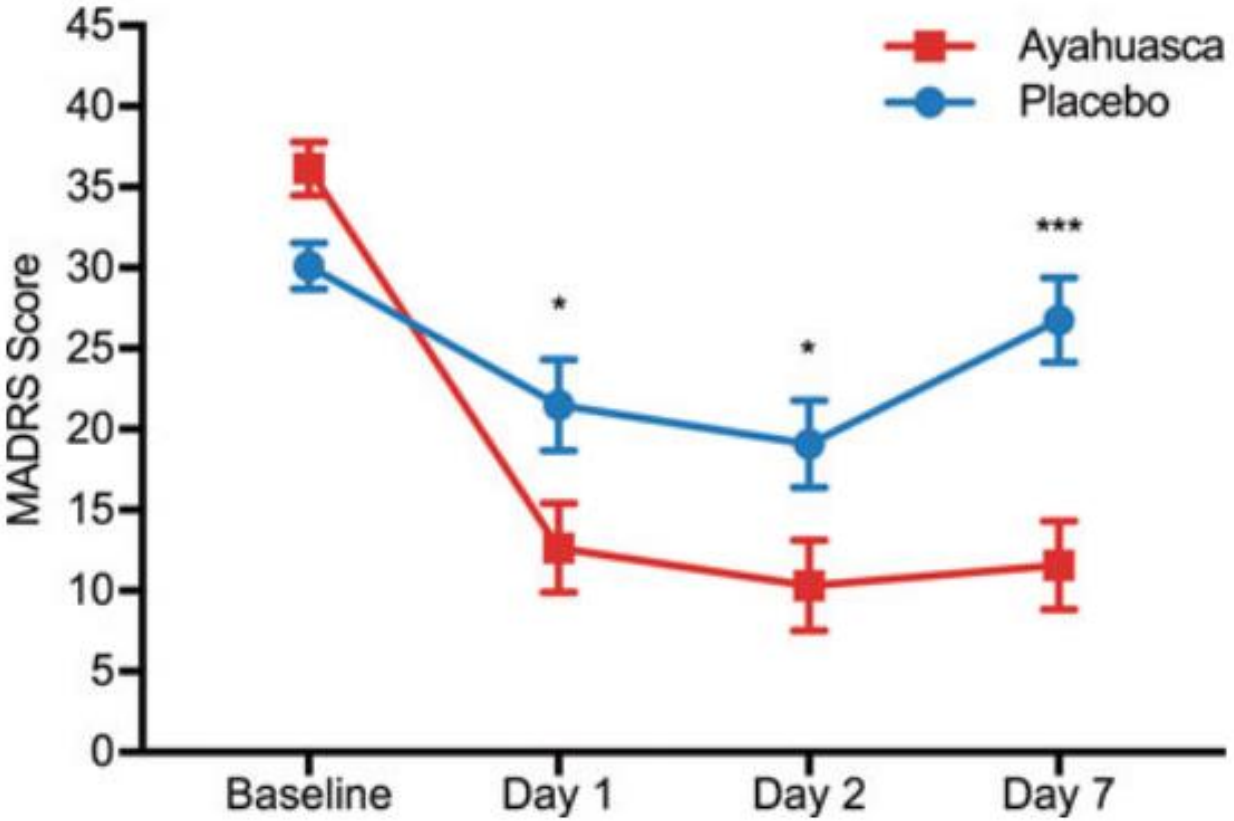
12-mo f/u

Palhano-Fontes et al. (2019)

- N = 29 TRD
- Moderate to severe (HAMD > 16)
- 76% personality disorder dx
- Mostly clinician referred
- Ayahuasca vs placebo (sham ayahuasca)

Palhano-Fontes et al. (2019)





Palhano-Fontes et al. (2019) - Remission

Drug	**Remission (%)**
Ayahuasca	36%
Placebo	7%

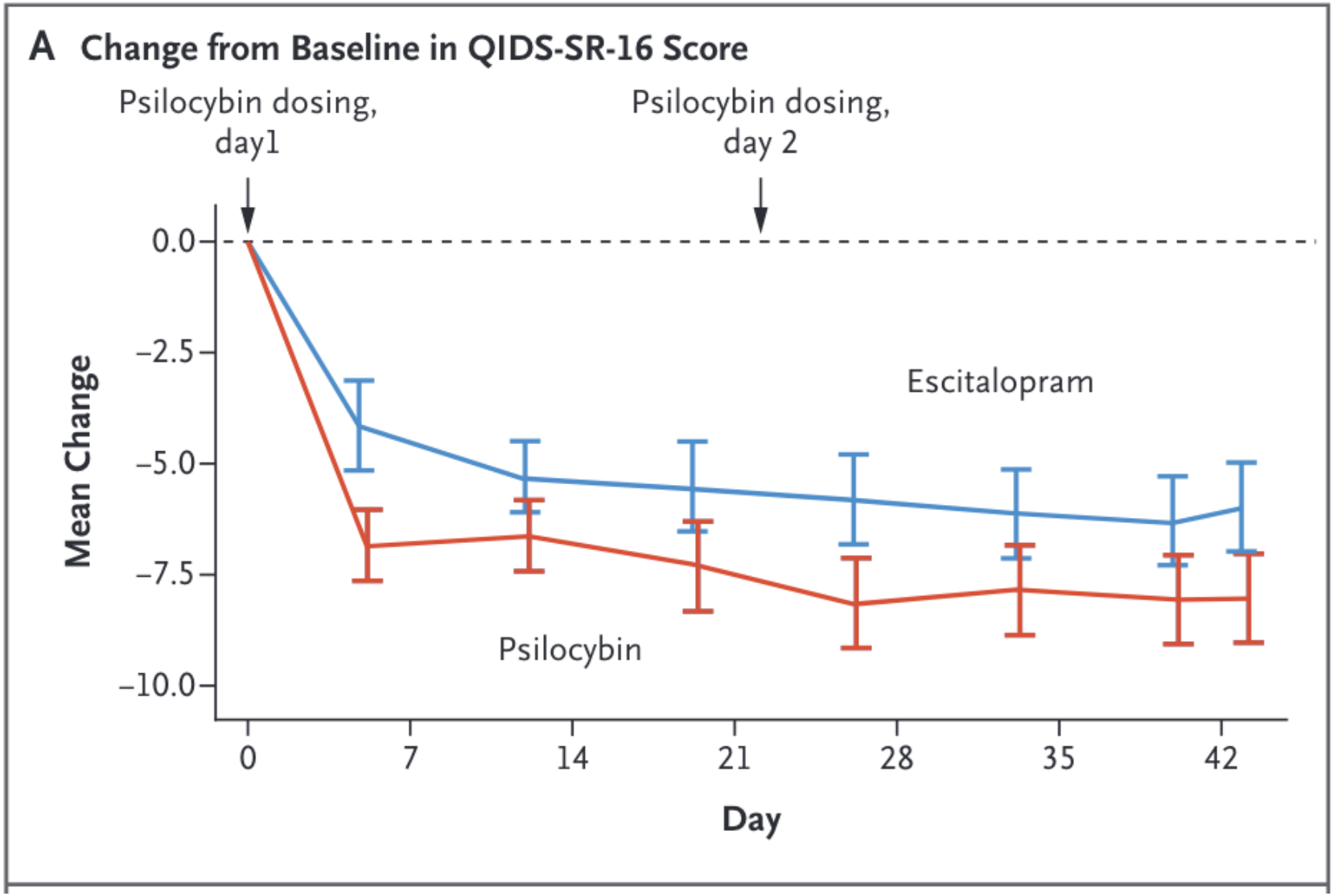
Palhano-Fontes et al. (2019)

- Between group effect size: d = 1.0
- Within group effect size
  - Placebo: d = 0.5

Palhano-Fontes et al. (2019)

- Between group effect size: d = 1.0
- Within group effect size
  - Placebo: d = 0.5

- Meta-analysis of placebo group effect size in TRD: g = 1.1 (Jones et al., 2021)

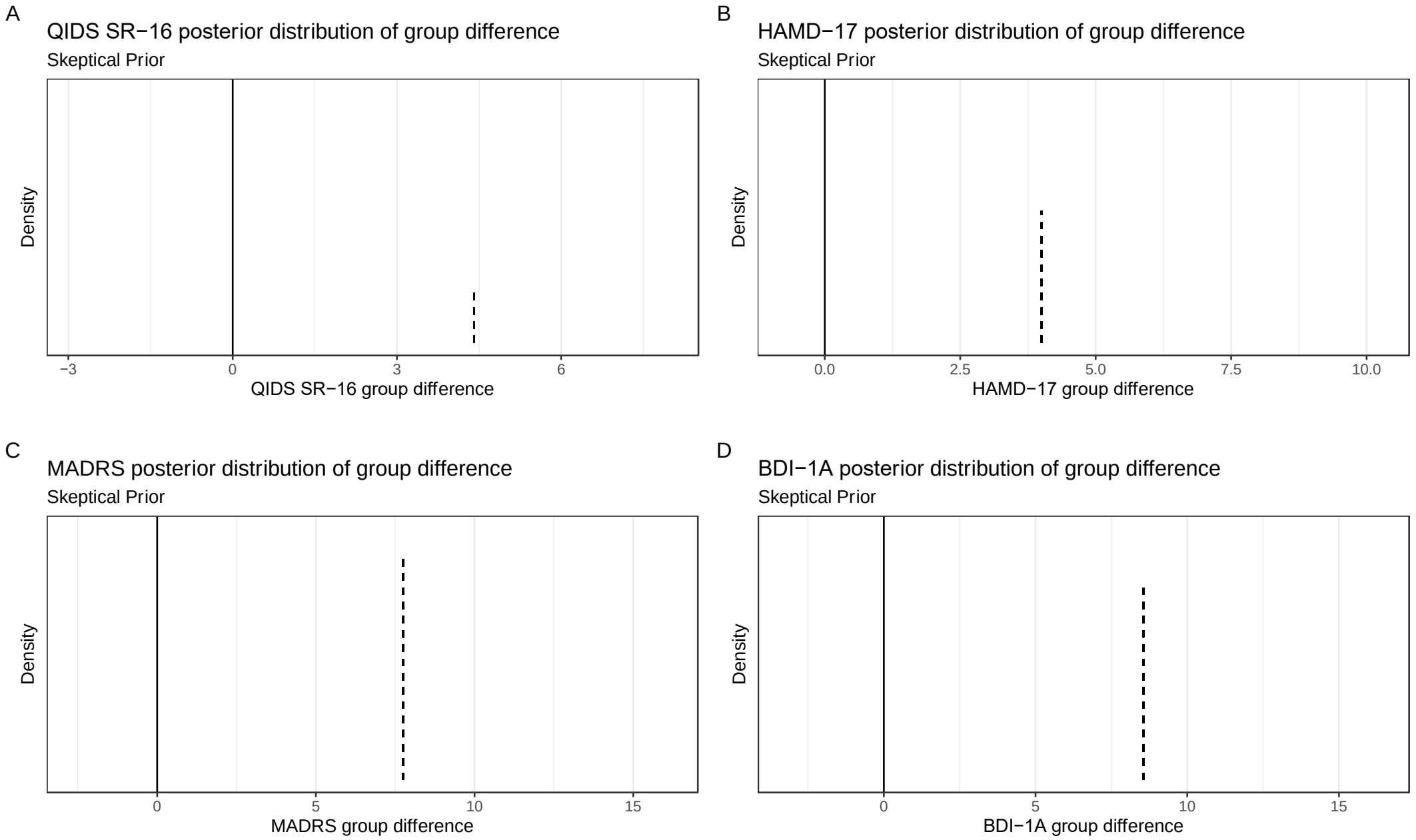


Imperial College London

(Carhart-Harris et al., 2021)

Carhart-Harris et al. (2021) - Remission

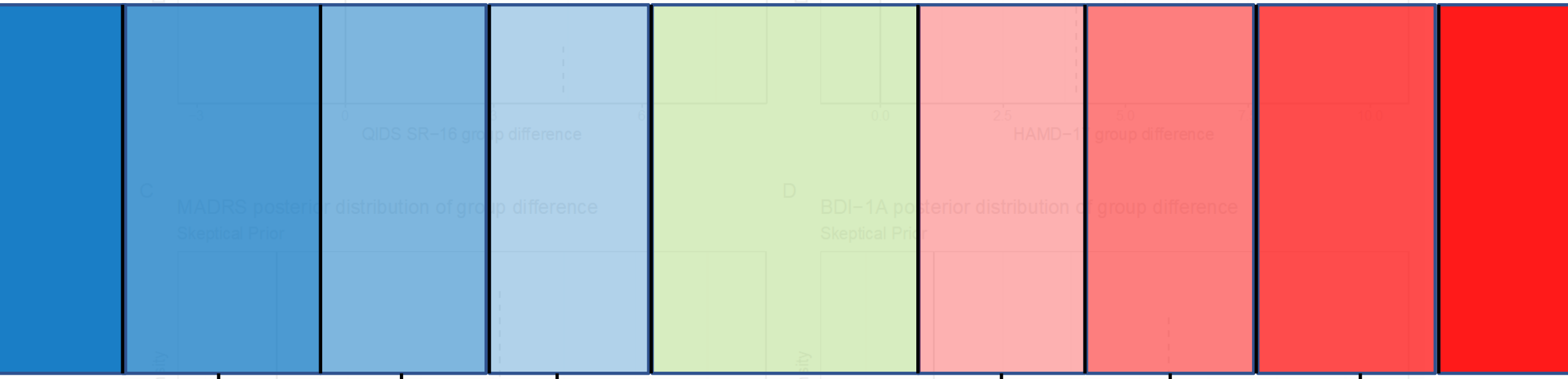
Drug	**Remission (%)**
Psilocybin	57%
Escitalopram	28%



Nayak et al., 2022

Dotted line indicates Minimally Clinically Important Difference (MCID)
Bar indicates median and 95% CI

Evidence for any superiority



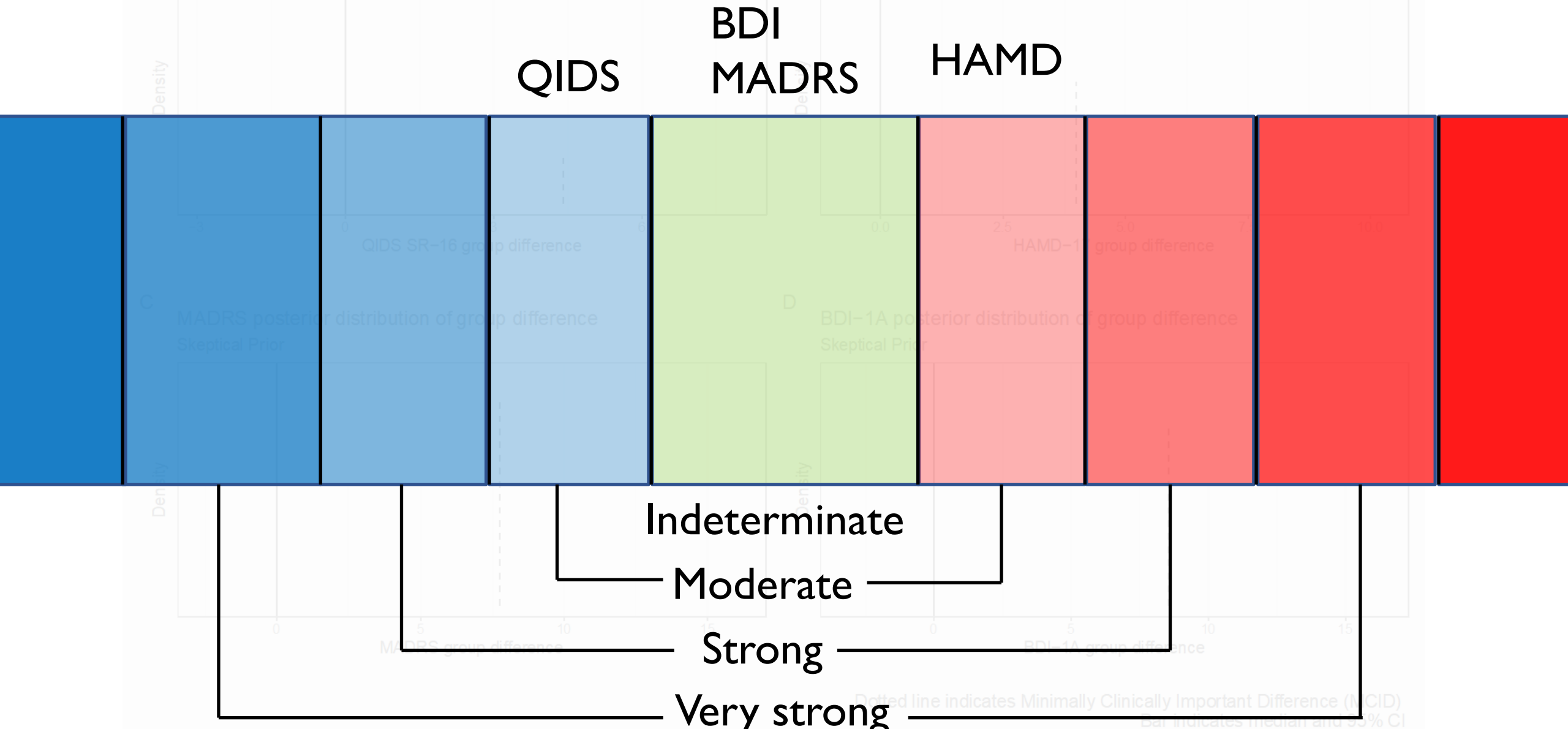
Indeterminate

Moderate

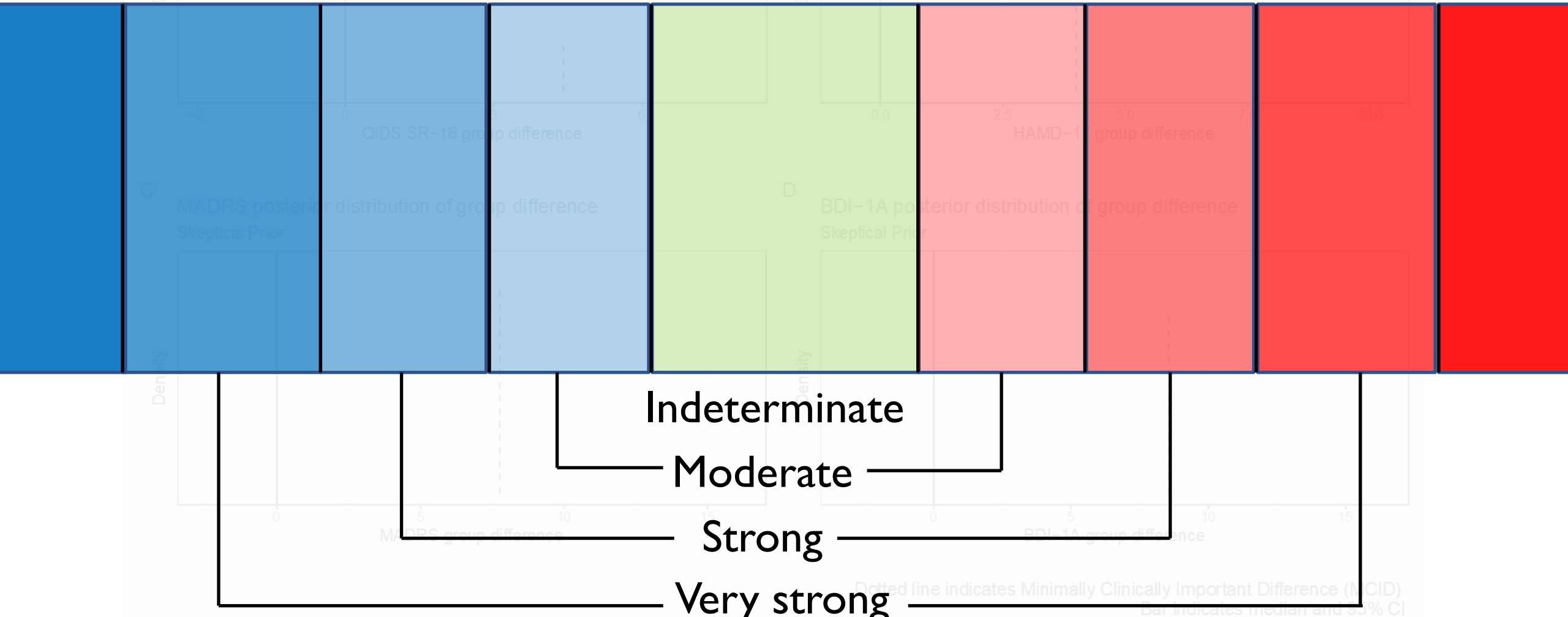
Strong

Very strong

Evidence for clinically meaningful superiority



Evidence for non-inferiority



Compass Phase 2 – Goodwin et al., (2022)

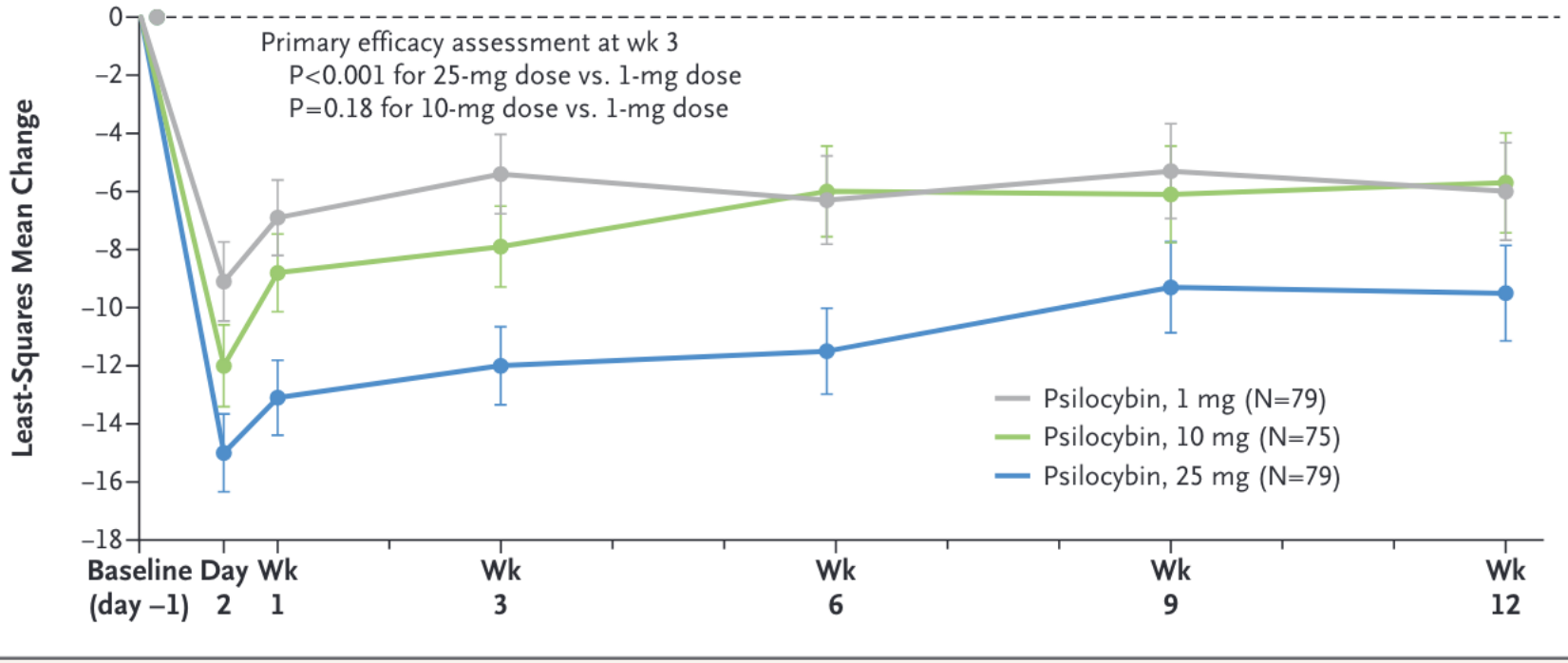


Figure 2. Change from Baseline in MADRS Total Score (Modified Intention-to-Treat Population).

Total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating greater severity of depression. I bars represent standard errors.

Compass Phase 2- Remission

Drug	**Remission (%) 3-week**	**Remission (%) 12-week**
Psilocybin 25mg	29%	27%
Psilocybin 10mg	9%	7%
Psilocybin 1mg	8%	11%

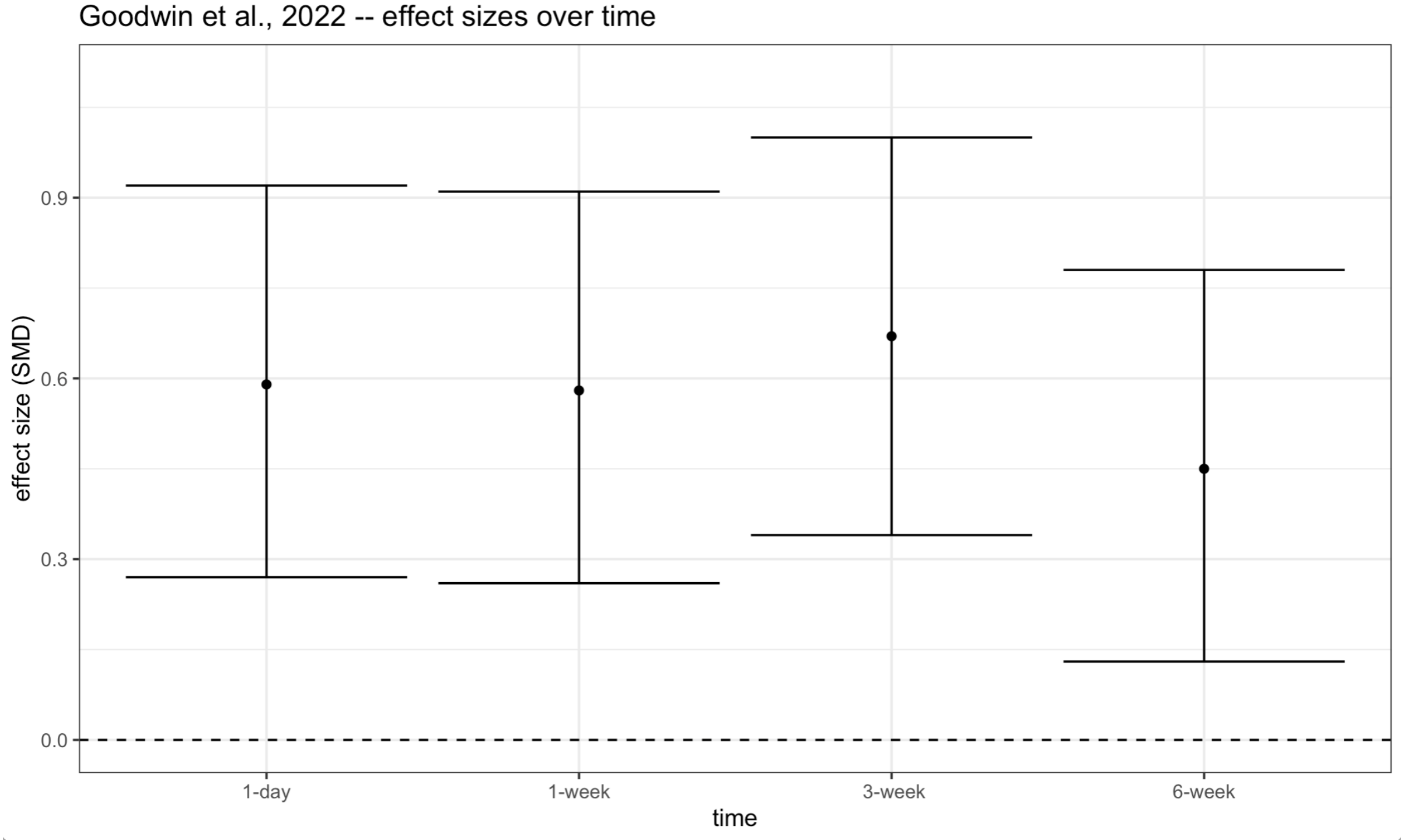

Goodwin et al., 2022 -- effect sizes over time
effect size (SMD)
0.9
0.6
0.3
0.0
1-day
1-week
3-week
6-week
time

Table 3. Adverse Events Reported on Day 1, from Day 2 up to Week 3, and after Week 3 up to Week 12 (Safety Population).*

Adverse Event	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
		number (percent)	
Day 2 up to wk 3			
Any serious adverse event	4 (5)	4 (5)	0
Suicidal ideation	2 (3)	2 (3)	0
Intentional self-injury	2 (3)	1 (1)	0
Hospitalization	0	1 (1)	0
After wk 3 up to wk 12			
Any serious adverse event	4 (5)	3 (4)	1 (1)
Suicidal behavior	3 (4)	0	0
Intentional self-injury	0	1 (1)	1 (1)
Adjustment disorder with anxiety and depressed mood	1 (1)	0	0
Depression	0	1 (1)	0
Drug withdrawal syndrome†	1 (1)	0	0
Suicidal ideation	0	1 (1)	0

Compass Phase 2- Serious adverse events

Table 3. Adverse Events Reported on Day 1, from Day 2 up to Week 3, and after Week 3 up to Week 12 (Safety Population).*

Adverse Event	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
		number (percent)	
Day 2 up to wk 3			
Any serious adverse event	4 (5)	4 (5)	0
Suicidal ideation	2 (3)	2 (3)	0
Intentional self-injury	2 (3)	1 (1)	0
Hospitalization	0	1 (1)	0
After wk 3 up to wk 12			
Any serious adverse event	4 (5)	3 (4)	1 (1)
Suicidal behavior	3 (4)	0	0
Intentional self-injury	0	1 (1)	1 (1)
Adjustment disorder with anxiety and depressed mood	1 (1)	0	0
Depression	0	1 (1)	0
Drug withdrawal syndrome†	1 (1)	0	0
Suicidal ideation	0	1 (1)	0

Compass Phase 2- Serious adverse events

Table 3. Adverse Events Reported on Day 1, from Day 2 up to Week 3, and after Week 3 up to Week 12 (Safety Population).*

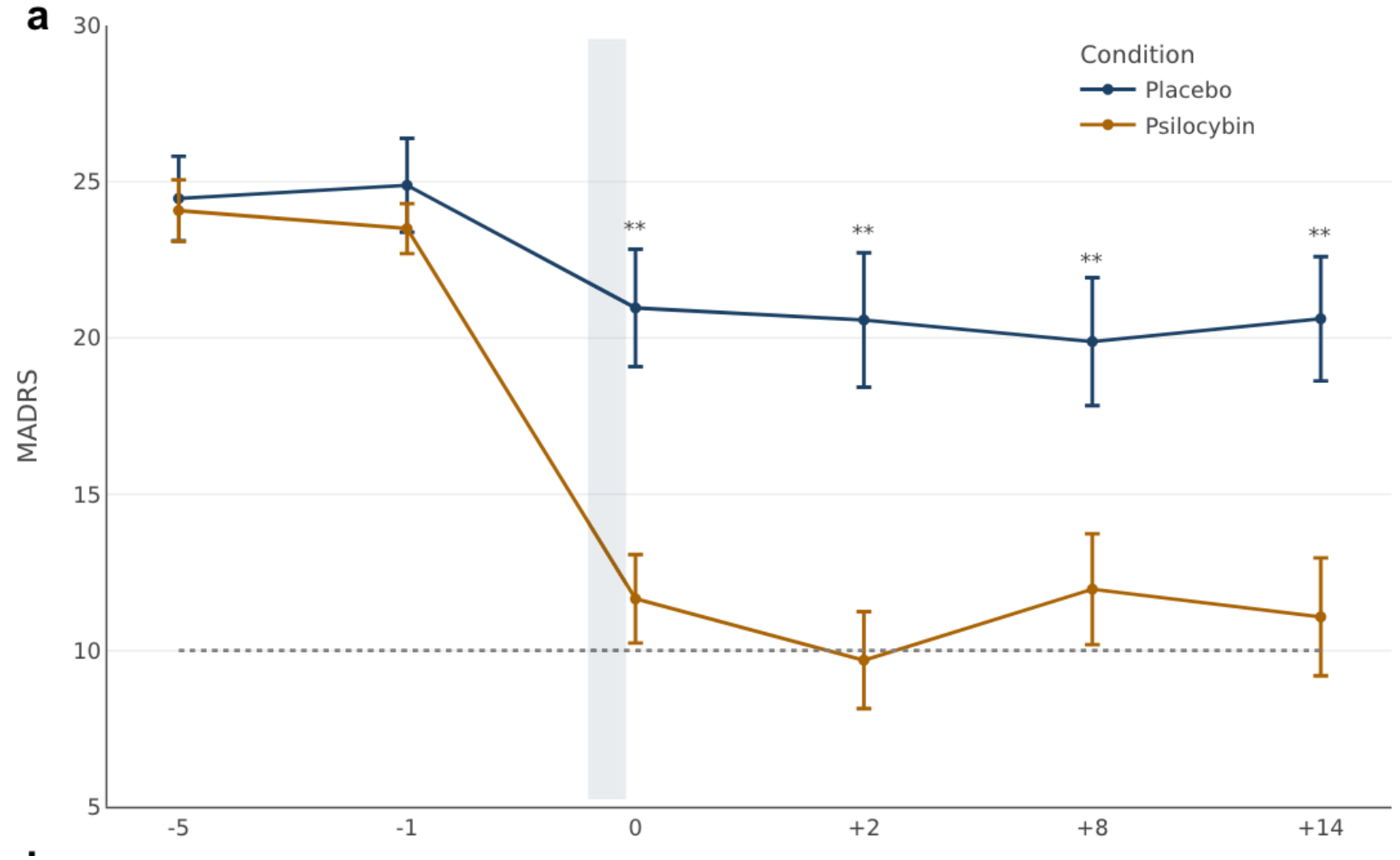
Adverse Event	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
		number (percent)	
Day 2 up to wk 3			
Any serious adverse event	4 (5)	4 (5)	0
Suicidal ideation	2 (3)	2 (3)	0
Intentional self-injury	2 (3)	1 (1)	0
Hospitalization	0	1 (1)	0
After wk 3 up to wk 12			
Any serious adverse event	4 (5)	3 (4)	1 (1)
Suicidal behavior	3 (4)	0	0
Intentional self-injury	0	1 (1)	1 (1)
Adjustment disorder with anxiety and depressed mood	1 (1)	0	0
Depression	0	1 (1)	0
Drug withdrawal syndrome†	1 (1)	0	0
Suicidal ideation	0	1 (1)	0

Compass Phase 2- Serious adverse events

Von Rotz et al., 2023

- N = 52 MDD
- Single dose psilocybin (0.215 mg/kg psilocybin = 15mg for 70kg) vs placebo
- 14-day primary outcome

Von Rotz et al., 2023 - MADRS



Von Rotz et al., (2023) – Effect sizes

- Between group effect size: d = 1.0

Von Rotz et al., (2023) - Remission

Drug	**Remission (%)**
Psilocybin ~ 15mg/70kg	54%
Placebo	12%

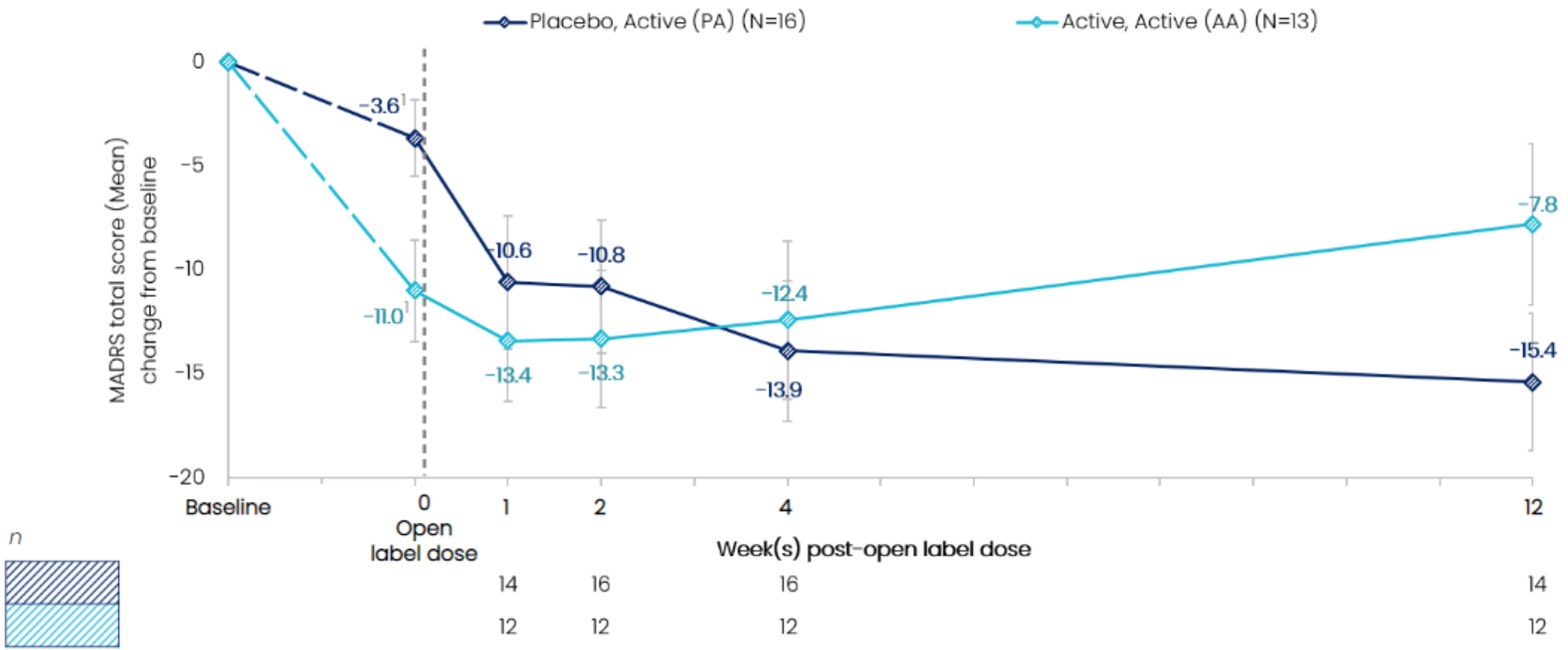
	Davis (2021)	**Palhano-Fontes (2016)**	**Carhart-Harris (2021)**	**Compass (2022)**	**Von Rotz (2023)**
Effect size b/w group	2.6	1.0	0.4	0.7	1.0
Time	1-month post session 2	7-days	6-weeks after 1st dose	3 weeks	2 weeks

	Davis (2021)	Palhano-Fontes (2016)	Carhart-Harris (2021)	Compass (2022)	Von Rotz (2023)
Remission - drug	45%	36%	57%	29%	54%
Remission – control	0%	7%	28%	8%	12%
Remission diff	45%	29%	29%	21%	42%

	Davis (2021)	**Palhano-Fontes (2016)**	**Carhart-Harris (2021)**	**Compass (2022)**	**Von Rotz (2023)**
Time	1-month post session 2	7-days	6-weeks after 1st dose	3 weeks	2 weeks
Interv.	25mg psil x2 vs waitlist	Aya (lowish dose) vs PCB; TRD	25mg psil x 2 vs ESC	25mg psil vs 1mg psil; TRD	~15mg/70 kg psil vs PCB

Change in MADRS over time

One and two dose regimens of IV SPL026 with supportive therapy show ***durable reduction in depression symptoms***



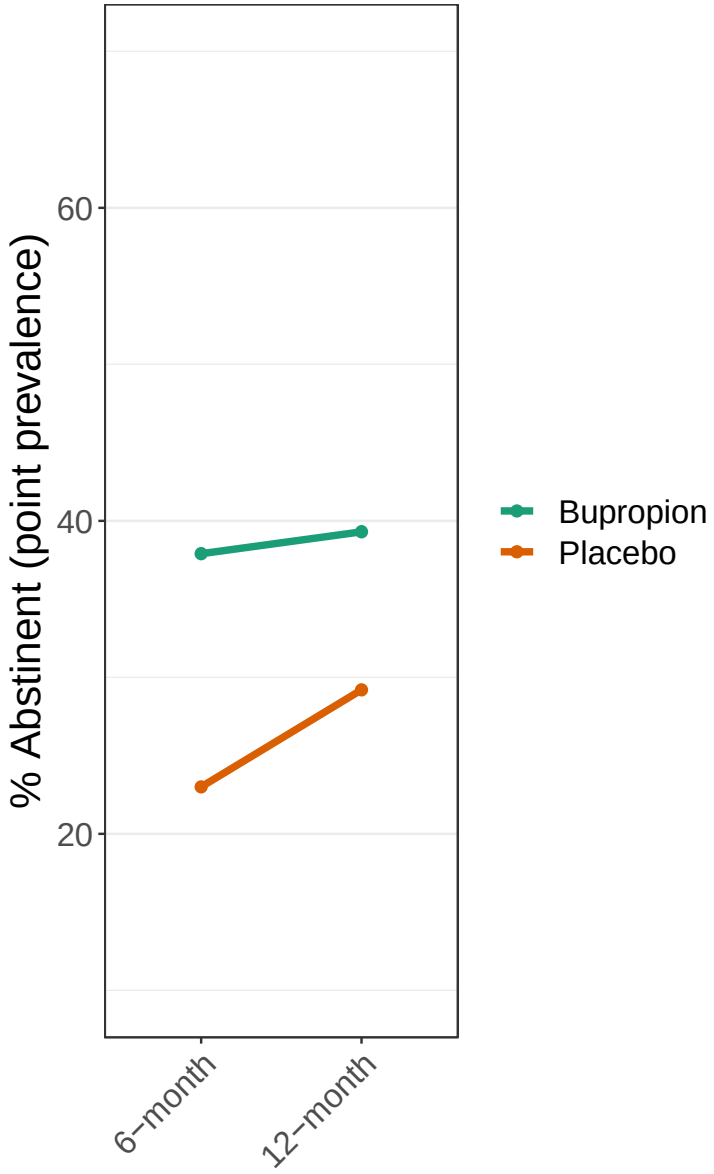
Other trials

- Completed
  - Usona Phase 2 MDD
- Ongoing
  - EPIsoDE (Germany)
  - MDD-AUD
  - PsiDeR (Kings' College London)

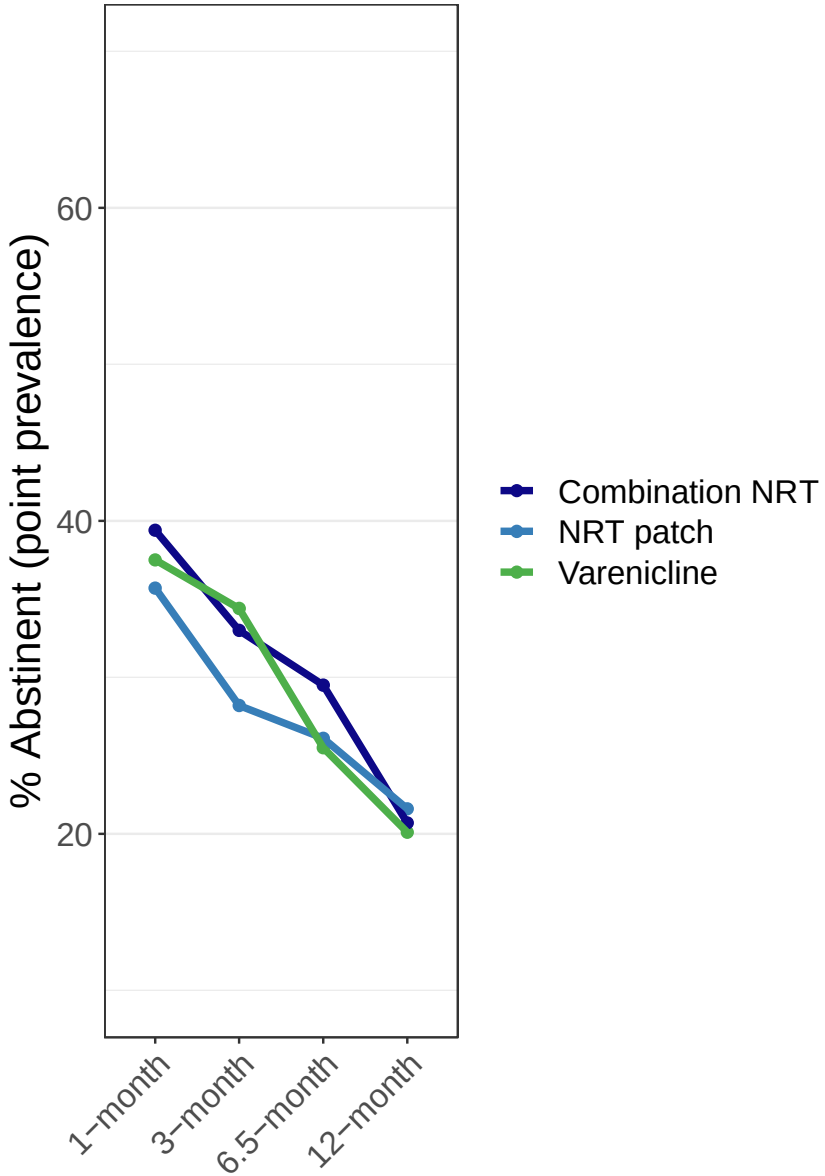
Critiques of psychedelic clinical trials

- De facto unblinding
- Driven by expectancy effects
  - Enthusiastic participants
  - Disappointed placebo group

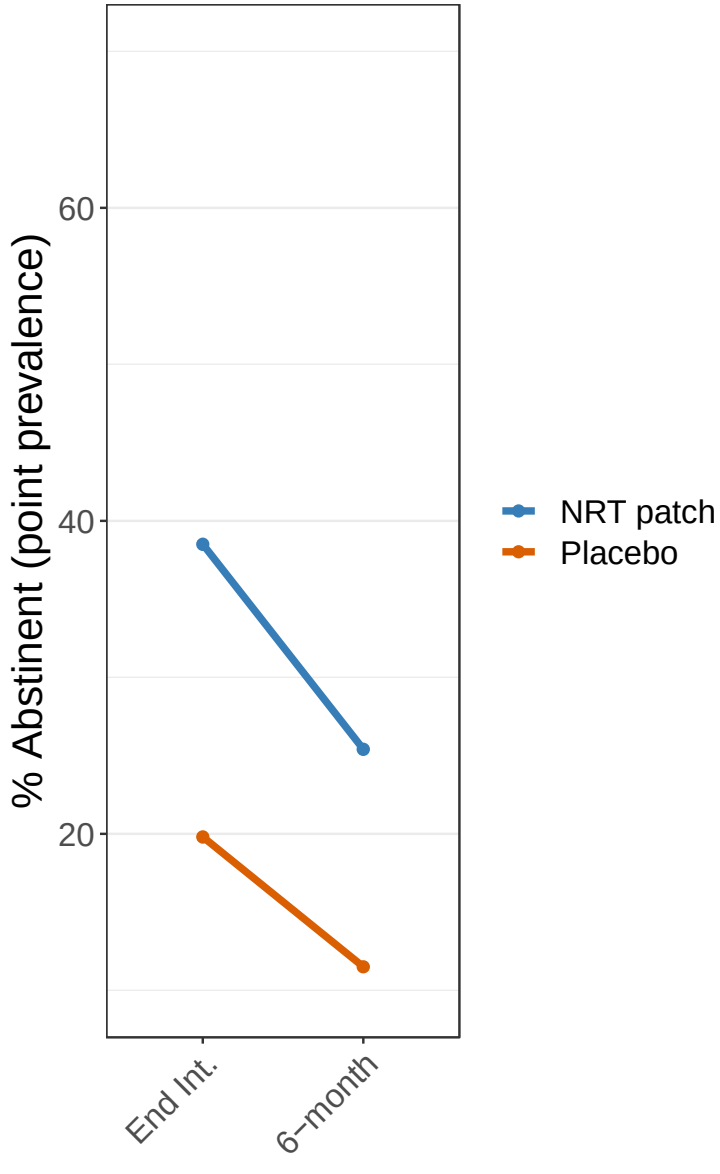
Paszek et al., 2017
Meta−analysis:
5 bupropion trials



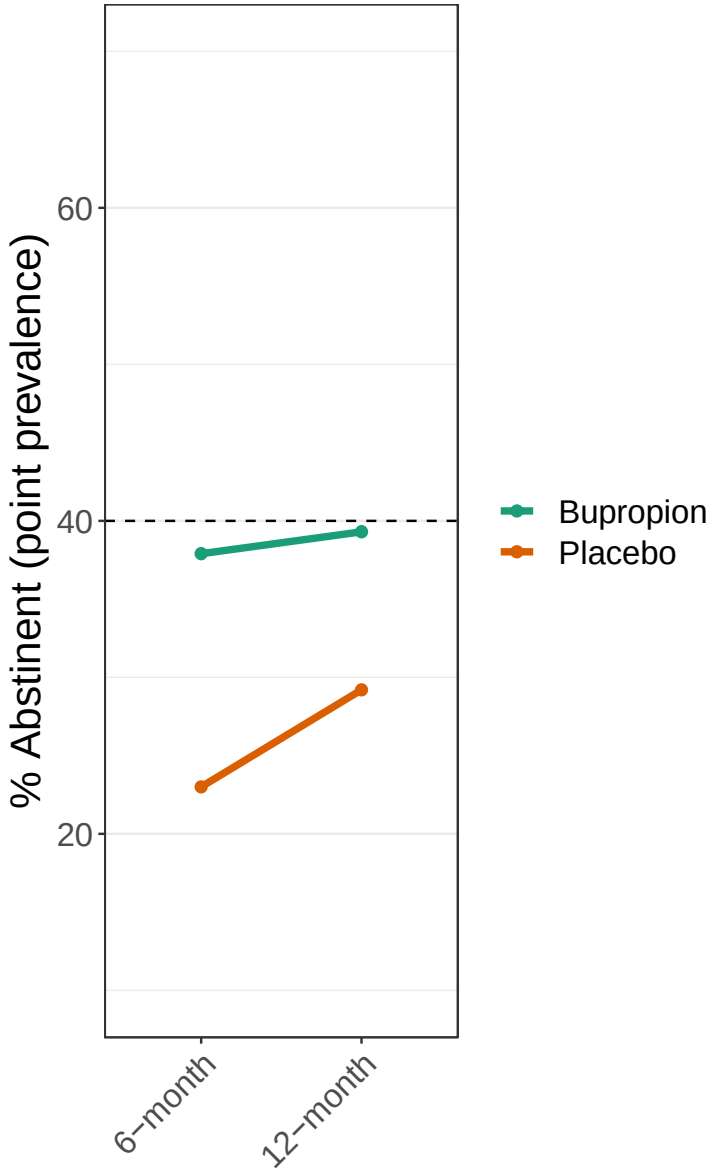
Baker et al., 2016
Varenicline vs. NRT



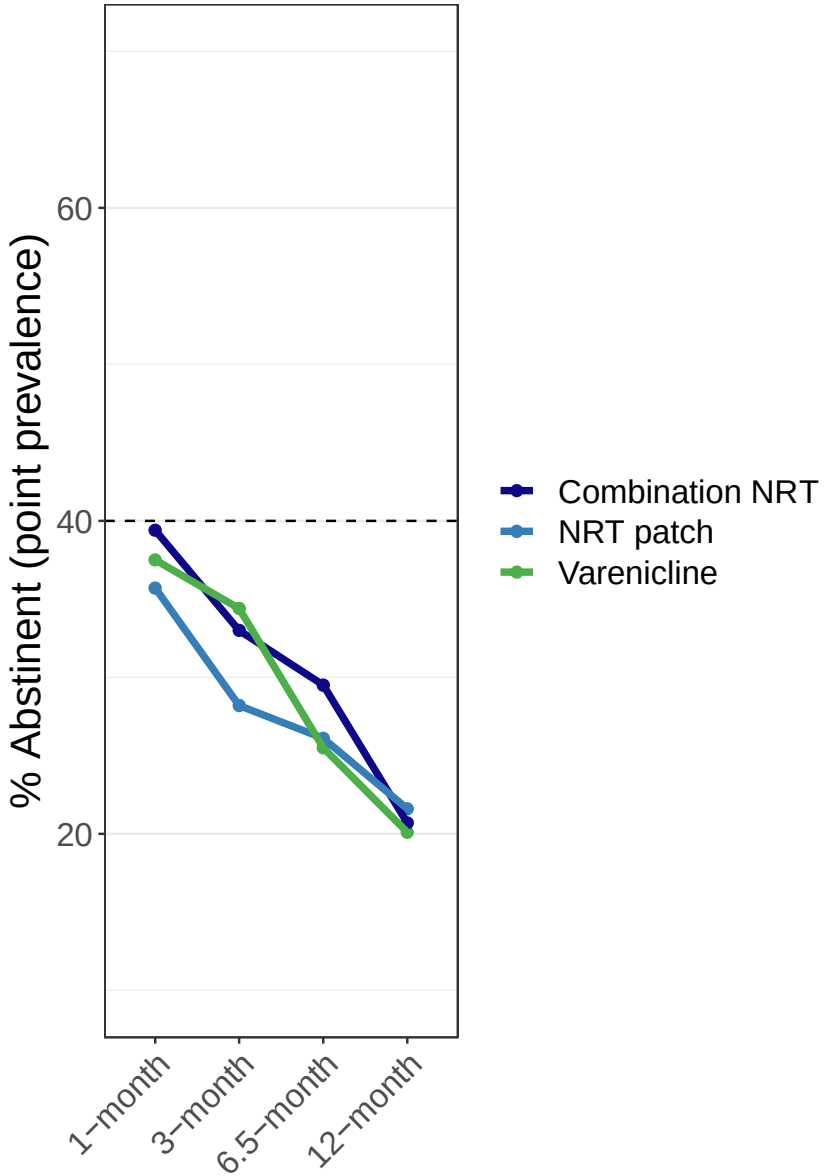
Fiore et al., 1994
Meta−analysis:
13 nicotine patch trials



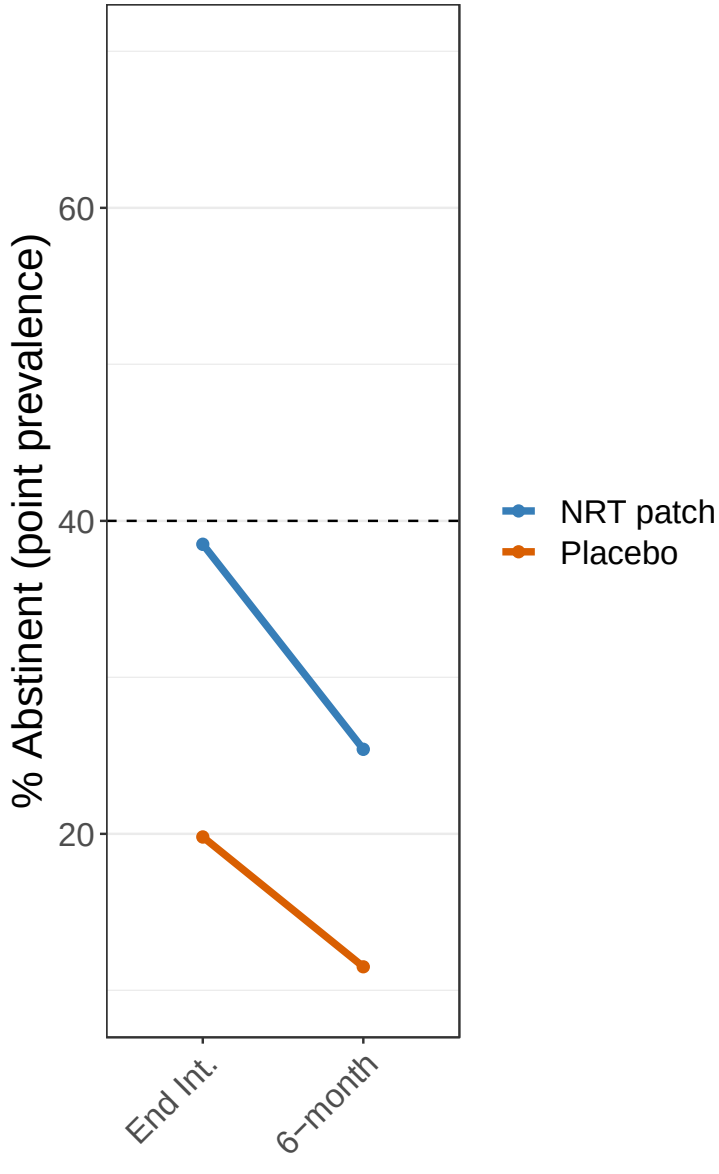
Paszek et al., 2017
Meta−analysis:
5 bupropion trials



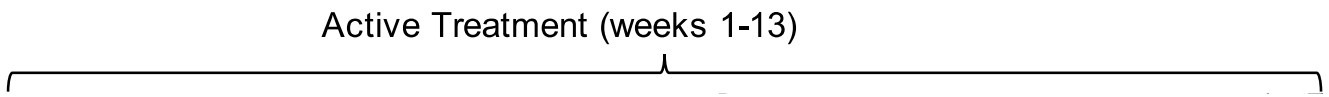
Baker et al., 2016
Varenicline vs. NRT



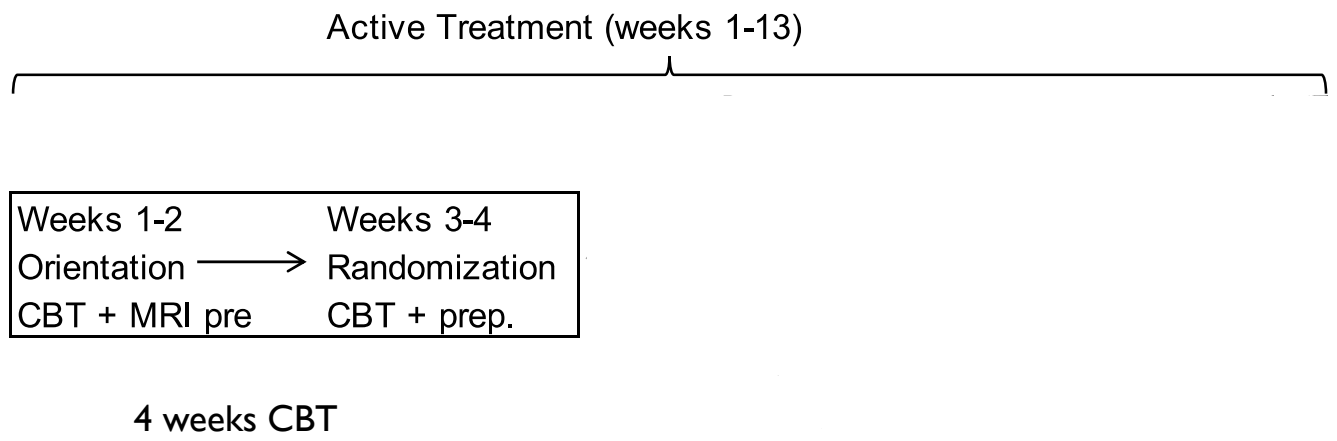
Fiore et al., 1994
Meta−analysis:
13 nicotine patch trials



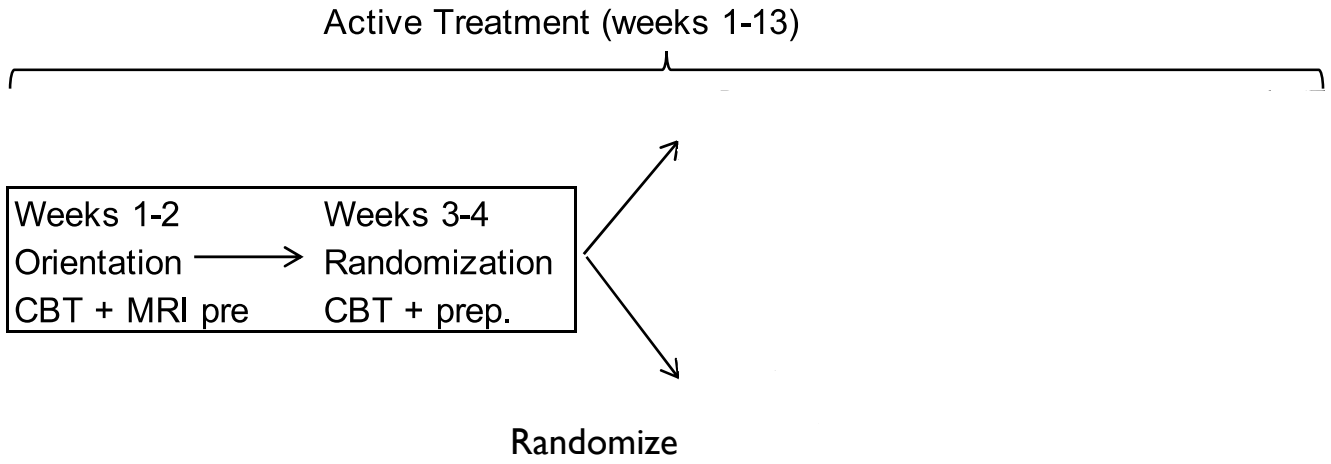
Ongoing open-label comparative effectiveness trial – tobacco smoking



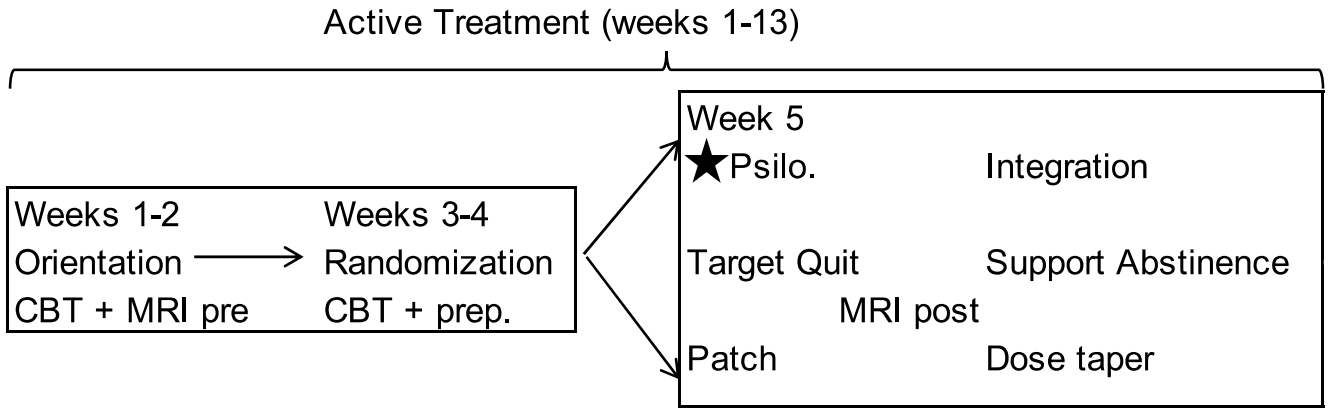
Ongoing open-label comparative effectiveness trial – tobacco smoking



Ongoing open-label comparative effectiveness trial – tobacco smoking

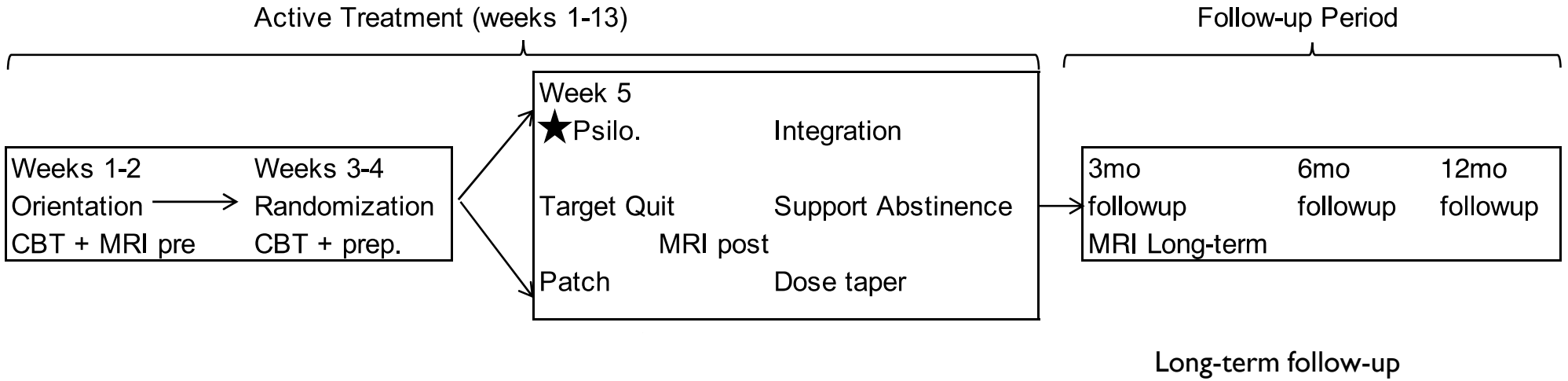


Ongoing open-label comparative effectiveness trial – tobacco smoking



Psilocybin vs Nicotine patch

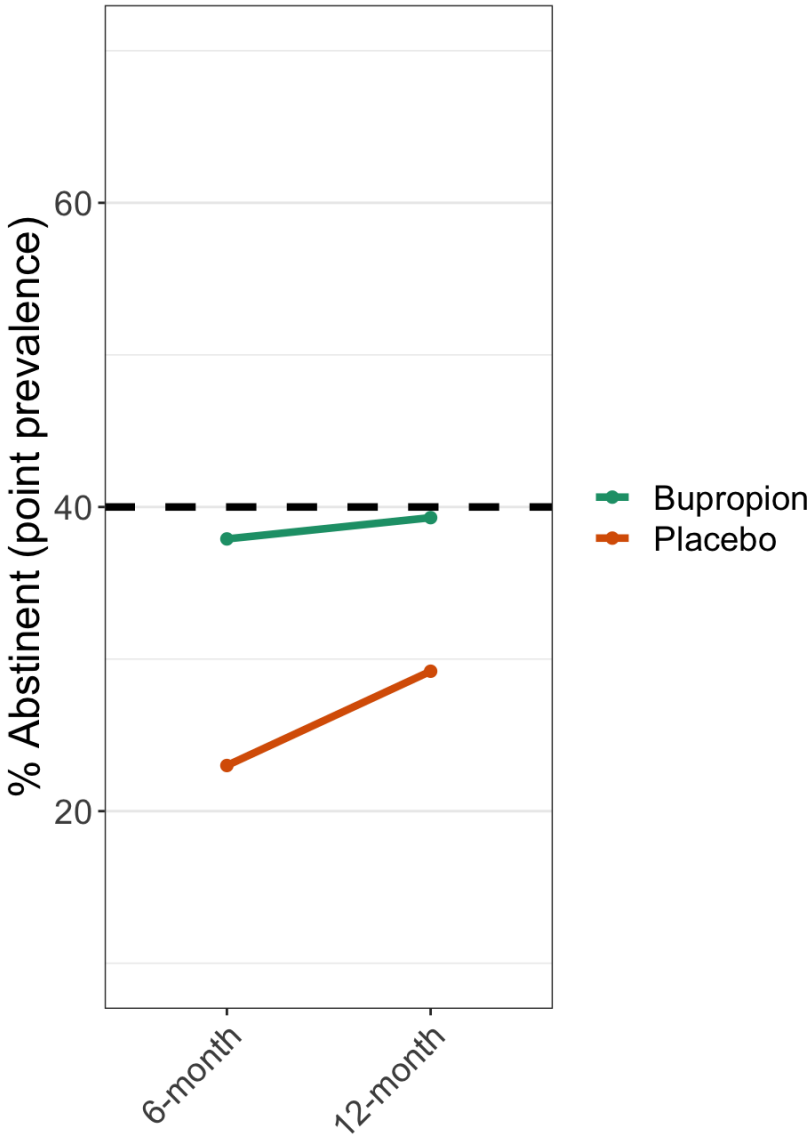
Ongoing open-label comparative effectiveness trial – tobacco smoking



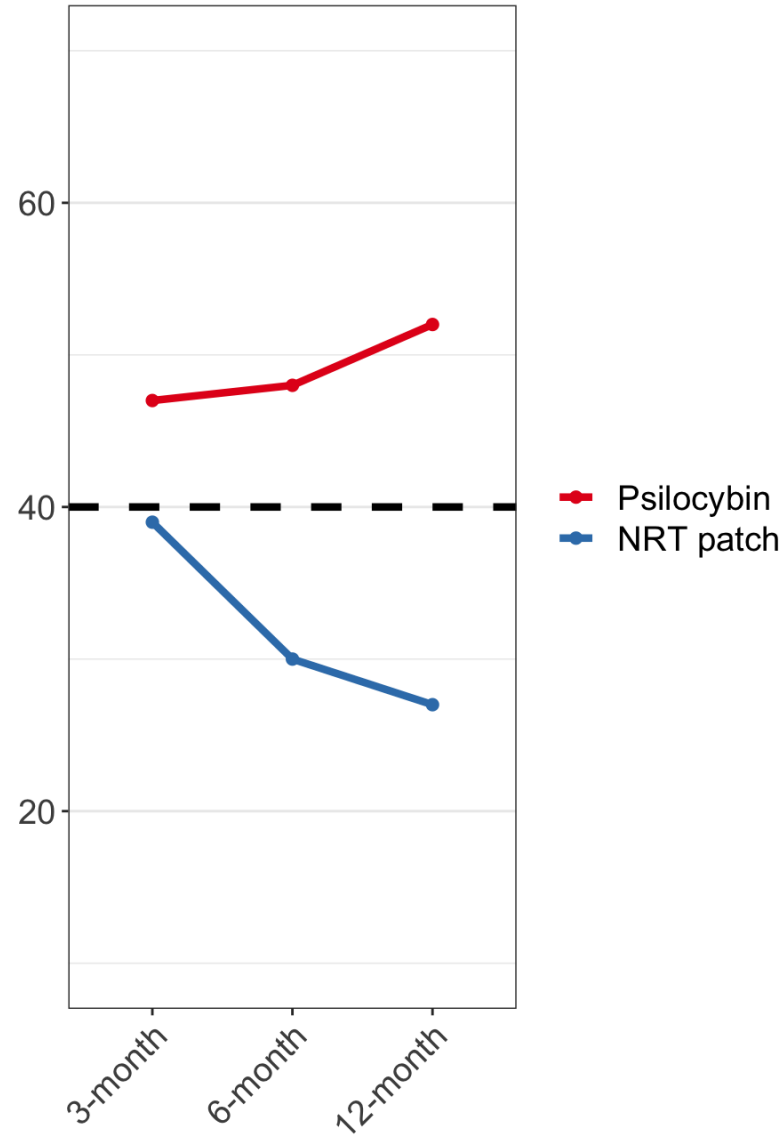
	Categories	Psilocybin n=27	NRT n=29	Total sample n=56
Sex , *n* (%)	Female	10 (37%)	9 (31%)	19 (34%)
	Male	17 (63%)	20 (69%)	37 (66%)
Age (years)	Mean (SD); Range	45 (11); 27 – 70	46 (12); 26 – 65	46 (11); 26 – 70
Race / Ethnicity *n* (%) [a]	White	24 (89%)	25 (86%)	49 (88%)
	Black / African American	3 (11%)	0 (0%)	3 (5%)
	Hispanic / Latino	1 (4%)	0 (0%)	1 (2%)
	Asian / South Asian	0 (0%)	2 (7%)	2 (4%)
	Biracial	0 (0%)	2 (7%)	2 (4%)
Education, *n* (%)	High School / G.E.D.	1 (4%)	2 (7%)	3 (5%)
	Some College / Trade School	10 (37%)	7 (24%)	17 (30%)
	Bachelor's Degree	10 (37%)	6 (21%)	16 (29%)
	Graduate Degree	6 (22%)	14 (48%)	20 (36%)
Prior Hallucinogen	No	8 (30%)	6 (21%)	14 (25%)
	Yes	19 (70%)	23 (79%)	42 (75%)
Cigarettes per Day	Mean (SD); Range	17 (6); 5 - 30	16 (8); 5 - 40	17 (7); 5 - 40
Years Smoking	Mean (SD); Range	25 (9); 8 - 52	26 (13); 4 - 48	26 (11); 4 - 52
Previous quit attempts	Mean (SD); Range	8 (6); 3 - 25	6 (4); 2 - 20	7 (5); 2 - 25

- About 1 pack a day
- Mean duration 26 years
- Mean 7 quit attempts

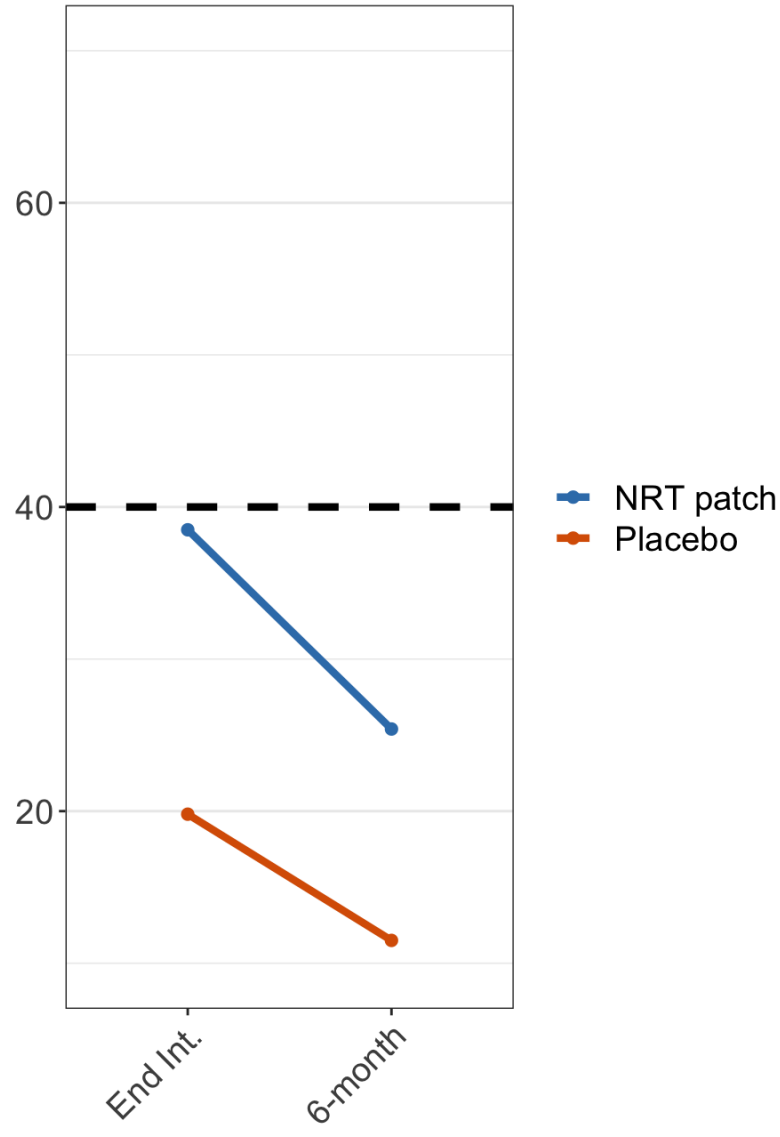
Paszek et al., 2017
Meta-analysis:
5 bupropion trials



Hopkins, ongoing



Fiore et al., 1994
Meta-analysis:
13 nicotine patch trials



Older psychedelic studies for palliative

- (Kast 1962, 1964, 1966, 1967; Cohen 1965; Pahnke 1969; Fisher 1970; Grof et al. 1973; Richards et al. 1977)

RCT of psychedelic for palliative / cancer

- Grob et al. (2011)
- Gasser et al. (2014)
- Griffiths et al. (2016)
- Ross et al. (2016)

Grob (2011)

- N = 12, within-subject cross-over
- Advanced stage terminal cancer (6mo – 1 year) PLUS
- DSM-IV acute stress do, GAD, adjustment disorder with anxiety

- Psil 14mg / 70kg

- Safe but no significant diff in anxiety at f/u

Gasser (2014)

- N = 12
- Advanced stage life threatening illness (survival > 6mo) PLUS
- DSM-IV anxiety do OR score ≥40 on STAI

- LSD 200mcg vs 20mcg

- Safe, significant decreases in anxiety to 2mo f/u with a large effect size of 1.1.

Griffiths (2016)

- N = 51
- Life-threatening cancer dx
  - Active with poor prognosis (stage III or IV)
  - Recurrence or possibility of recurrence PLUS
- DSM-IV GAD, acute stress do, PTSD, mild/moderate MDD, dysthymic disorder, adjustment disorder

- PSI 22-30mg/70kg VS 1-3mg/70kg

- Improvements in wellbeing, anxiety, and depression, persisted for 6 months in majority (80%)

Ross (2016)

- N = 29
- Life-threatening cancer dx PLUS
  - Initially terminally ill stage IV but broadened to include remission
- DSM-IV GAD, acute stress do, adjustment disorder

- PSI 21mg/70kg VS niacin

- reduced anxiety, depression, and cancer-related demoralization

2. Psychedelic therapy delivery

a. Prep

b. Dose

c. Integration

Prep and Drug Sessions

- Prep sessions
- Drug session:
  - The 7-hr drug sessions are conducted in a living-room-like environment
  - Two monitors are present throughout the session

Follow-up (integration)

- Meetings with both facilitators in days and weeks following dosing sessions
- Review of experiences on session day and interim events
  - Goal is to help the participant understand and incorporate insights from the experience into their daily lives

3. Psychedelic therapy as psychotherapy

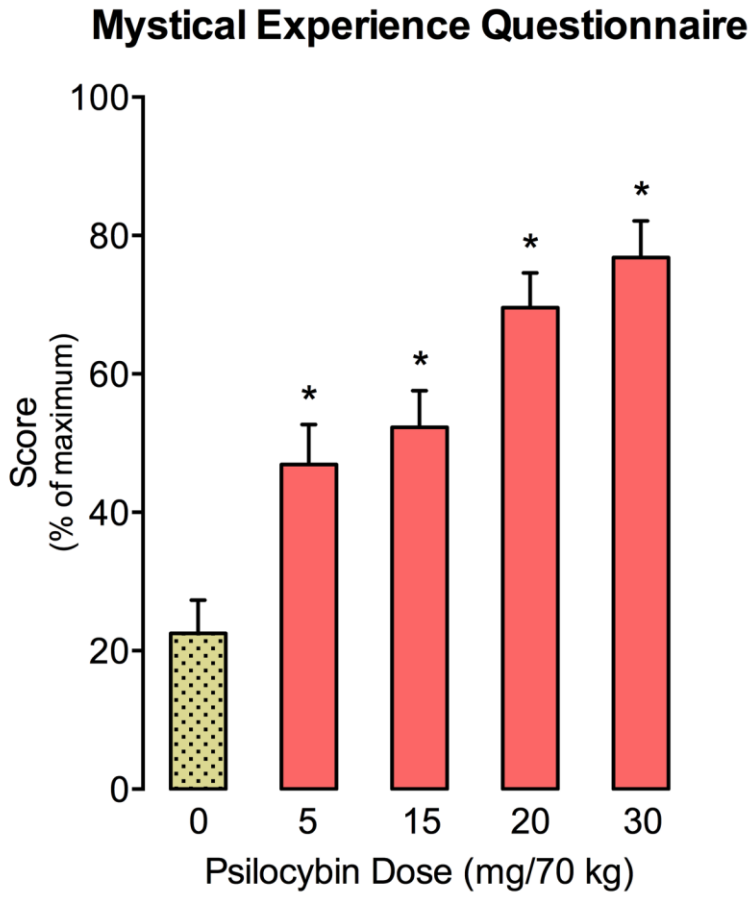
a. Subjective effects

b. Common factors of psychotherapy

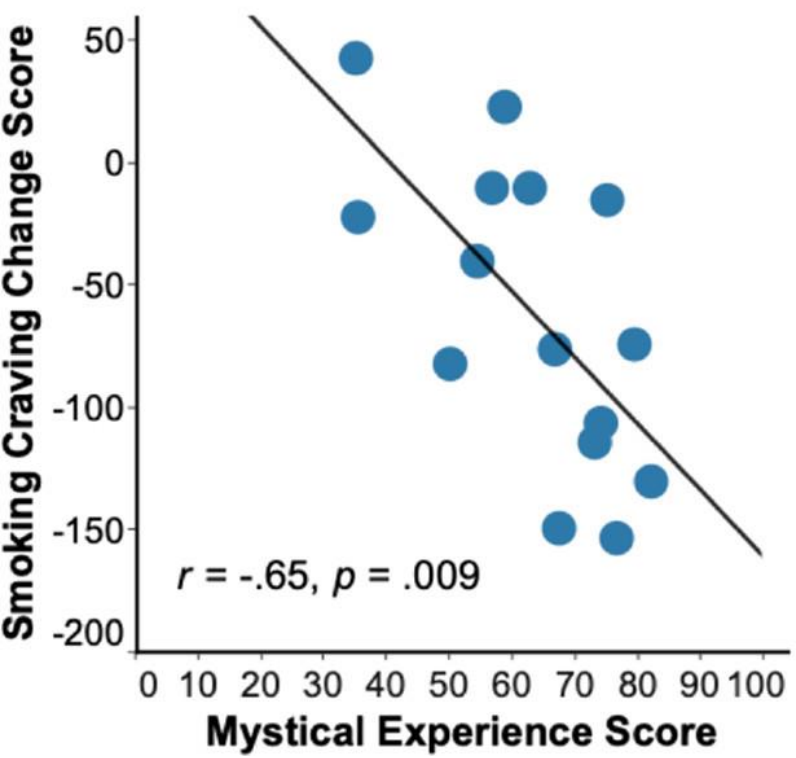
c. Cases

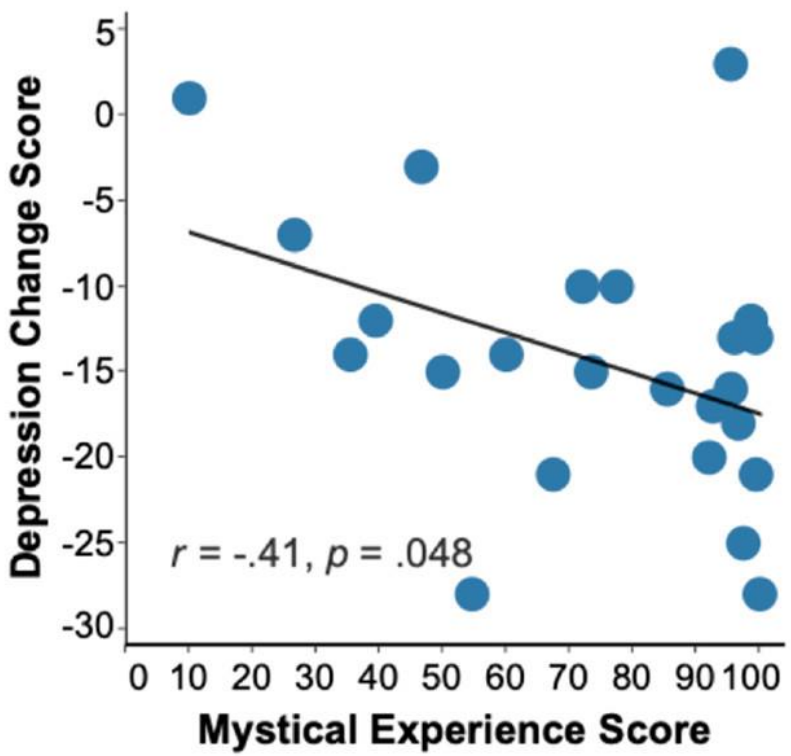
Psychological mechanisms of action

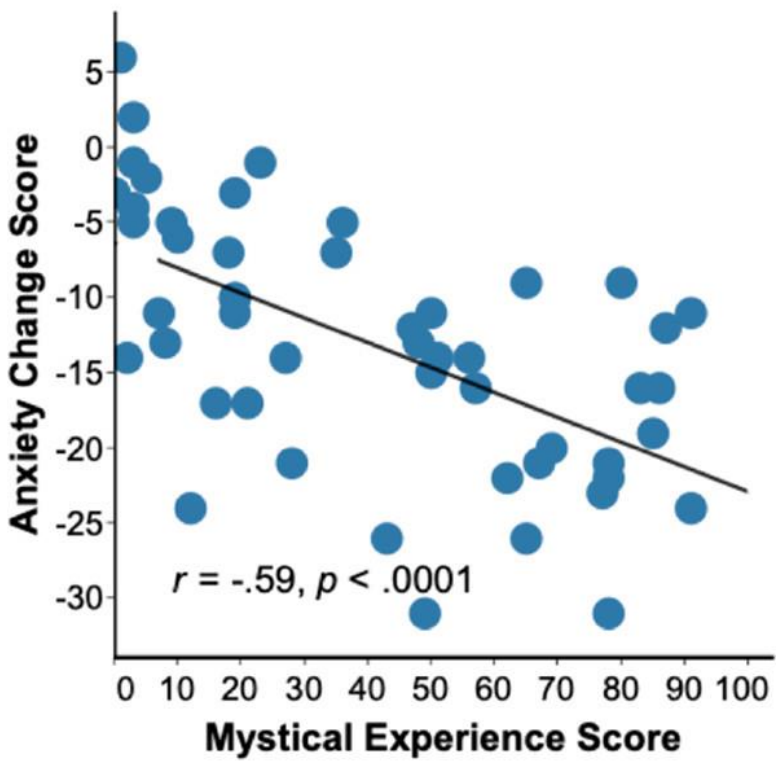
- Mystical experience Questionnaire
  - Unity, deeply felt positive mood, transcendence of space/time, ineffability, sense of reverence
  - Dose-dependent



Mystical Experience on Session Days Predicts Later Therapeutic Outcomes







Yaden & Griffiths (2021)

Mystical?

- MEQ ~ Near Death Experience
  - r = 0.8
- MEQ ~ Awe Experience Scale
  - r = 0.8
- MEQ ~ Oceanic boundlessness
  - r = 0.9

The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects

David B. Yaden and Roland R. Griffiths*

VS

The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects

David B. Yaden and Roland R. Griffiths*

VS

No, they're not

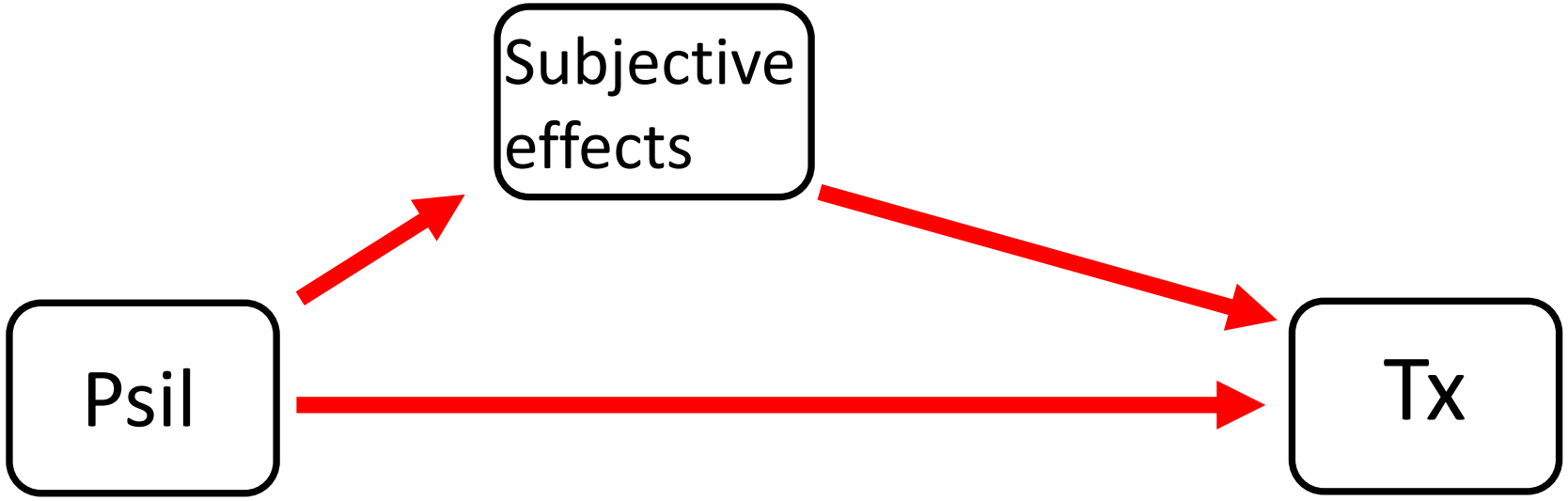
The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects

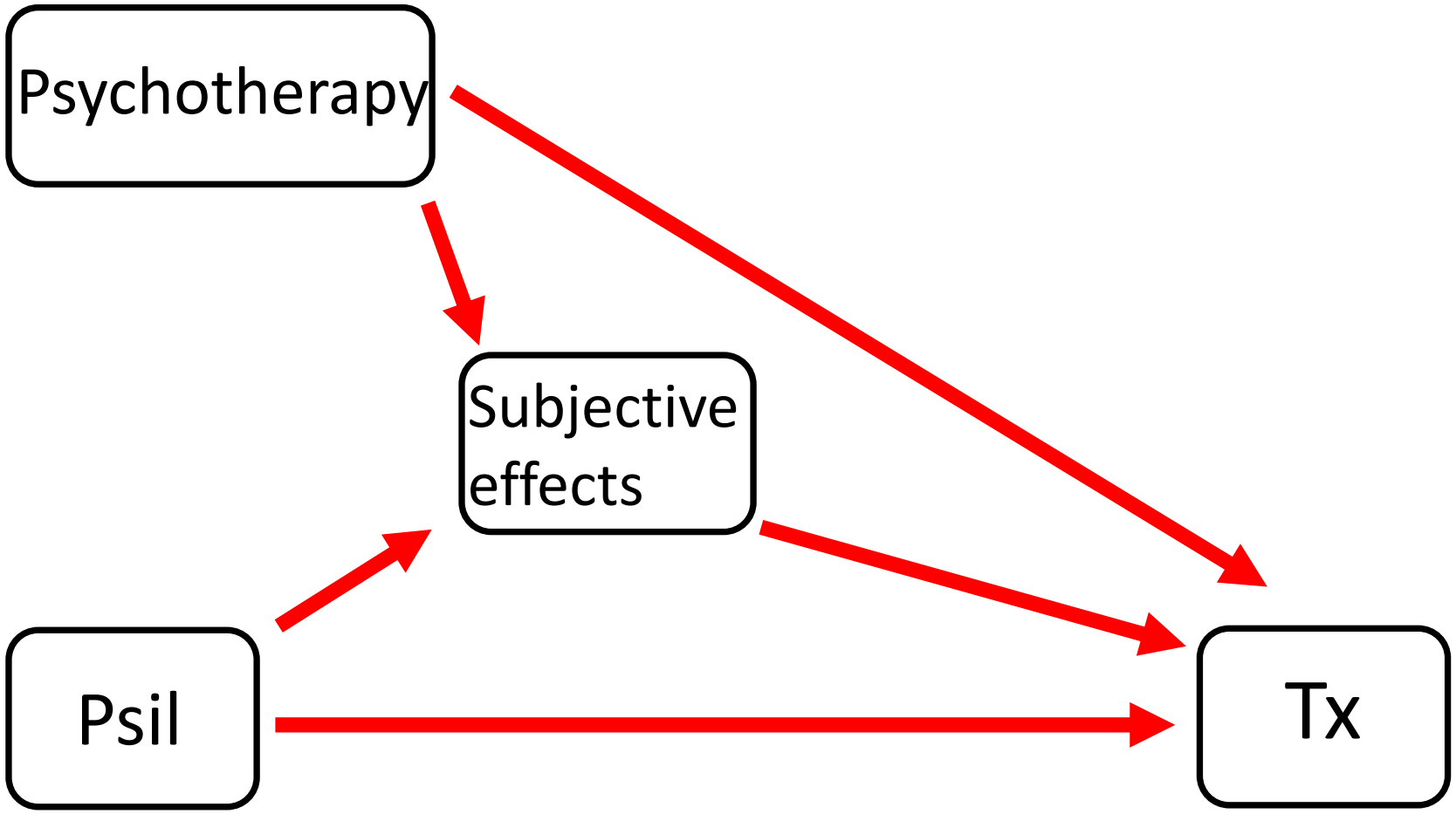
David B. Yaden and Roland R. Griffiths*

VS

The Subjective Effects of Psychedelics May Not Be Necessary for Their Enduring Therapeutic Effects

David E. Olson*


Subjective effects
Psil
Tx


Psychotherapy
Subjective effects
Psil
Tx

Common factors of psychotherapy

Dodo bird verdict

- “Everyone has won and all must have prizes”
- Introduced by Saul Rosenzweig in 1936
- Became the subject of empirical research by the 1970’s

Dodo bird verdict

- Luborsky et al. (2002)
  - Examined 17 meta-analyses of trials comparing 2 active psychotherapies
  - Statistically insignificant differences, on average d = 0.2
  - Also found that much of the specific effect of a therapy could be explained by researcher allegiance
- Dismantling studies find minimal effects of supposed active ingredient

Jerome Frank

- *Persuasion and Healing*

- Viewed psychotherapy as a salve for demoralization via repairing one's "assumptive world" (the set of enduring cognitive, affective and behavioral assumptions that guide perception and action)
- Pts "seek help not in response to the symptoms themselves but because their efforts to cope with the symptoms have failed"
- Psychotherapy exerts its impact on "the pathogenic meanings patients attribute to feelings and events in their lives"

Jerome Frank

- Common factors of psychotherapy (Frank, 1993):
  - emotionally charged, confiding relationship with an expert
  - healing setting
  - rationale, conceptual scheme, or myth
  - Therapeutic ritual
- Should allow:
  - Corrective emotional experiences
  - Skillbuilding
  - Rescripting ‘pathogenic meaning’

- Per Frank, the overall method of psychotherapeutic change is the rescripting of “pathogenic meanings”
- A successful psychotherapy must:
  - provide a plausible explanation of the patient’s problem that is consistent with emotional well-being and suggest a means to improve.
  - be emotionally arousing
    - The more intense “the experiential, as opposed to the purely cognitive, components of learning, the more likely they are to produce changes in the patients’ attitudes or behavior”

"It is curious how under LSD the fondest theories of the therapist are confirmed by his patient. Freudian symbols come out of the mouths of patients with Freudian analysts. Those who have Jungian therapists deal with the collective unconscious and with archetypal images. The patient senses the frame of reference to be employed, and his associations and dreams are molded to it. Therefore, the validity of any school of healing should not be based upon productions of the patient—especially LSD patients," (Cohen 1967, 578).

“I relived my own conception and various stages of my embryological development. While I was experiencing all the complexities of the embryogenesis, with details that surpassed the best medical handbooks, I was flashing back to an even more remote past, visualizing some phylogenetic vestiges from the life of my animal ancestors.

The scientist in me was struck by another riddle: can the genetic code, under certain circumstances, be translated into a conscious experience?… I felt, however, that something of utmost relevance had happened to me on this session day and that I would never be the same. I reached a new feeling of harmony and self-acceptance, and a global understanding of existence that is difficult to define (Grof 1975)”.

Mechanisms

- Psychotherapy
  - Psychological insight[1]
  - Increased mindfulness/acceptance[2-4]
  - Self-mastery/emotional skills
  - Interpersonally intimate, trusting environment
  - Suggestibility[5-6]

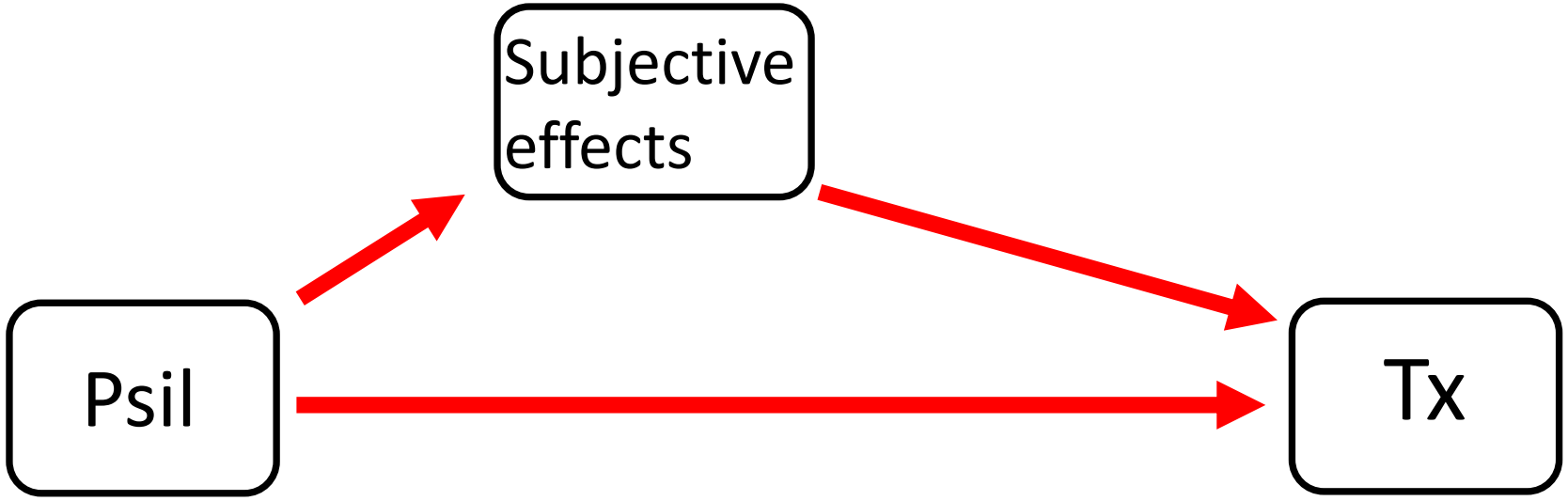
[1] Davis et al. (2021). *J. Psychopharmacol*, *35*(4), 437-446.
[2] Madsen et al. (2020). *Eur Neuropsychopharm* 2020; 5
[3] Soler et al. (2016) *Psychopharmacology (Berl)* 2016; 233: 823–829
[4] Wolff et al. (2020). *Front Psychiatry* 2020; 11: 5
[5] Carhart-Harris et al. (2015). *Psychopharm,* 232(4), 785-794

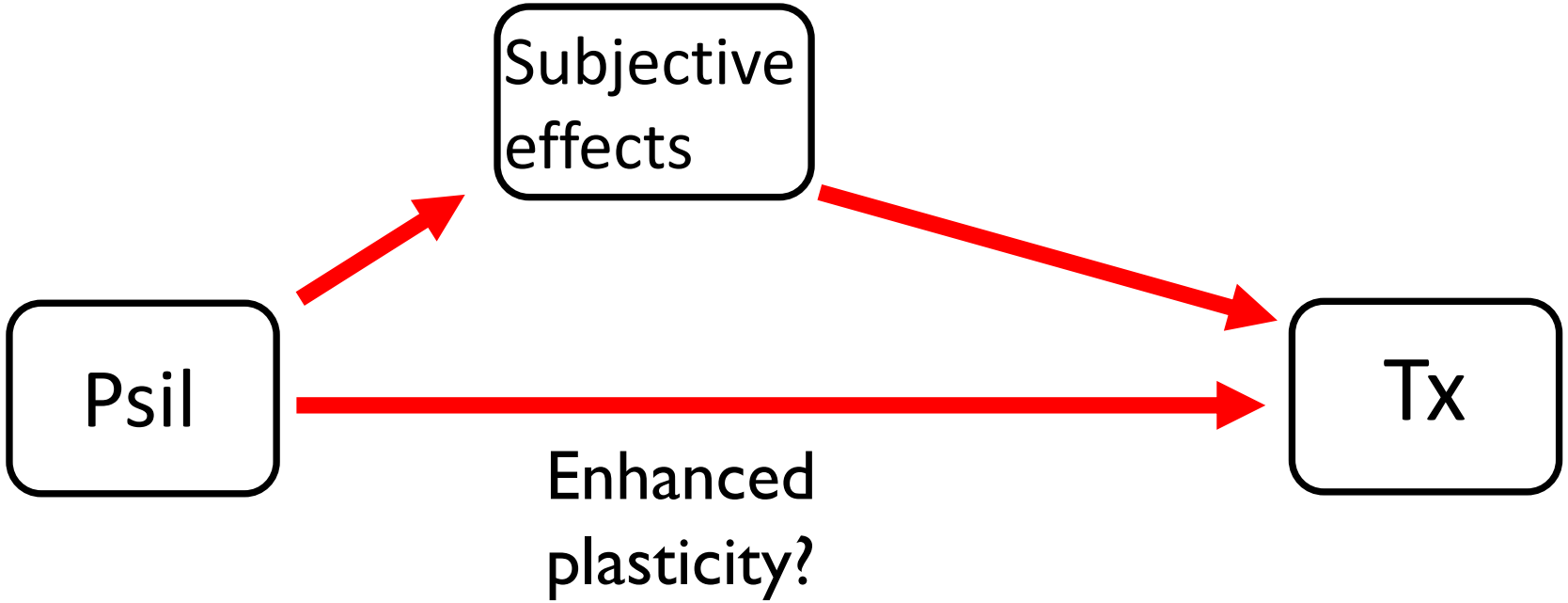
Cases

Cases

I was really hoping the experience would "cure" my depression. It has not. However, it has really changed my perspective about my own emotional state. I am much less stuck with the idea that my feelings are permanent, and I am embracing the idea that my emotional state is one of constant change.

It has allowed me to become more of a dispassionate observer of my emotions and has made me more curious about what my emotions are trying to tell me. For a long time, I was stuck on the what, now I am much more interested in the why.


Subjective effects
Psil
Tx


Subjective effects
Psil
Tx
Enhanced plasticity?

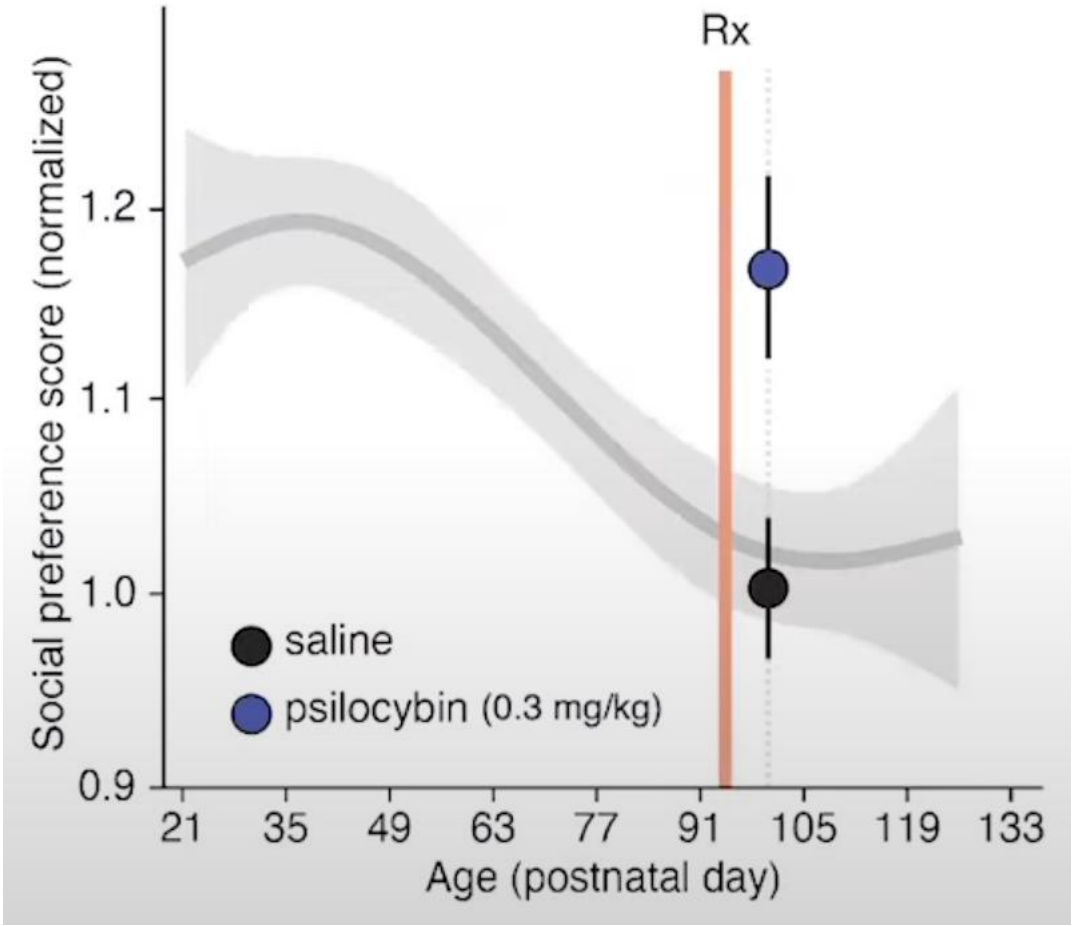
Enhanced structural and functional plasticity

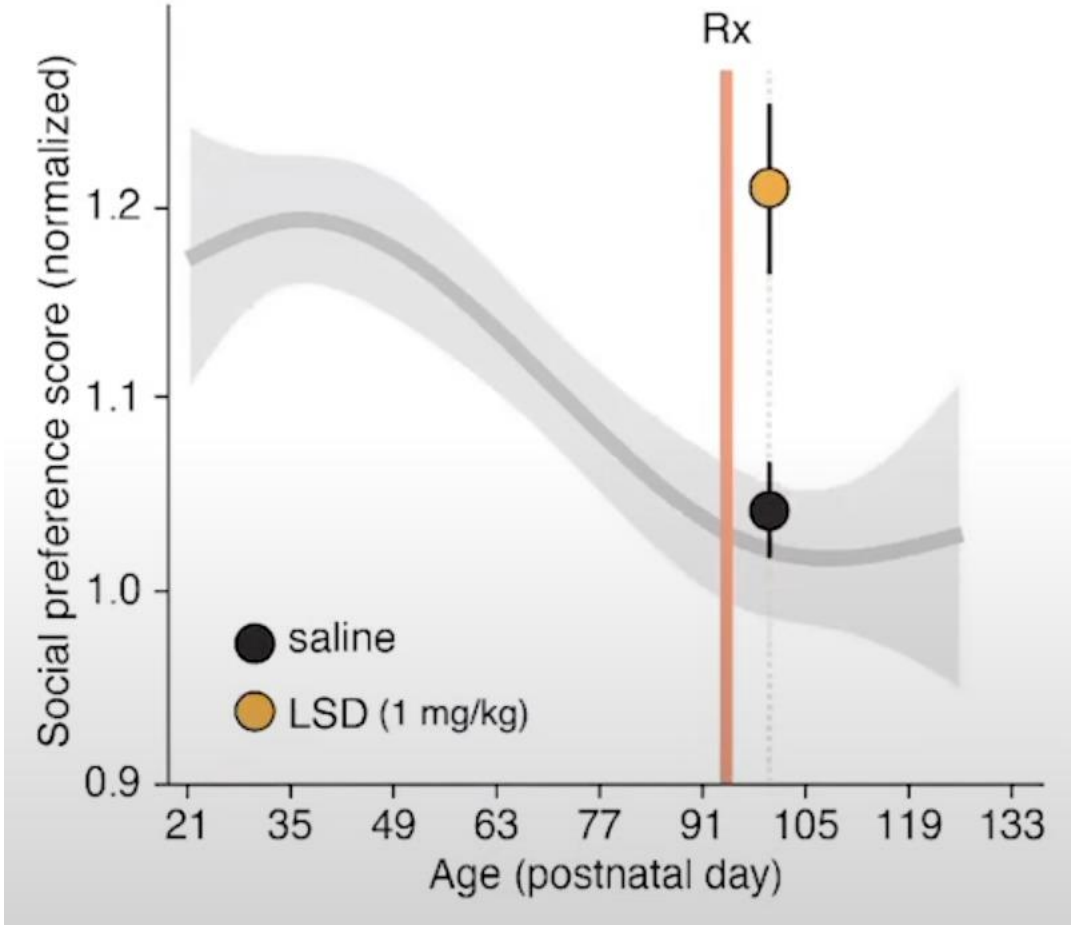
- Psilocybin induces rapid and persistent growth in dendritic spines and synapse formation in vitro[1] and in vivo[2] in rodents

[1]Ly, C., et al. (2018). *Cell reports*, *23*(11), 3170–3182.

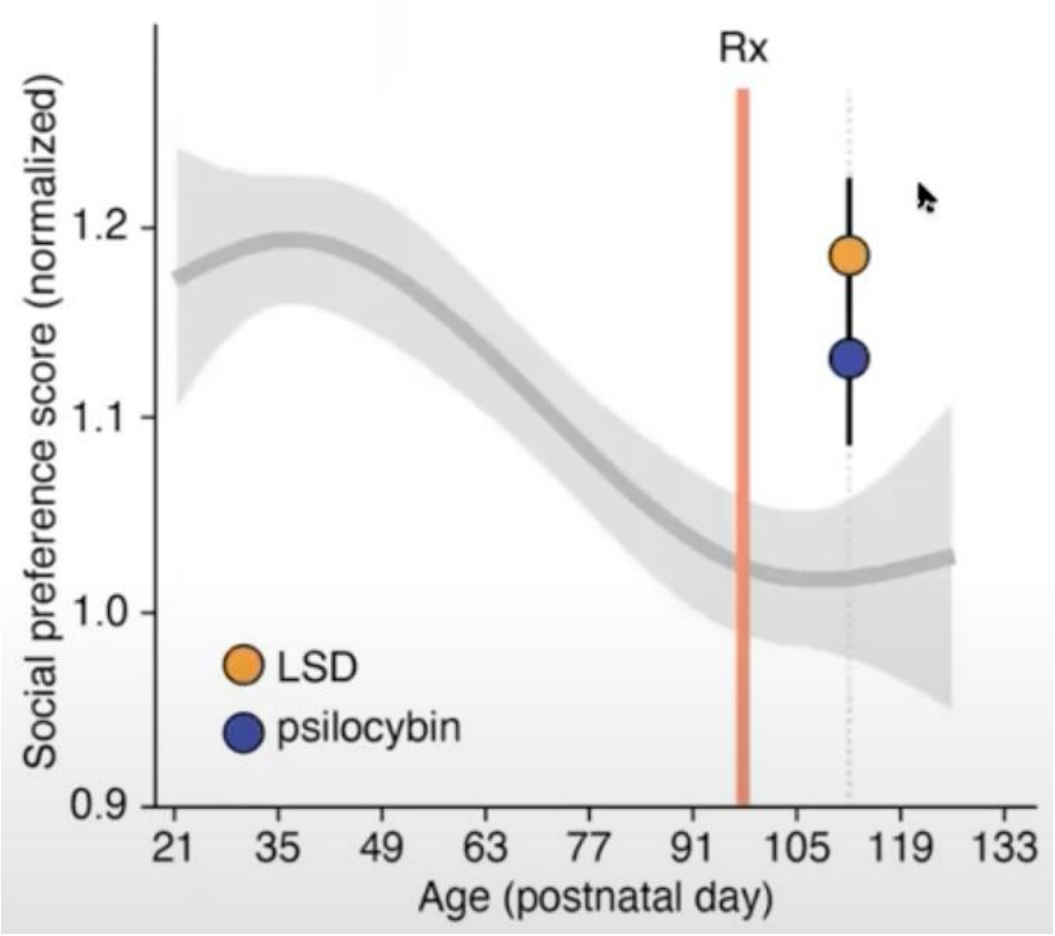
[2]Shao L-X, et al. (2021) *Neuron* 109(16): 2535-2544.e4.

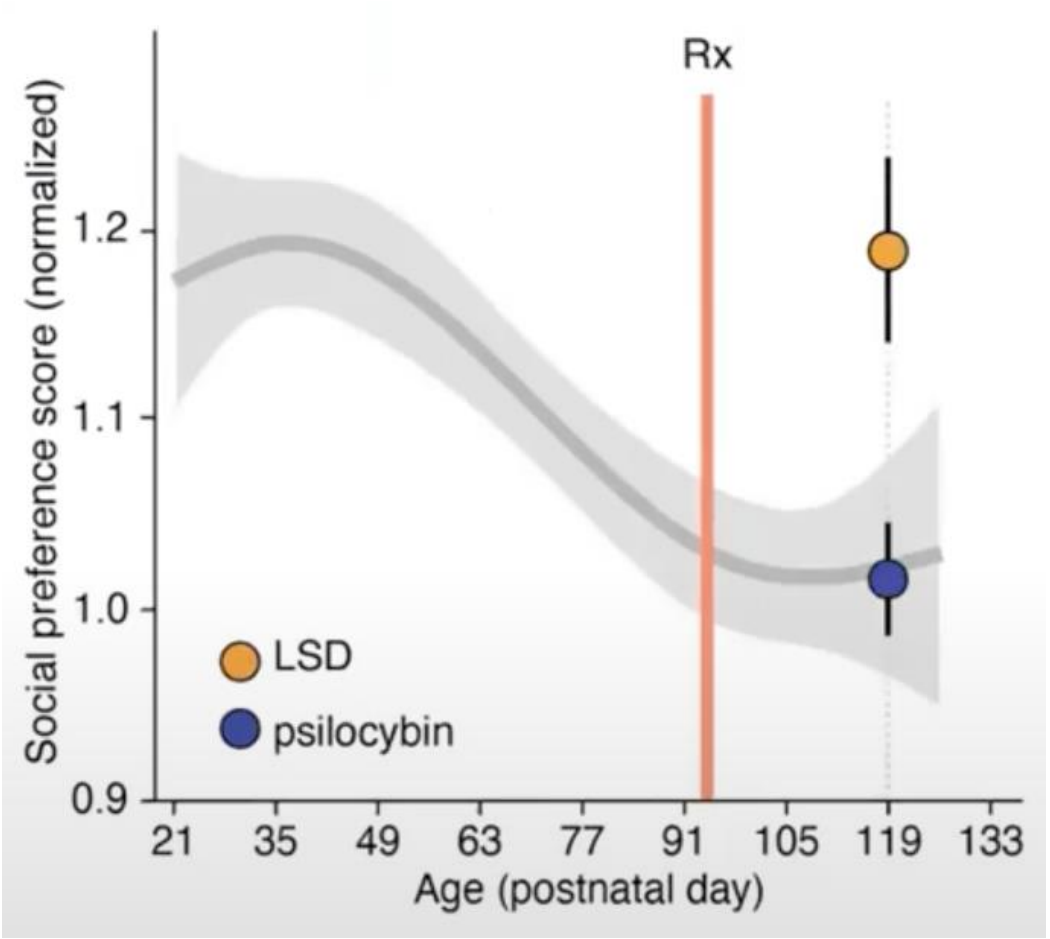
Psil and LSD reopen Social Reward Learning Critical Period





This effect lasts for weeks





4. Clinical issues and future directions

a. Serotonergic antidepressants
b. Bipolar disorder
c. Future trials

Serotonergic antidepressants

- Reduced psilocybin effects
- Serotonin syndrome

Reduced LSD effect after chronic serotonergic antidepressants

- Pts taking MAOI nialamide for several weeks were insensitive to the effects of LSD (Grof & Dytrych, 1965).
  - This effect lasted at least 14 days before eventually resolving

Reduced LSD effect after chronic serotonergic antidepressants

- Pts taking MAOI nialamide for several weeks were insensitive to the effects of LSD (Grof & Dytrych, 1965).
  - This effect lasted at least 14 days before eventually resolving

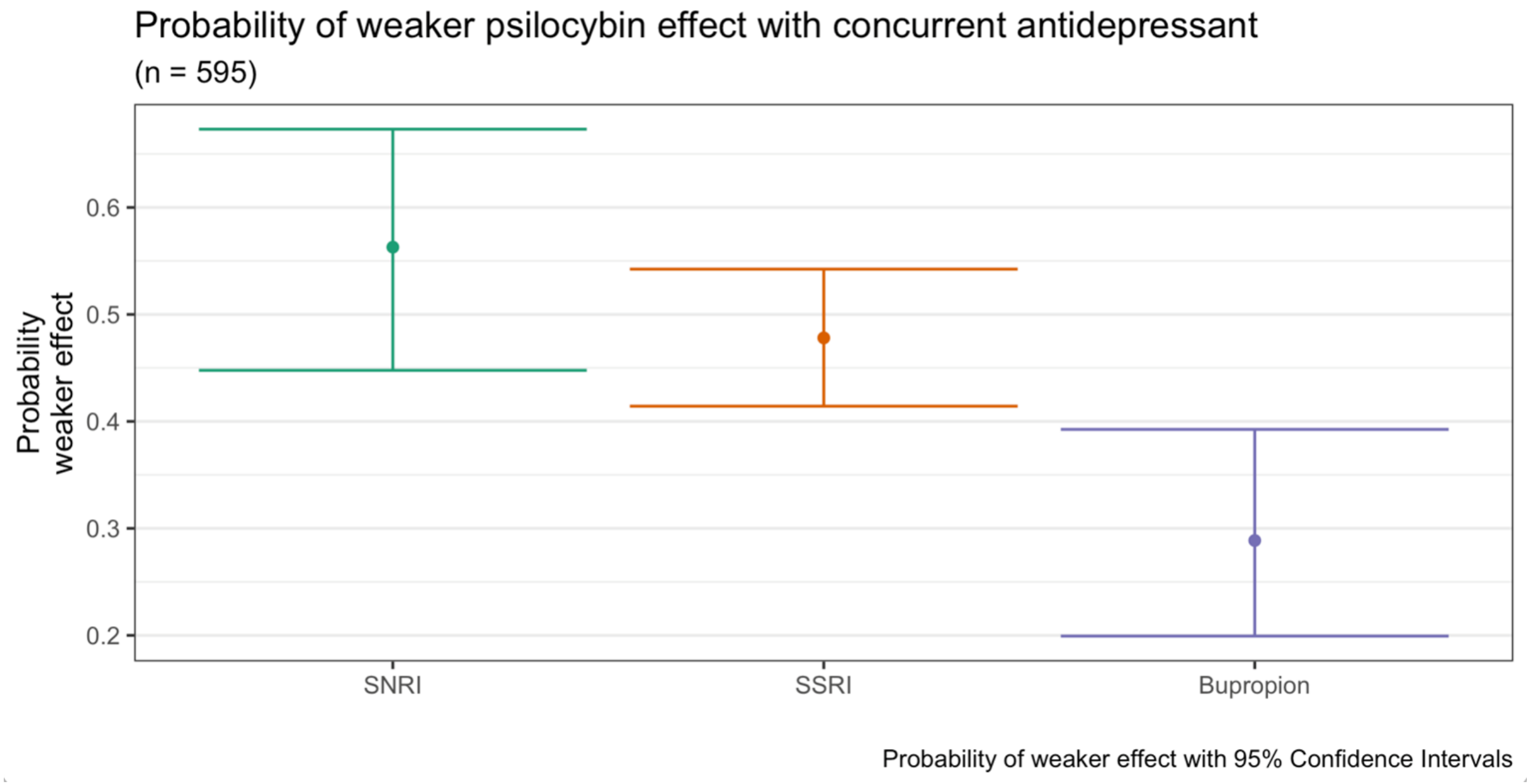
- Small survey studies of LSD users showed similar effects with SSRIs (Bonson et al., 1995) and MAOIs (Bonson et al., 1996).

Becker et al., 2021

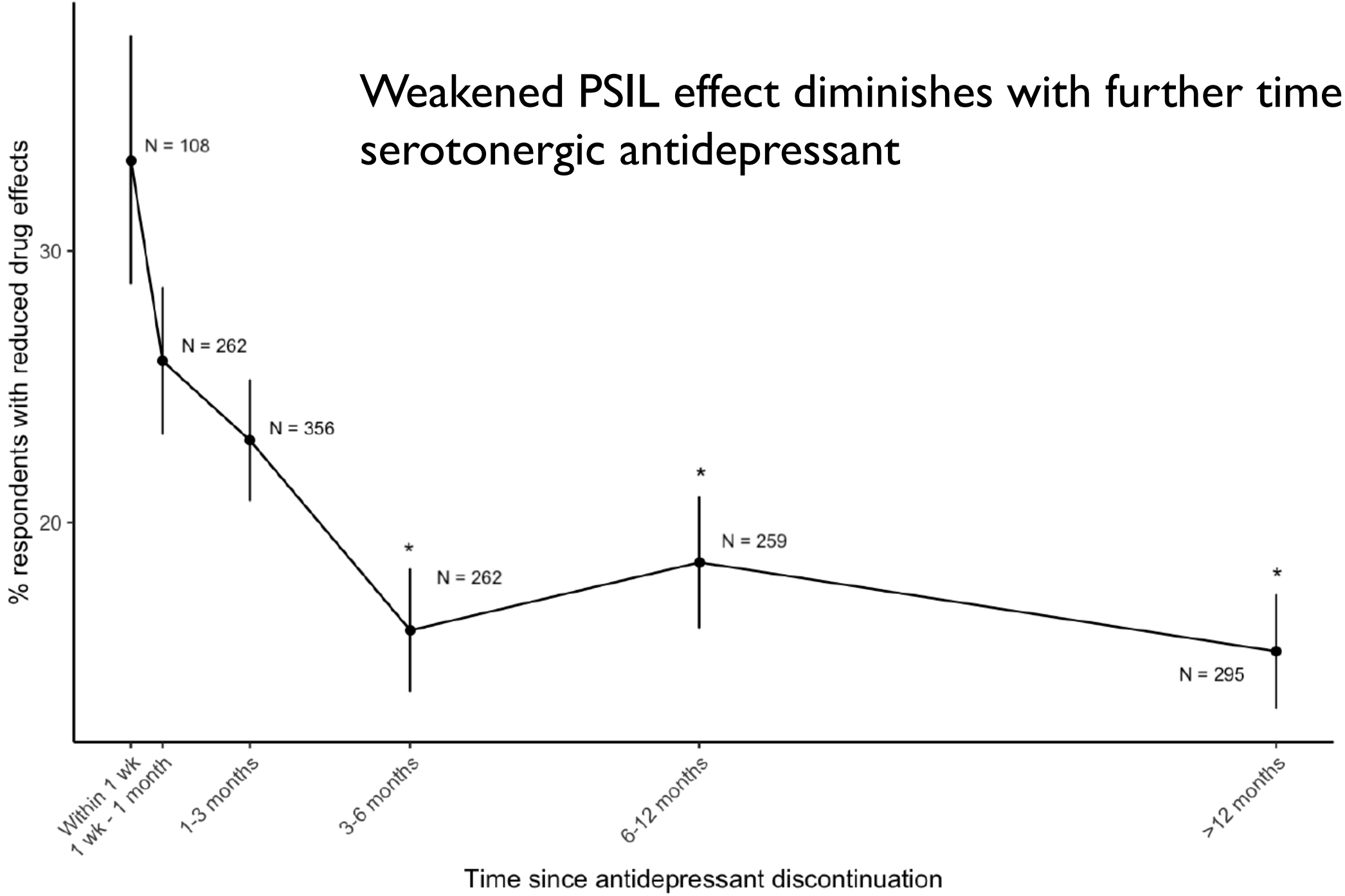
- Double-blind, pretreatment with escitalopram vs placebo, followed by psilocybin 25mg
  - Escitalopram 10mg x7 days -> 20mg x7 days

Becker et al., 2021

- Minimal decrement in psilocybin effects
- No indication of adverse events


Probability of weaker psilocybin effect with concurrent antidepressant
(n = 595)
Probability weaker effect
0.6
0.5
0.4
0.3
0.2
SNRI
SSRI
Bupropion
Probability of weaker effect with 95% Confidence Intervals

Weakened PSIL effect diminishes with further time off a serotonergic antidepressant



Serotonergic antidepressants

- Chronic serotonergic antidepressants probably weaken psychedelic effects
- This effect persists for weeks to months
- Yet many people do not report weakened effects

Serotonin syndrome

- Better called serotonin toxicity
- Vanishingly rare even in massive overdoses of LSD or psilocybin

- DMT is regularly administered with MAOIs without serotonin toxicity

Bipolar disorder

- Generally excluded from psychedelic trials due to risk of provoking mania

Bipolar disorder

- Pretty much every effective antidepressant can cause mania, mixed states or mood cycling
  - Antidepressants (Patel et al., 2015; Goldberg & Truman, 2003; Wehr et al., 1987)
  - Bright light therapy (Sit et al., 2007)
  - Acute sleep deprivation (Colombo et al., 1999; Wehr et al., 1982)
  - ECT (Lee et al., 2014)
  - Low dose atypical antipsychotics (Keating et al., 2005; Traber et al., 2007; Donohue, 2010)

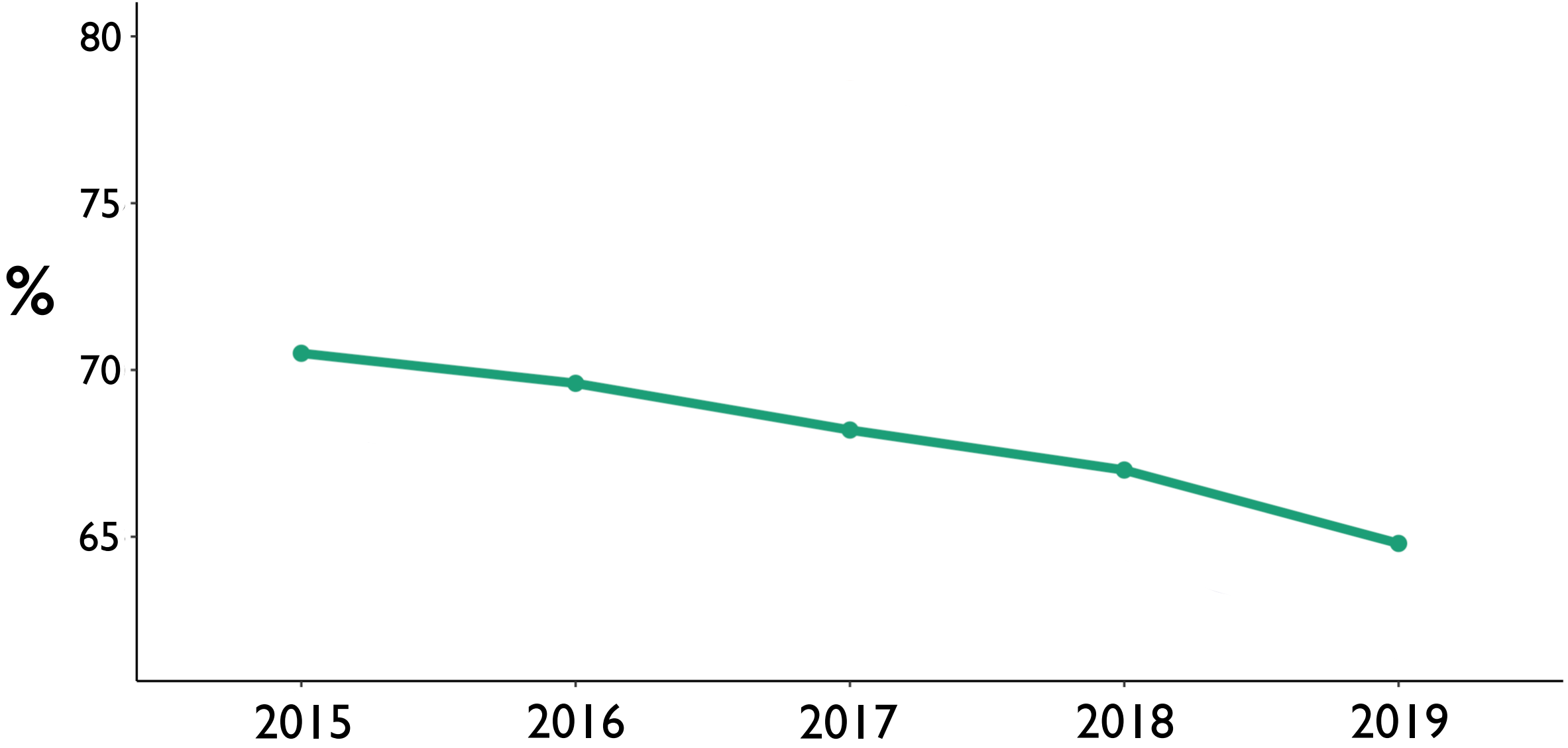
Bipolar disorder

- Majority of illness is spent in depressed episode
- Bipolar depression is difficult to treat

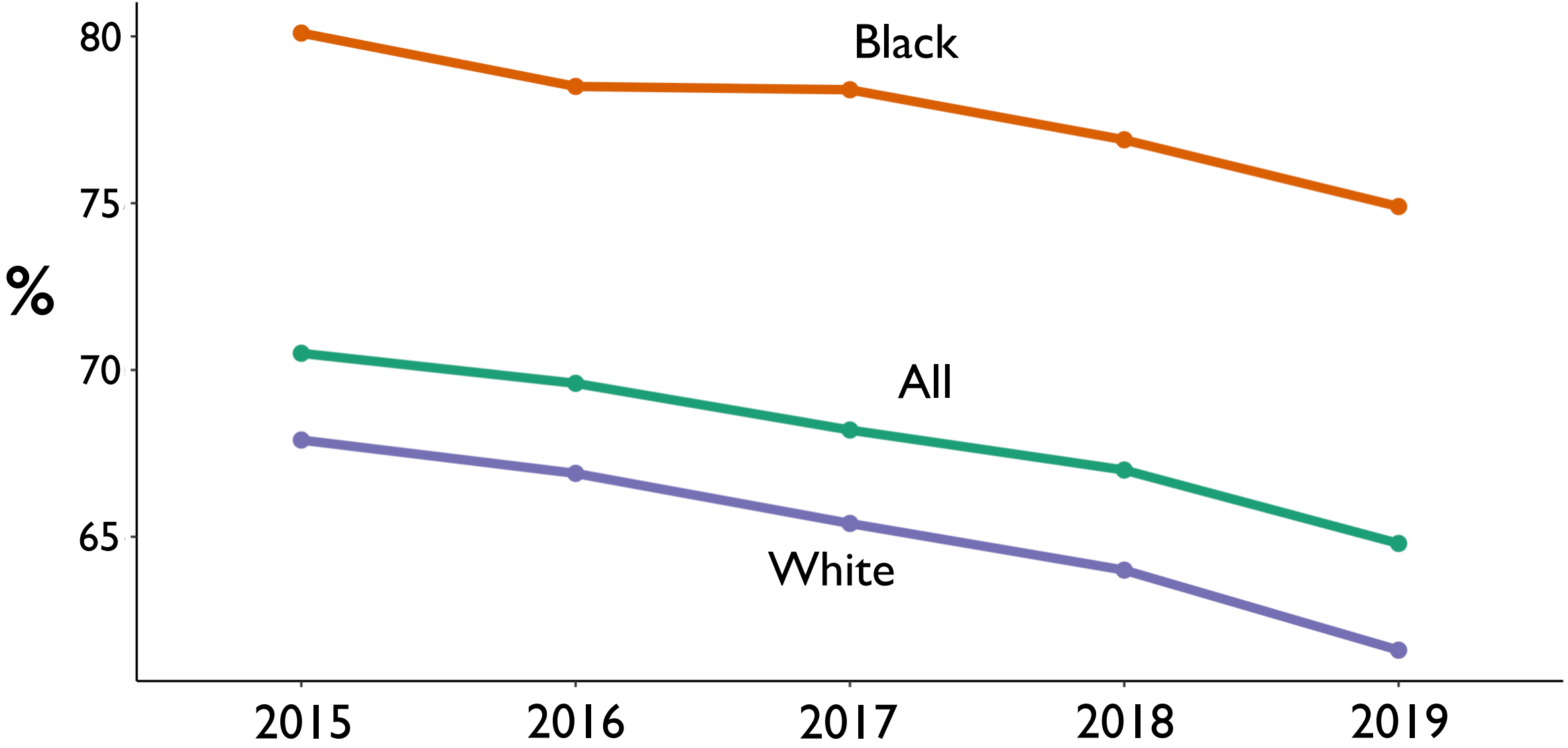
Populations

Ever used	All	White	Native American	Black
Psilocybin mushrooms	9%	12%	10%	1%
LSD	10%	13%	17%	2%

Perception of Great Risk of trying LSD once or twice



Perception of Great Risk of trying LSD once or twice

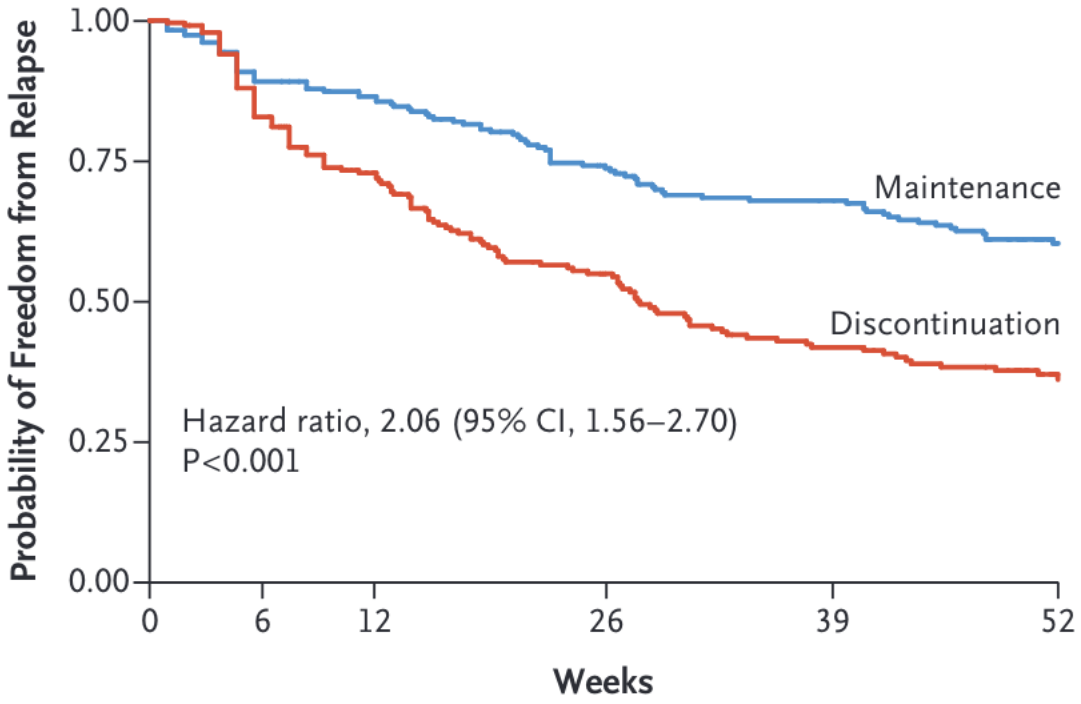


Future studies

- Bipolar disorder
- Postpartum depression
- Depressed inpatients
- Comparative efficacy vs ECT
- Comorbidity studies
- Shorter acting psychedelics
- Minimal psychotherapy
- Group dosing
- Antidepressant discontinuation

Antidepressant discontinuation

- ANTLER (Lewis et al., 2021): 478 pts:
  - maintained on antidepressant for ≥ 2 years
  - hx 2 depressive episodes
  - feel good enough to stop
- Randomized to continue or stop drug (placebo)



Legal initiatives

- Decriminalization initiatives
- Legalization for supported use
- Religious use

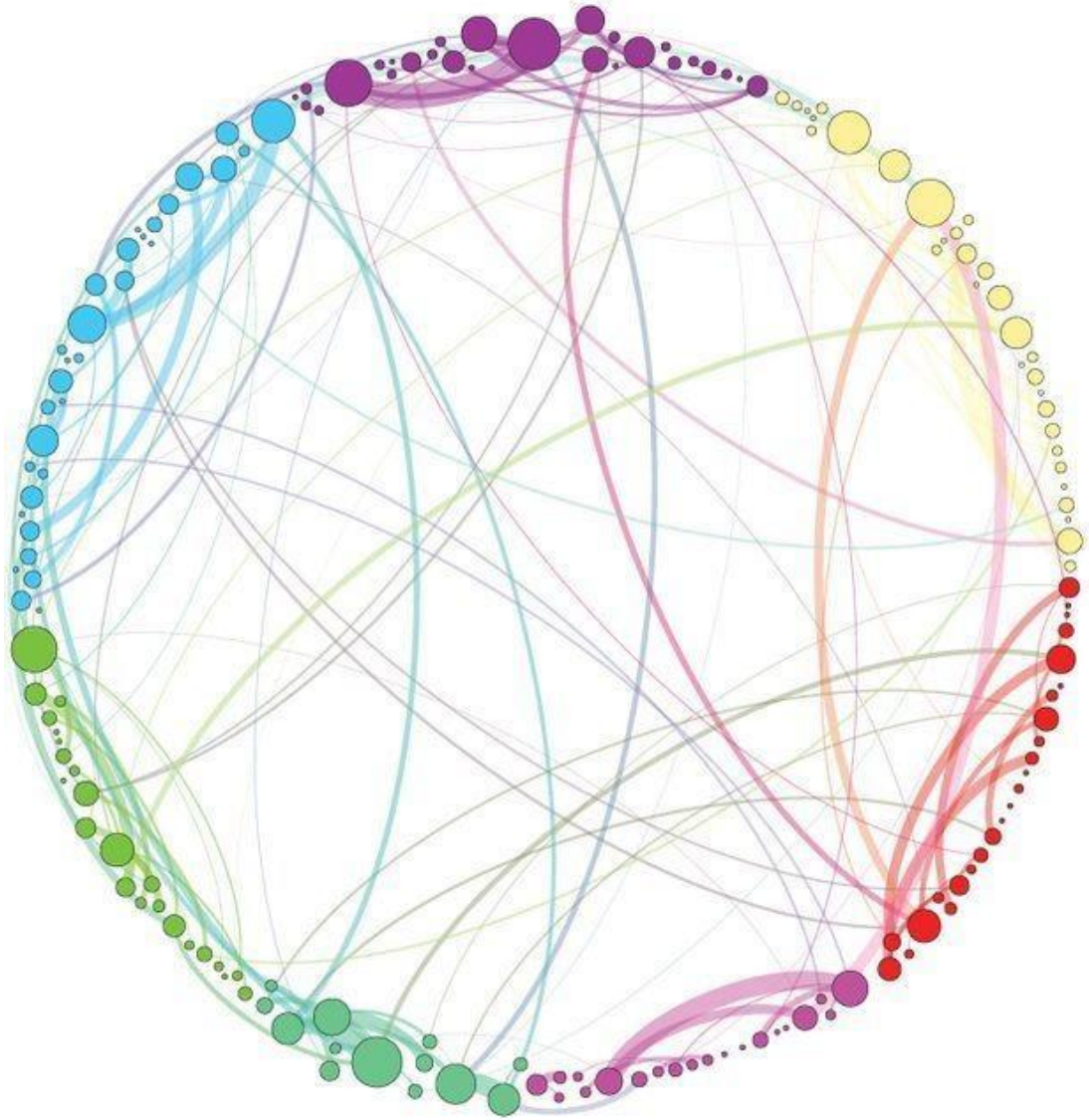
Thank you!

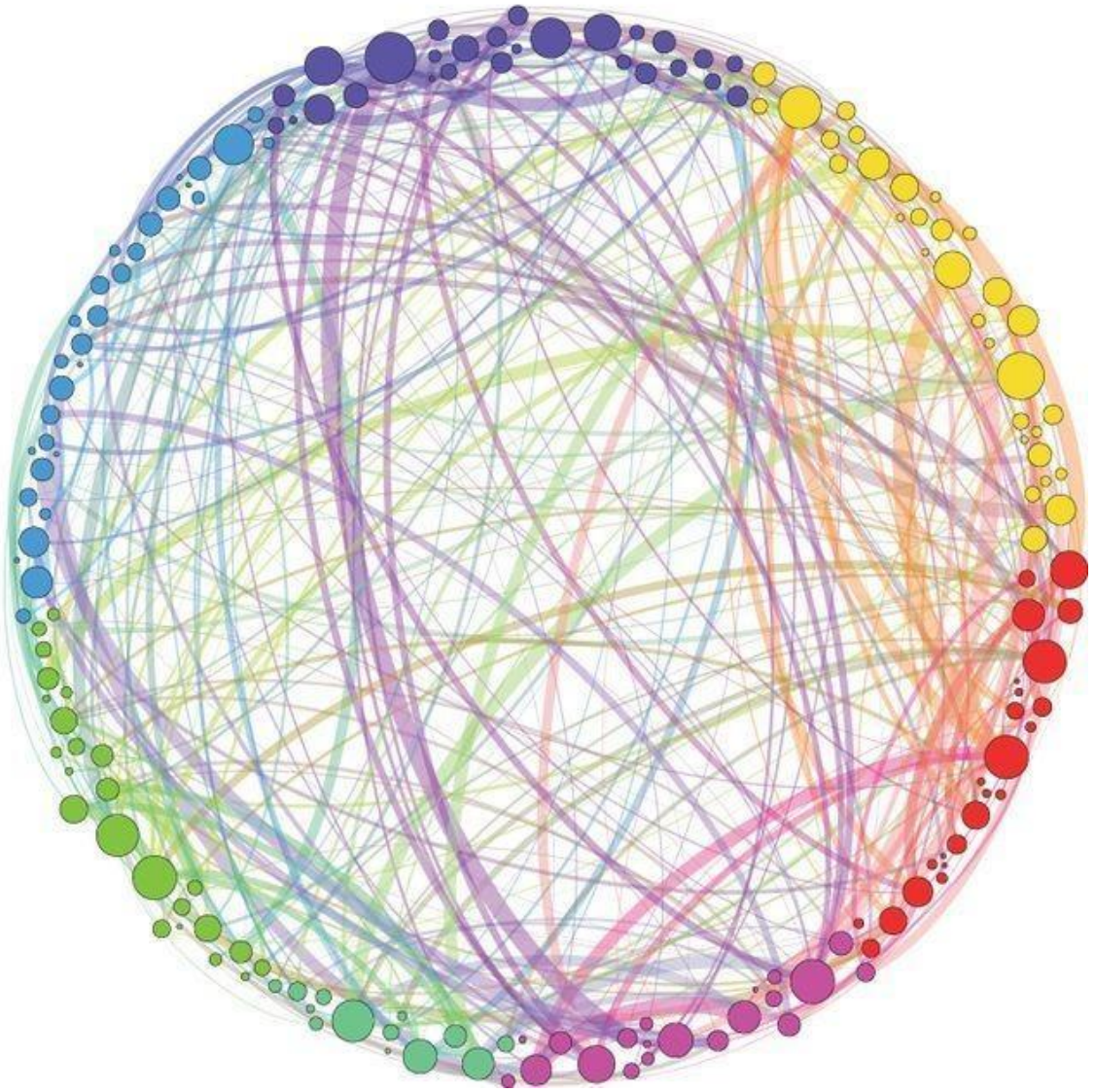
CPCR team members:

- Roland Griffiths, Ph.D.
- Fred Barrett, Ph.D.
- Albert Garcia-Romeu, Ph.D.
- Alan Davis, Ph.D.
- Mary Cosimano, M.S.W.
- William Richards, Ph.D.
- Natalie Gukasyan M.D.
- Manoj Doss, Ph.D.
- David Yaden, Ph.D.
- Ceyda Sayalı, Ph.D.
- Nate Sepeda
- Taylor Washington
- Sam Hilbert
- Sydney White
- Ian Geithner

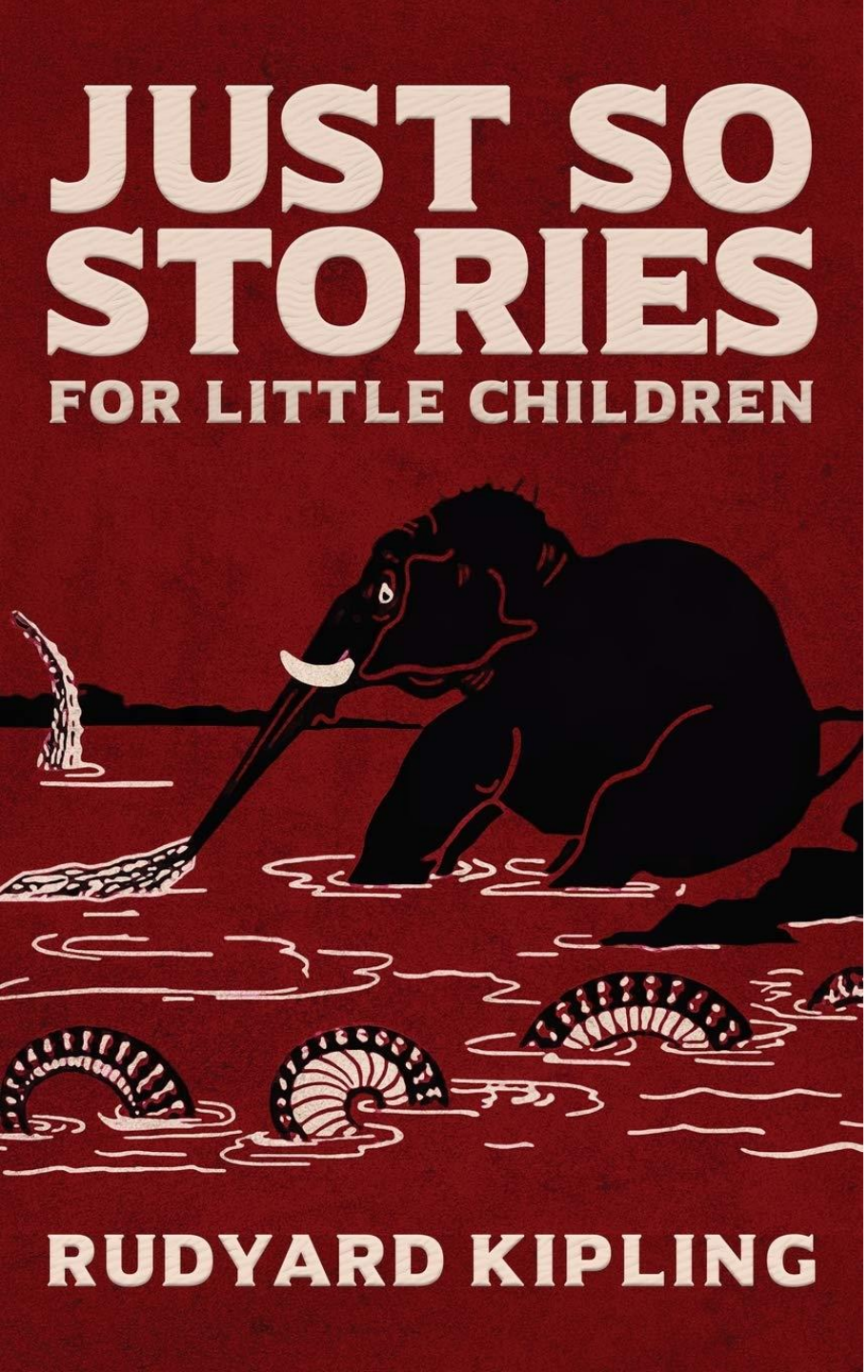
Placebo

Psilocybin





Petri et al., 2014



The Default-Mode Network Example

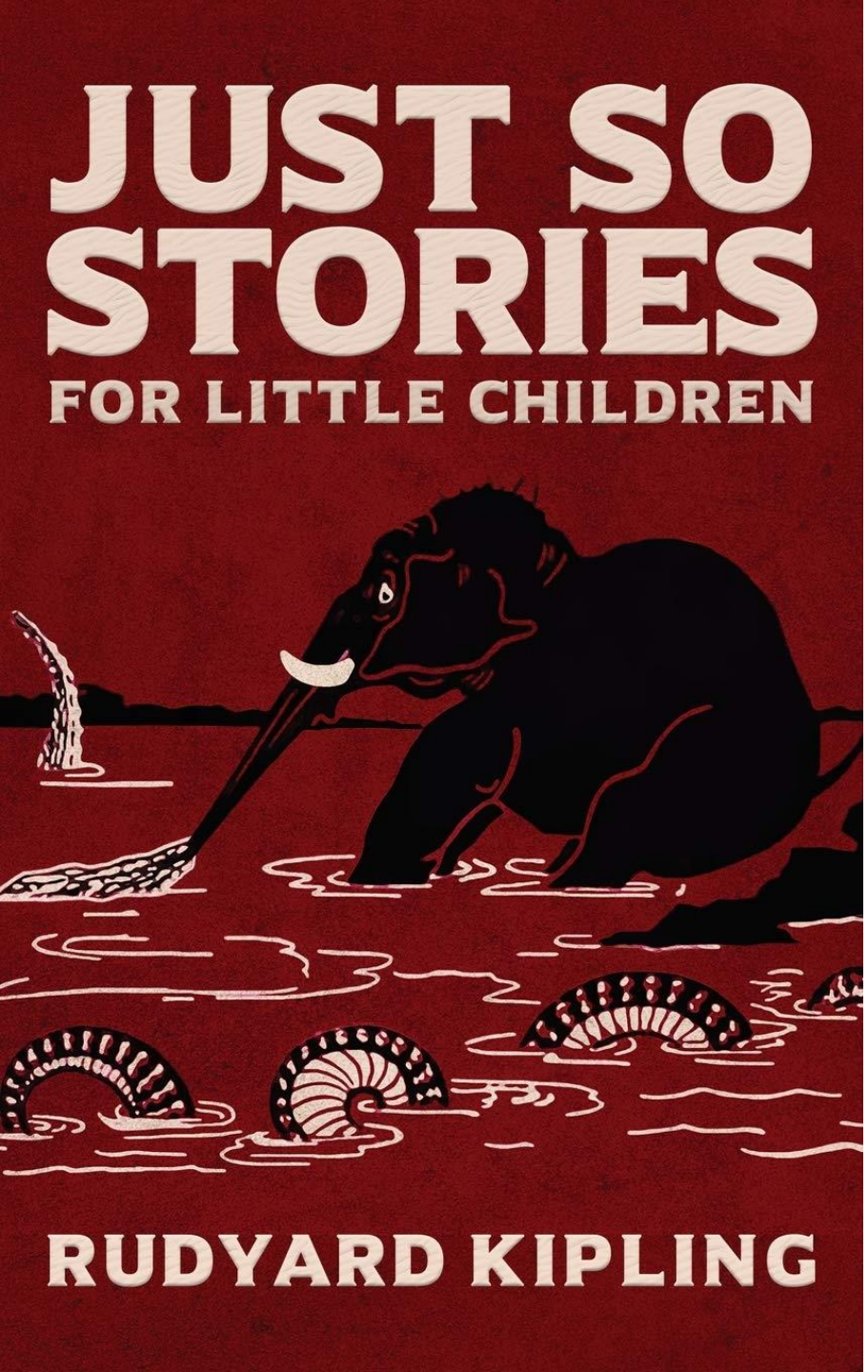
HelloMD

Why Interrupting the Default Mode Network with Psychedelics is Good for Mental Health

pamela January 14, 2020

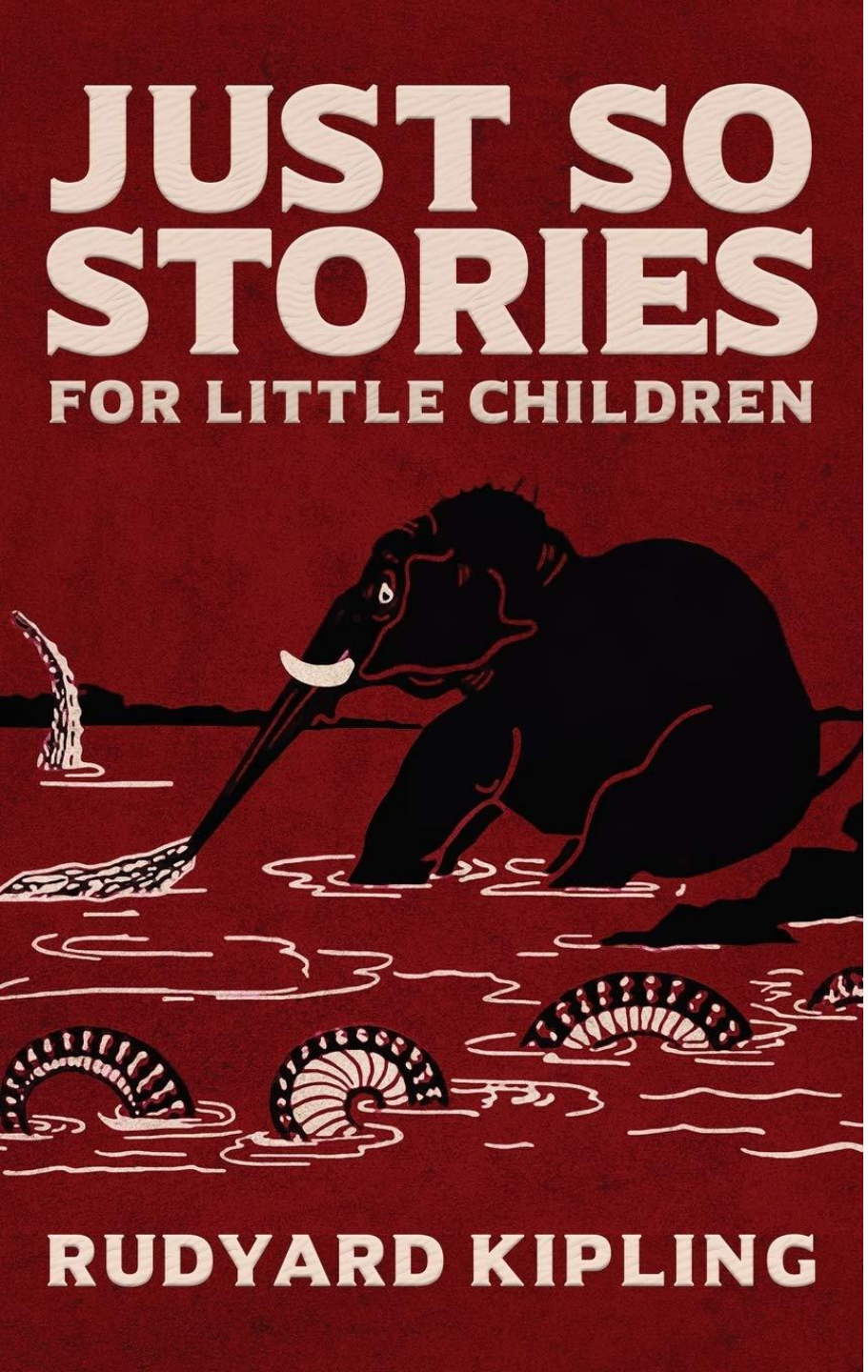
How To Tame the "Default Mode" of Your Wild Mind

Liberate yourself from repetitive, unhelpful thought patterns in 5 steps



The Default-Mode Network Example

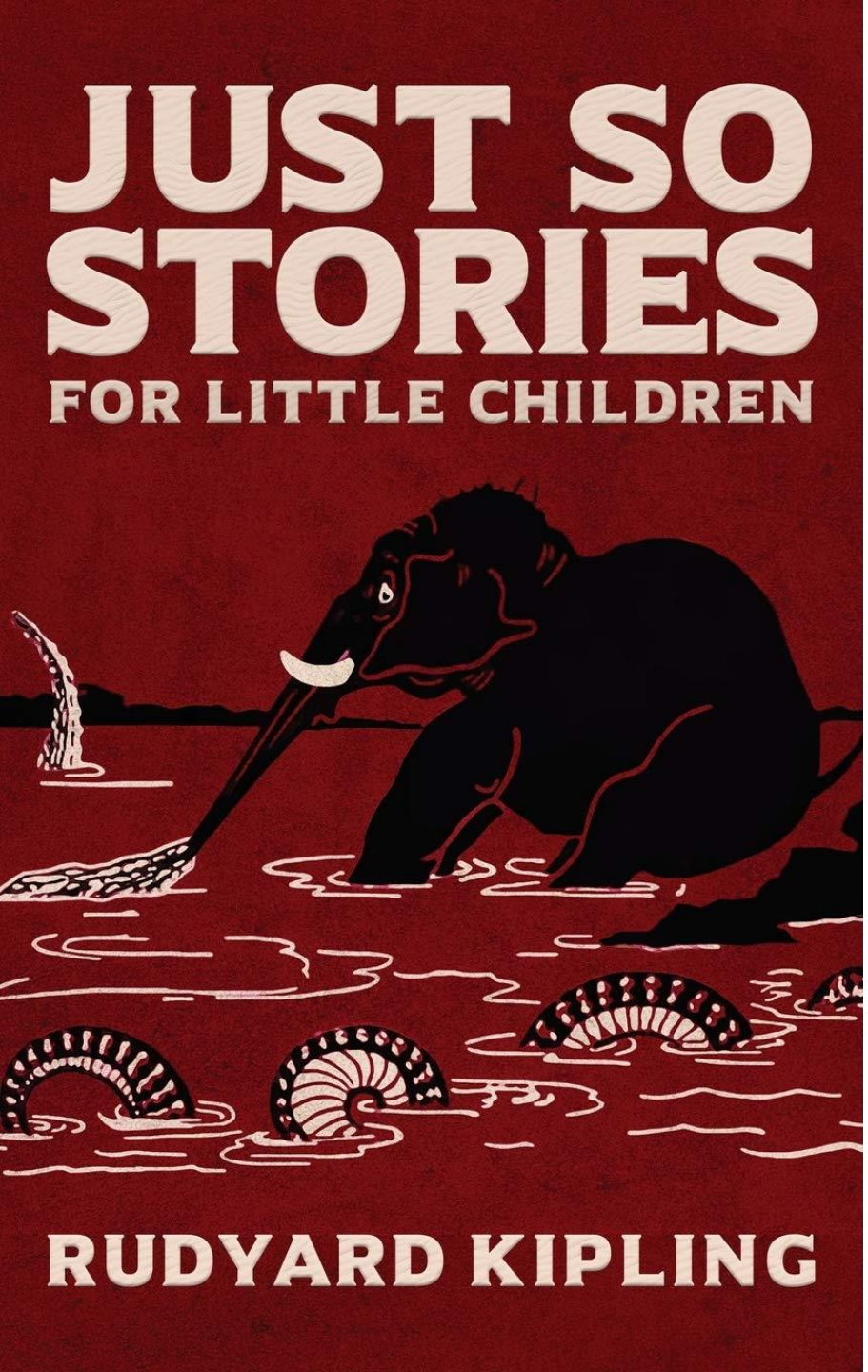
- DMN assoc w/ self-processing
- Psychedelics reduce DMN activity
- Psychedelics cause “ego dissolution”



The Default-Mode Network Example

- DMN assoc w/ self-processing
- Psychedelics reduce DMN activity
- Psychedelics cause “ego dissolution”

- dMn IS tHE egO
- dmn reDUctIOn IS The meChanIsM OF pSYcHEDELIc ego dIsSOLUTION



The Default-Mode Network Example

- However:
  - DMN decoherence rarely the strongest effect
  - Doesn't always correlate well with relevant subjective measures
  - Seen with other drugs

Meta-Analysis of controlled trials of LSD for Alcoholism:
Across studies, LSD doubled the odds a patient would be alcohol free

Krebs T S , Johansen P J Psychopharmacol 2012;26:994-1002

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

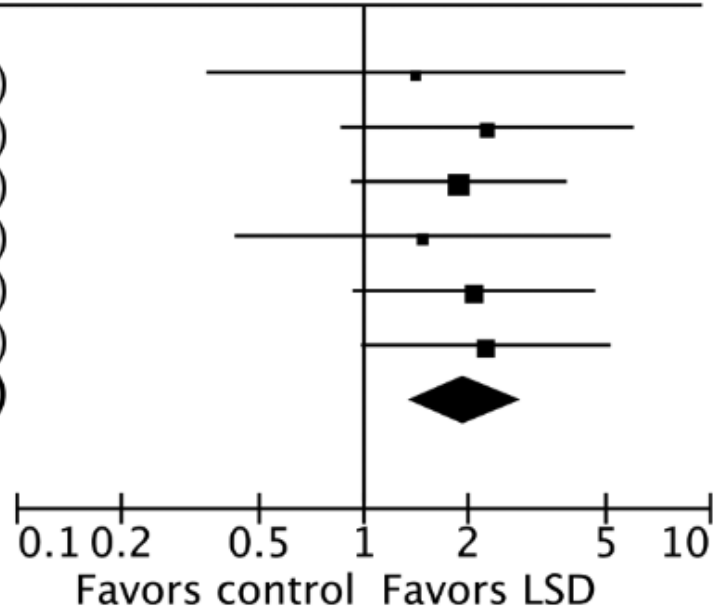


Figure 2. Improvement on alcohol misuse at the first available follow-up after LSD versus control treatments.

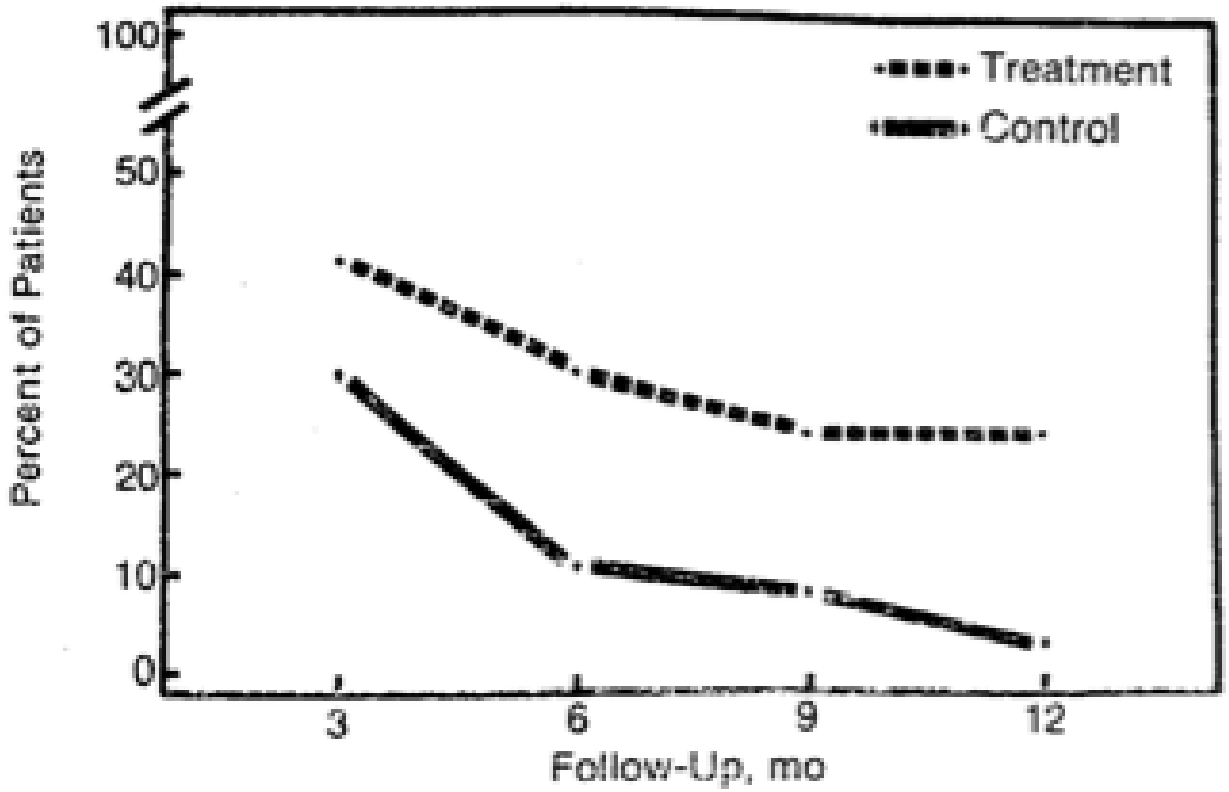
[a]Continuous outcome data.

Residential Psychedelic (LSD) Therapy for the Narcotic Addict

A Controlled Study

Charles Savage, MD, O. Lee McCabe, PhD, Baltimore

Fig 1.—Percent of patients maintaining total abstinence at 3-, 6-, 9-, and 12-month follow-up.



References

Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. JAMA, 315(4), 371–379.

Becker, A. M., Holze, F., Grandinetti, T., Klaiber, A., Toedtli, V. E., Kolaczynska, K. E., Duthaler, U., Varghese, N., Eckert, A., Grünblatt, E., & Liechti, M. E. (2022). Acute effects of psilocybin after escitalopram or placebo pretreatment in a randomized, double-blind, placebo-controlled, cross-over study in healthy subjects. Clinical Pharmacology & Therapeutics, 111(4), 886--895.

Bonson, K. R., & Murphy, D. L. (1995). Alterations in responses to LSD in humans associated with chronic administration of tricyclic antidepressants, monoamine oxidase inhibitors or lithium. Behavioural Brain Research, 73(1–2), 229–233.

Bonson, K. (1996). Chronic Administration of Serotonergic Antidepressants Attenuates the Subjective Effects of LSD in Humans. Neuropsychopharmacology, 14(6), 425–436.

Carhart-Harris, R. L., Kaelen, M., Whalley, M. G., Bolstridge, M., Feilding, A., & Nutt, D. J. (2015). LSD enhances suggestibility in healthy volunteers. Psychopharmacology, 232(4), 785–794.

Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D., & Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. New England Journal of Medicine, 384(15), 1402–1411.

Cohen, S. (1967). Psychotherapy with LSD: Pro and con. In H. A. Abramson (Ed.), The use of LSD in psychotherapy and alcoholism. The Bobbs-Merrill Company.

Colombo, C., Benedetti, F., Barbini, B., Campori, E., & Smeraldi, E. (1999). Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. Psychiatry research, 86(3), 267-270.

Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry.

Davis, A. K., Barrett, F. S., So, S., Gukasyan, N., Swift, T., & Griffiths, R. R. (2021). Development of the Psychological Insight Questionnaire among a sample of people who have consumed psilocybin or LSD. Journal of Psychopharmacology.

Donohue, A. (2010). First manic episode in a 55-year-old man after initiation of aripiprazole. Psychiatry (Edgmont), 7(4), 37.

Fiore, M. C., Smith, S. S., Jorenby, D. E., & Baker, T. B. (1994). The Effectiveness of the Nicotine Patch for Smoking Cessation: A Meta-analysis. JAMA, 271(24), 1940–1947.

Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., & Brenneisen, R. (2014). Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. Journal of Nervous and Mental Disease, 202(7), 513–520.

Goldberg, J. F., & Truman, C. J. (2003). Antidepressant-induced mania: an overview of current controversies. Bipolar disorders, 5(6), 407-420.

Goodwin, G. M., Aaronson, S. T., Alvarez, O., Arden, P. C., Baker, A., Bennett, J. C., Bird, C., Blom, R. E., Brennan, C., Brusch, D., Burke, L., Campbell-Coker, K., Carhart-Harris, R., Cattell, J., Daniel, A., DeBattista, C., Dunlop, B. W., Eisen, K., Feifel, D., … Rademaker, M. C. (2022). Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. N Engl j Med, 12.

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. Journal of Psychopharmacology, 30(12), 1181–1197.

Grob, C., Danforth, A., Chopra, G., Hagerty, M., Mckay, C., Halberstadt, A., & Greer, G. (2011). Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Archives of General Psychiatry, 68, 71–78.

Grof, S., & Dytrych, Z. (1965). Blocking of LSD reaction by premedication with Niamid. Activitas Nervosa Superior, 7(3), 306.

Grof, S., Goodman, L. E., Richards, W. A., & Kurland, A. A. (1973). LSD-Assisted Psychotherapy in Patients with Terminal Cancer. International Pharmacopsychiatry, 8(3), 129–144.

Gukasyan, N., Davis, A. K., Barrett, F. S., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., & Griffiths, R. R. (2022). Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. Journal of Psychopharmacology, 36(2), 151–158.

Jones, B. D., Razza, L. B., Weissman, C. R., Karbi, J., Vine, T., Mulsant, L. S., ... & Daskalakis, Z. J. (2021). Magnitude of the placebo response across treatment modalities used for treatment-resistant depression in adults: a systematic review and meta-analysis. JAMA Network Open, 4(9), e2125531-e2125531.

Kast, E. C., & Collins, V. J. (1964). Study of Lysergic Acid Diethylamide As an Analgesic Agent. Anesthesia and Analgesia, 43(February), 285–291.

Kast, E. (1966). LSD and the Dying Patient. Chicago Medical School Quarterly, 26(2), 80–87.

Kast, E. (1967). Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide. The Psychiatric Quarterly, 41(4), 646–657.

Keating, A. M., Aoun, S. L., & Dean, C. E. (2005). Ziprasidone-associated mania: a review and report of 2 additional cases. Clinical neuropharmacology, 28(2), 83-86

Kwan, A. C., Olson, D. E., Preller, K. H., & Roth, B. L. (2022). The neural basis of psychedelic action. Nature Neuroscience, 25(11), 1407–1419.

Lee, J., Arcand, L., Narang, P., & Lippmann, S. (2014). ECT-induced mania. Innovations in Clinical Neuroscience, 11(11-12), 27.

Lewis, G., Marston, L., Duffy, L., Freemantle, N., Gilbody, S., Hunter, R., Kendrick, T., Kessler, D., Mangin, D., King, M., Lanham, P., Moore, M., Nazareth, I., Wiles, N., Bacon, F., Bird, M., Brabyn, S., Burns, A., Clarke, C. S., … Lewis, G. (2021). Maintenance or Discontinuation of Antidepressants in Primary Care. New England Journal of Medicine, 385(14), 1257–1267.

References

Luborsky, L., Rosenthal, R., Diguer, L., Andrusyna, T. P., Berman, J. S., Levitt, J. T., Seligman, D. A., & Krause, E. D. (2002). The Dodo bird verdict is alive and well—Mostly. Clinical Psychology: Science and Practice, 9(1), 2–12..

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Soltanzadeh Zarandi, S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics promote structural and functional neural plasticity. Cell Reports, 23(11), 3170–3182.

Madsen, M. K., Fisher, P. M. D., Stenbæk, D. S., Kristiansen, S., Burmester, D., Lehel, S., Páleníček, T., Kuchař, M., Svarer, C., Ozenne, B., & Knudsen, G. M. (2020). A single psilocybin dose is associated with long-term increased mindfulness, preceded by a proportional change in neocortical 5-HT2A receptor binding. European Neuropsychopharmacology, 33, 71–80.

Middlefell, R. (1967). The effects of LSD on body sway suggestibility in a group of hospital patients. British Journal of Psychiatry, 113(496), 277–280.

Nayak, S. M., & Johnson, M. W. (2020). Psychedelics and psychotherapy. Pharmacopsychiatry.

Nayak, S. M., Bari, B. A., Yaden, D. B., Spriggs, M. J., Rosas, F. E., Peill, J. M., Giribaldi, B., Erritzoe, D., Nutt, D. J., & Carhart-Harris, R. (2022). A Bayesian Reanalysis of a Trial of Psilocybin Versus Escitalopram for Depression. Psychedelic Medicine, psymed.2022.0002.

Olson, D. E. (2020). The subjective effects of psychedelics may not be necessary for their enduring therapeutic effects. ACS Pharmacology & Translational Science, 4(2), 563-567.

Pahnke, W., Kurland, A., Goodman, L., & Richards, W. (1969). LSD-Assisted Psychotherapy with Terminal Cancer Patients. Current Psychiatric Therapies, 9, 144–152.

Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., Mota-Rolim, S. A., Osório, F. L., Sanches, R., dos Santos, R. G., Tófoli, L. F., de Oliveira Silveira, G., Yonamine, M., Riba, J., Santos, F. R., Silva-Junior, A. A., Alchieri, J. C., Galvão-Coelho, N. L.,

Lobão-Soares, B., … Araújo, D. B. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: A randomized placebo-controlled trial. Psychological Medicine, 49(4), 655–663.

Paszek, A. (2017). A Meta-Analysis of the Efficacy of Bupropion Sustained-Release for Smoking Cessation in Heavy Smokers. Impulse, 11.

Patel, R., Reiss, P., Shetty, H., Broadbent, M., Stewart, R., McGuire, P., & Taylor, M. (2015). Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. BMJ open, 5(12), e008341.

Richards, W., Rhead, J., DiLeo, Francesco, Yensen, R., & Kurland, A. (1977). The Peak Experience Variable in DPT-Assisted Psychotherapy with Cancer Patients. Journal of Psychedelic Drugs, 9, 1–10.

Rief, W., Nestoriuc, Y., Weiss, S., Welzel, E., Barsky, A. J., & Hofmann, S. G. (2009). Meta-analysis of the placebo response in antidepressant trials. Journal of affective disorders, 118(1-3), 1-8.

Rosenzweig, S. (1936). Some implicit common factors in diverse methods of psychotherapy. American Journal of Orthopsychiatry, 6(3), 412–415.

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. Journal of Psychopharmacology, 30(12), 1165–1180.

Rotz, R. von, Schindowski, E. M., Jungwirth, J., Schuldt, A., Rieser, N. M., Zahoranszky, K., Seifritz, E., Nowak, A., Nowak, P., Jäncke, L., Preller, K. H., & Vollenweider, F. X. (2023). Single-dose psilocybin-assisted therapy in major depressive disorder: A placebo-controlled, double-blind, randomised clinical trial. EClinicalMedicine, 56.

Shao, L.-X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., & Kwan, A. C. (2021). Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. Neuron, 109(16), 2535-2544.e4.

Sit, D. K., McGowan, J., Wiltrout, C., Diler, R. S., Dills, J., Luther, J., ... & Wisner, K. L. (2018). Adjunctive bright light therapy for bipolar depression: a randomized double-blind placebo-controlled trial. American Journal of Psychiatry, 175(2), 131-139.

Soler, J., Elices, M., Franquesa, A., Barker, S., Friedlander, P., Feilding, A., Pascual, J. C., & Riba, J. (2016). Exploring the therapeutic potential of Ayahuasca: Acute intake increases mindfulness-related capacities. Psychopharmacology, 233(5), 823–829.

Traber, R., Schneiter, R., & Modestin, J. (2007). A case of aripiprazole-induced mania. Pharmacopsychiatry, 40(01), 37-38.

Wallace, A. F. C. (1959). Cultural Determinants of Response to Hallucinatory Experience. Archives of General Psychiatry, 1(1), 58.

Wehr, T. A., & Sack, D. A. (1987). Sleep disruption: A treatment for depression and a cause of mania. Psychiatric Annals, 17(10), 654-663.

Wolff, M., Evens, R., Mertens, L. J., Koslowski, M., Betzler, F., Gründer, G., & Jungaberle, H. (2020). Learning to Let Go: A Cognitive-Behavioral Model of How Psychedelic Therapy Promotes Acceptance. Frontiers in Psychiatry, 11, 5.

Yaden, D. B., & Griffiths, R. R. (2021). The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. ACS Pharmacology and Translational Science, 4(2), 568–572.