

Psychedelic Medicine

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Disclosures

If you have disclosures, state:

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Cybin, Compass – personal stock, divested in 2026

Apex Labs – SAB

Tryp Therapeutics – research support

Why are psychedelics suddenly of interest?

- Rising rates of psychiatric diagnoses, psychotropic drug prescriptions
- Rampant rates of depression, anxiety, addictions, suicide
- Psychiatric drug development at a standstill after “heyday” of psychopharmacology of 1980s-1990s
- Psychedelics offer promise to radically change the mental healthcare system
- Media hype, massive investment, talk of “paradigm shift”
- How to ensure the safe, equitable, and most effective (re)entry of psychedelics?

What do psychedelics do?

Classical Psychedelics

- Change in consciousness
- Deeply felt personal meaning
- Ego dissolution
- Increased connectedness
- Enriched sensory/phenomenal experience
- Visual hallucinations

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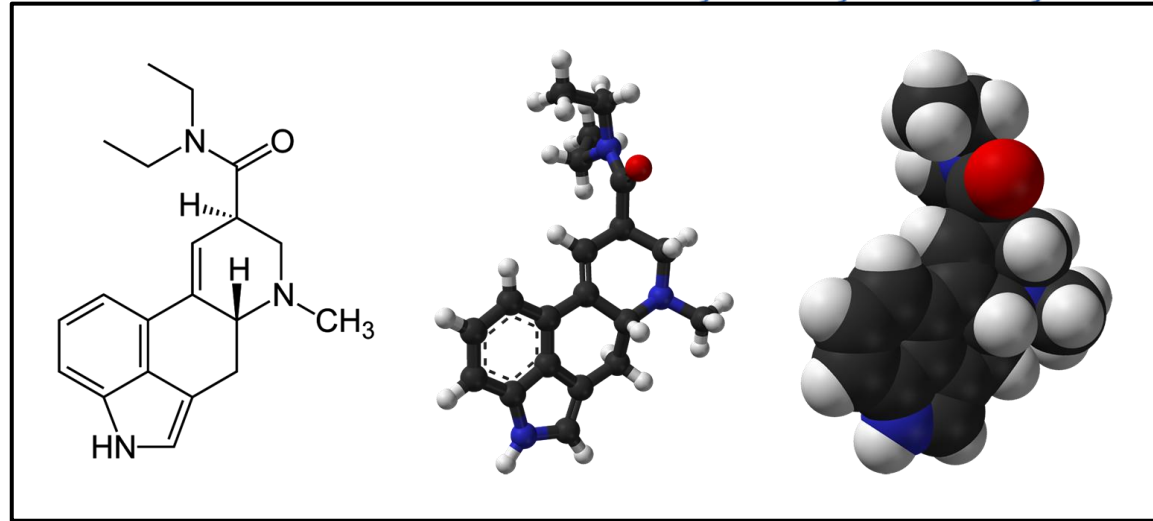
MDMA/empathogens

- Change in consciousness
- Increased trust, empathy
- Euphoria
- Social connectedness
- Sensory enhancement

Both: durable changes over time (?)

Tryptamines

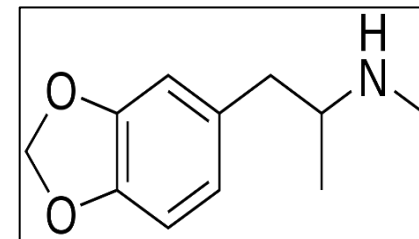
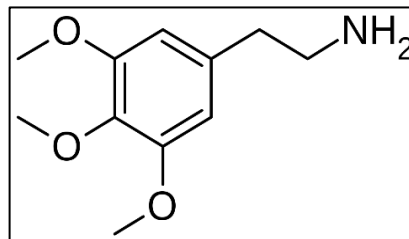
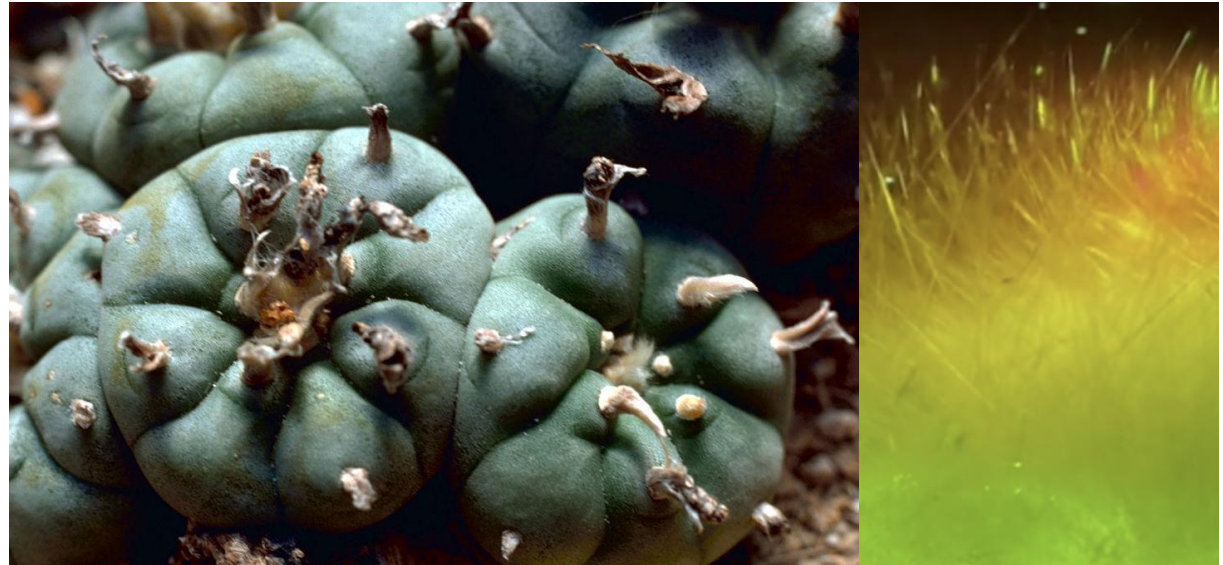
- All based on structural backbone of serotonin (5-hydroxytryptamine)
- Psilocybin (4-phosphoryloxy-DMT)
- *N,N*-DMT
- 5-MeO-DMT
- LSD (technically, an ergoline)



Phenethylamines

- Substituted phenethylamines include a wide array of drug classes
- Psychedelics include mescaline, MDMA
- Other than MDMA, less well-researched

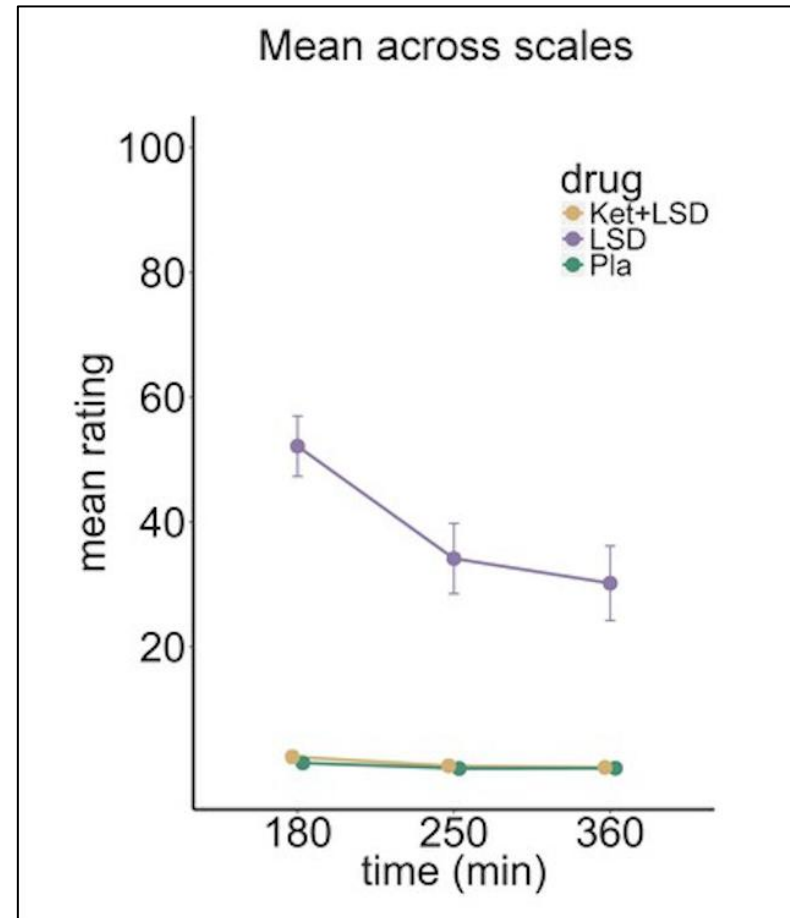
CNS stimulants, decongestants, antidepressants, anti-Parkinson agents, vasopressors, bronchodilators, and neurotransmitters epinephrine, norepinephrine and dopamine



Pharmacology

Classical Psychedelics

- Agonist or partial agonist activity at 5HT-2A receptor
- Ketanserin (2A antagonist) blocks effects of psilocybin, LSD
- Atypical antipsychotics more effective blockade/abortive than haloperidol

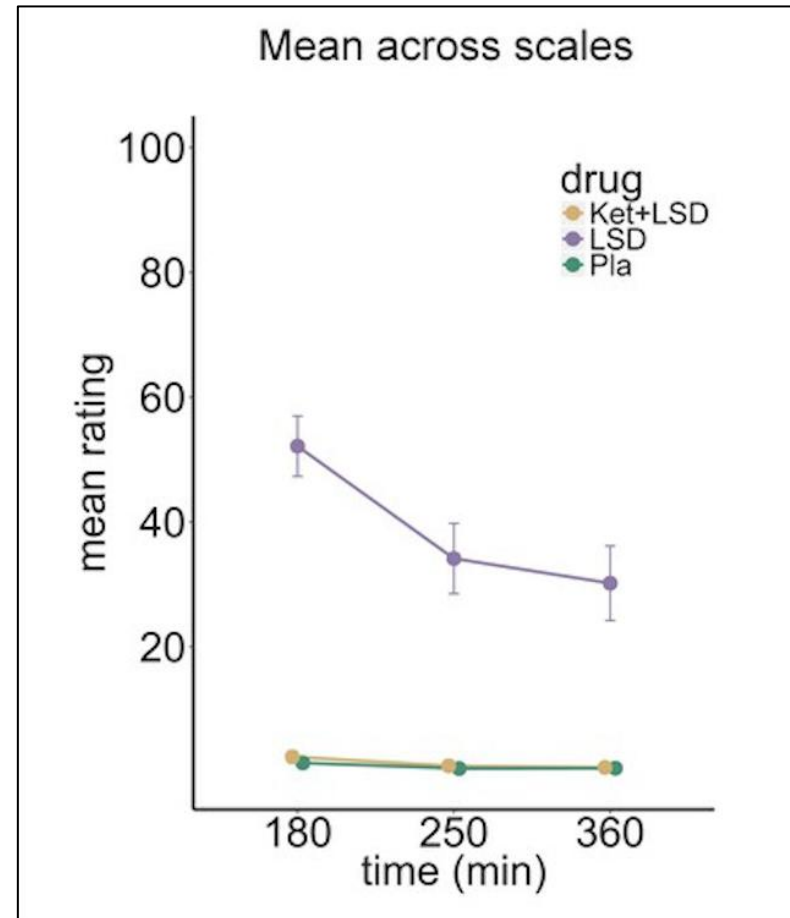


Liechti et al., *J Psychopharmacol*, 2000

Pharmacology

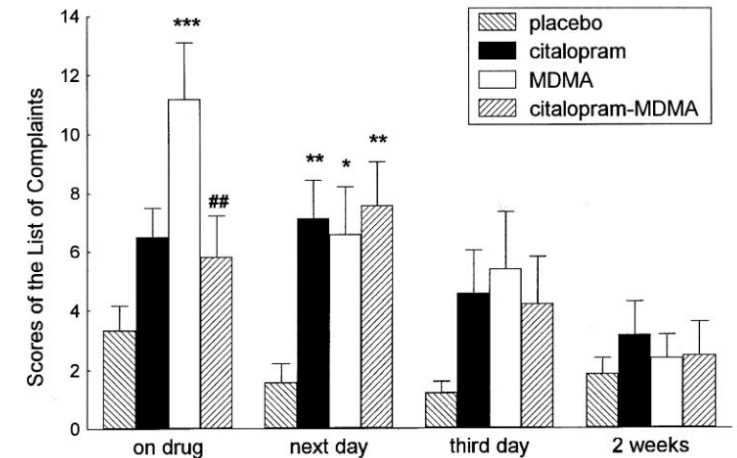
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Empathogens (MDMA)

- Monoamine releaser
- 5HT release (primary)
- DA and NE (secondary)
- SSRIs/SNRIs block (most) MDMA effects



Liechti et al., *J Psychopharmacol*, 2000

Physiologic and psychologic adverse effects

Classical psychedelics

Acute adverse effects

- Headache, fatigue, nausea common
- Mild sympathetic increase
- Psychiatric: transient anxiety, psychological discomfort, delusional thinking
- Safe in overdose

Chronic adverse effects

- 5HT_{2B} receptors and cardiac disease: theoretical – microdosing?

MDMA

Acute adverse effects

- Bruxism, hyperthermia, SIADH
- Nausea, appetite suppression
- Sympathomimetic >> classical psych's
- Psychiatric: anxiety
- Overdose possible

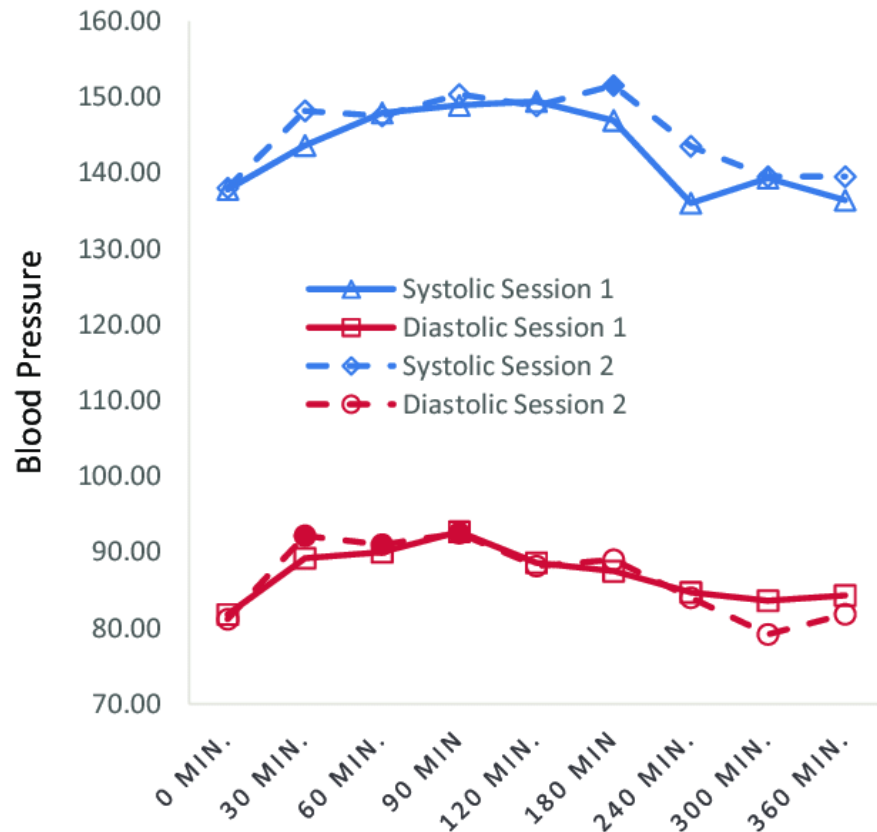
Chronic adverse effects

- ?Neurotoxicity – controversial, not proven
- Decreased 5HT-R density w heavy chronic use

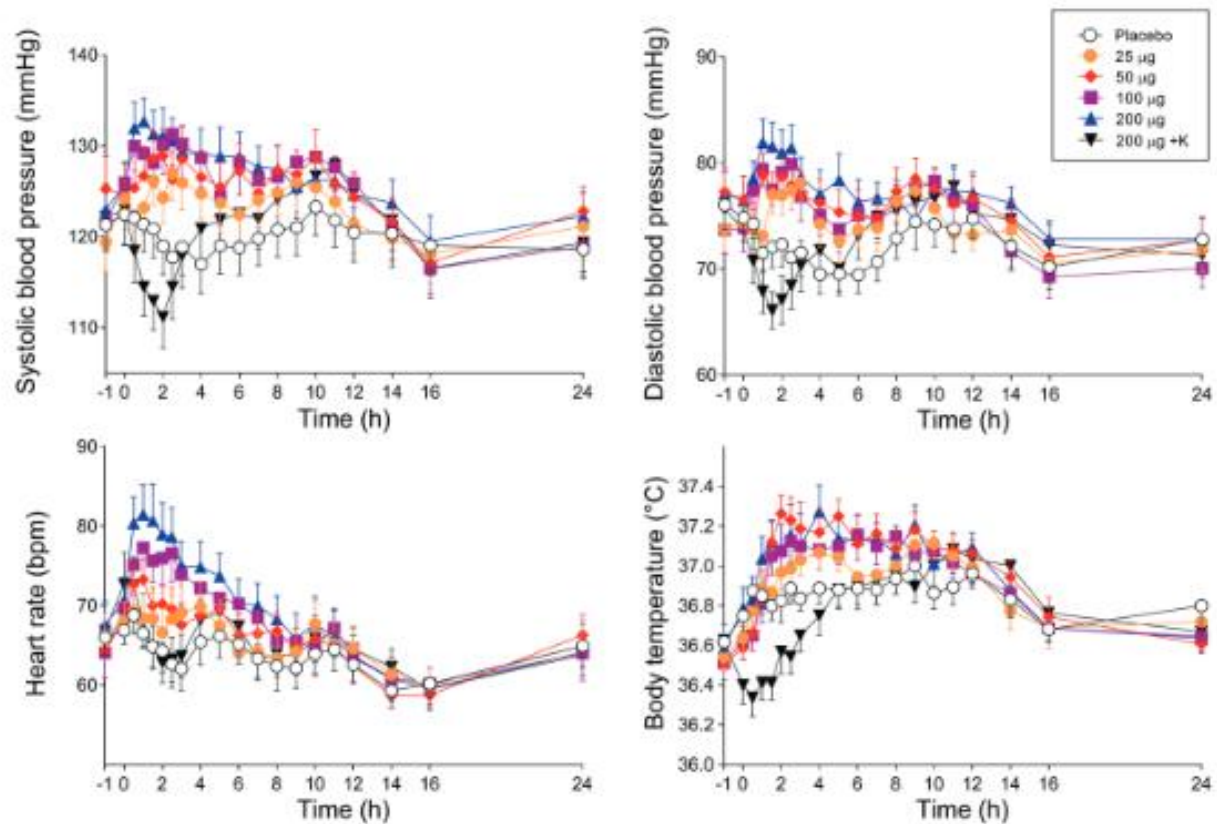
Passie CNS Neuroscience and Therapeutics 2008

Autonomic effects

LSD 📌



Psilocybin 📌



F Holze et al.

Bogenschutz *Psychopharmacology* 2015, Holze *Neuropsychopharmacology* 2021

Tachyphylaxis and addictive potential

- For classical psychedelics, tachyphylaxis occurs within 3-4 days of daily administration, lasts days to weeks
- Cross-tolerance between different agents
- Correlates with downregulation of 5HT-2A receptors in animal models
- Biological (and psychological) dependence on psychedelics is not observed
- For MDMA, abuse/addiction potential is higher, likely due to dopaminergic effects

Psychological Safety

- In clinical settings, primary intervention is interpersonal support (pharm rescue usually not needed)
- Risk of psychosis/HPPD?
 - Prolonged psychoses and/or HPPD seen in 1960s clinical applications of LSD
 - Not seen (?yet) in modern trials
 - Possibly specific to LSD (LSD is D2 partial agonist; psilocybin is not)
 - Recent population-level data have not found association between psychedelic use and emergence of psychosis
 - Emergence of mania possibly greater risk than psychosis
 - Screening: no personal or primary FHx of psychotic episode or BPAD1

Simonsson et al, *JAMA Psychiatry* 2024; Honk et al, *J Affect Disord* 2024;
Halpern et al, *Curr Top Behav Neurosci* 2018

A brief history of psychedelics in psychiatry

Psycholytic psychotherapy

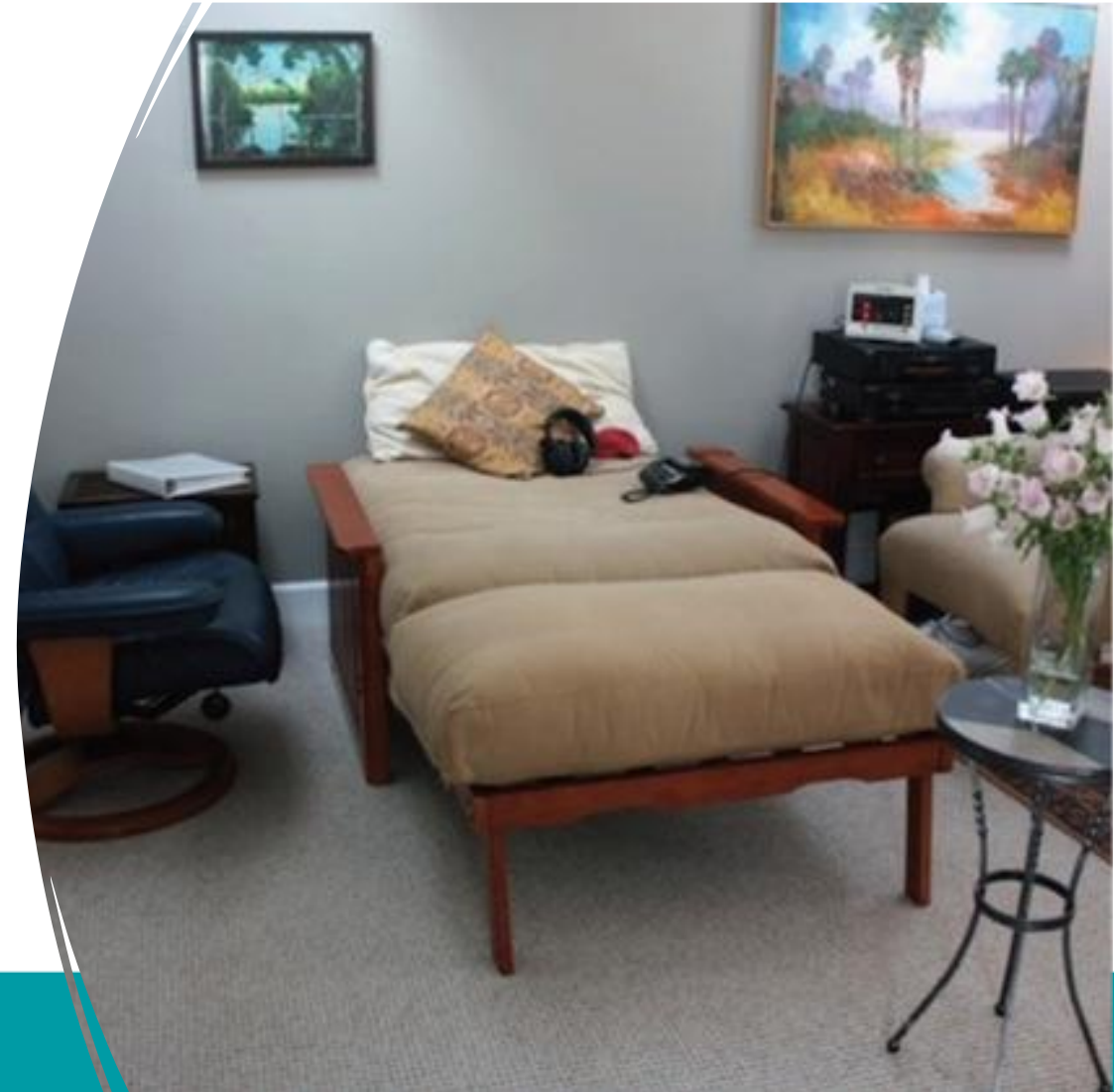
- Psychoanalytic context: amplification of psychodynamic processes, reduction of ego defenses
- Psychedelic as an adjunct to therapy, not a cure in and of itself
- Many, frequent, moderate dose psychedelic sessions within longer, traditional dynamic therapy paradigm
- Dominant model in Europe during initial wave of research

Psychedelic psychotherapy

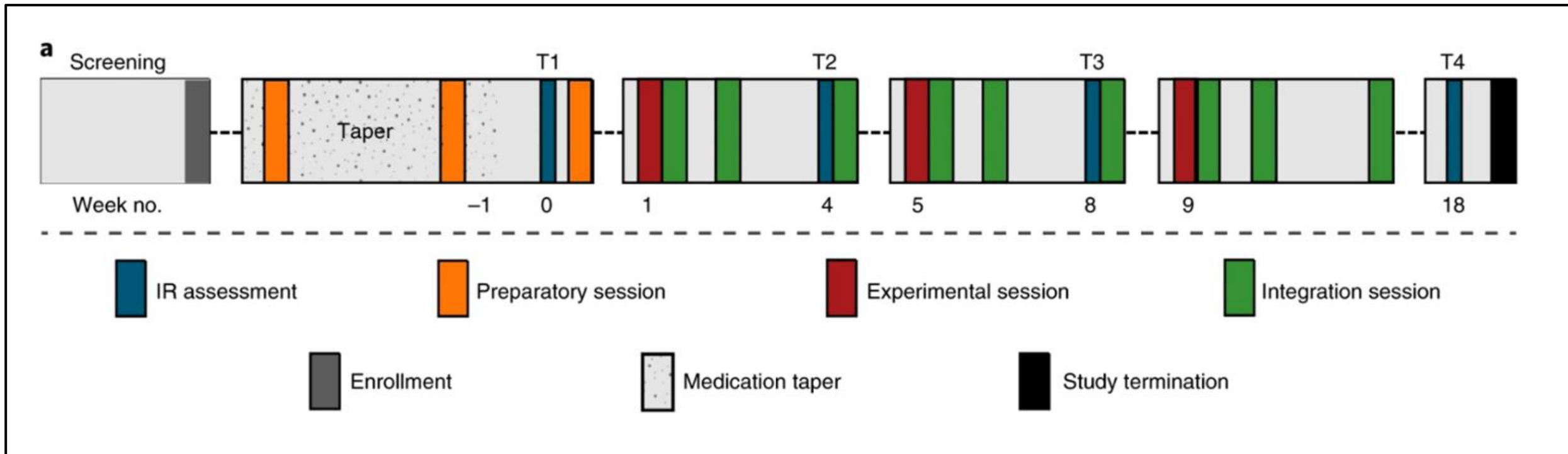
Inadvertent observations of spirituality of experiences reported by research patients
Concurrent with refocus within American psychology on transcendent states (Maslow)
Growing awareness of Indigenous practices and ritualized use of psychedelics
Intentional use of suggestibility and ritual to achieve a **mystical experience**

Psychedelic-assisted Psychotherapy

- Preparation and integration
- Therapist is present, but patients encouraged to have an internal experience
- Approach psychedelic content with openness and curiosity
- Quiet room, calming décor, instrumental music, eye shades, non-directive therapy



PAT has a LOT of therapy



No therapy?

Preliminary Communication

Single Treatment With MM120 (Lysergide) in Generalized Anxiety Disorder

A Randomized Clinical Trial

Reid Robison, MD¹; Robert Barrow, MS²; Craig Conant, BA² ; et al

No therapy?

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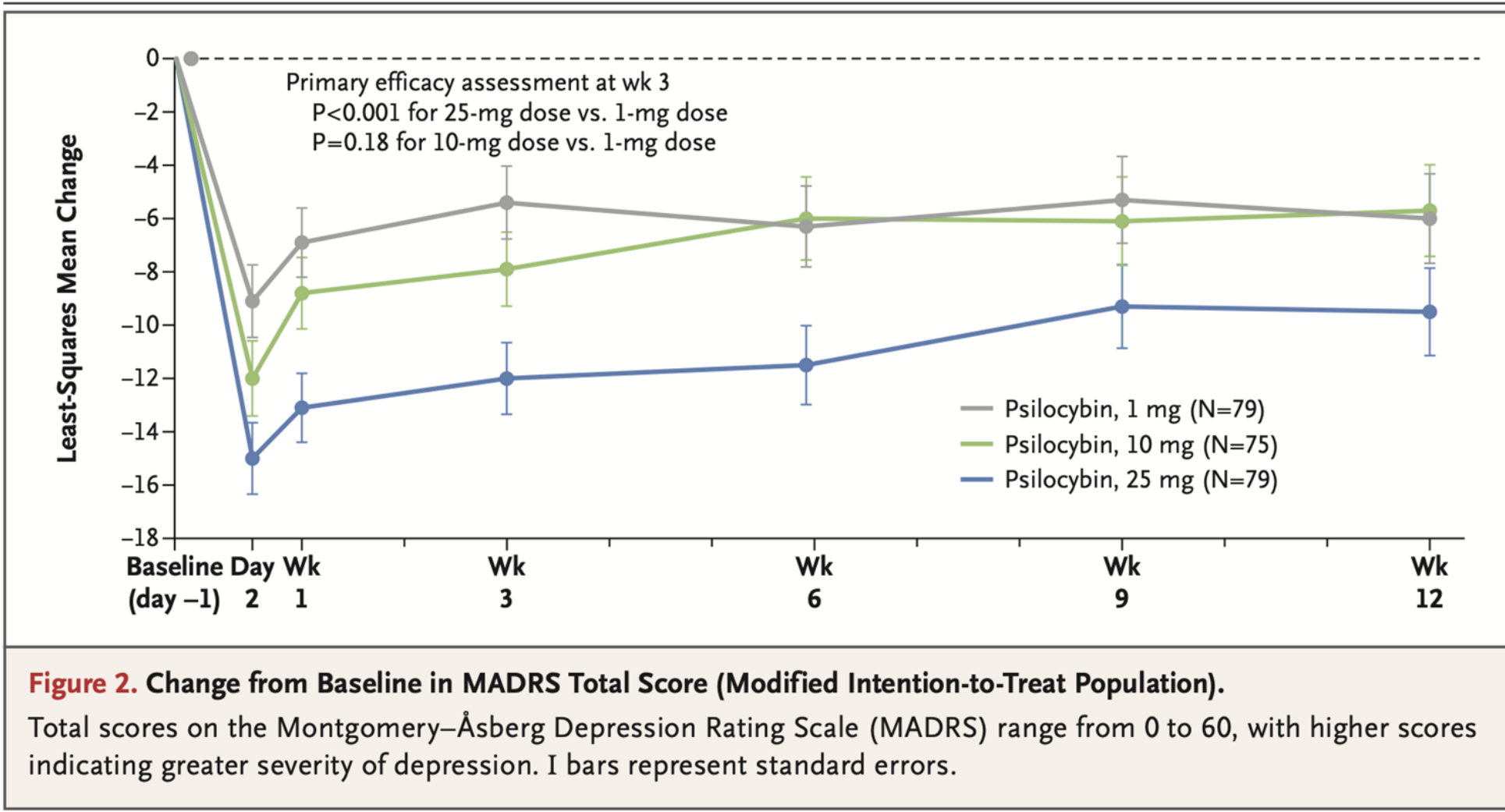
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Studies proclaiming no therapy still have at least one “non-therapist” present who possess full, independent licensure

Psilocybin with psychological support for TRD

N=233

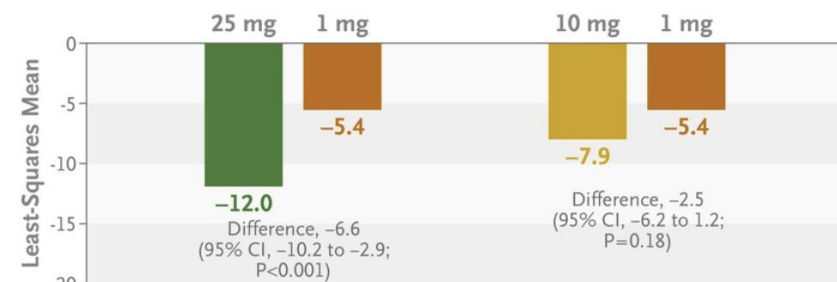


RESEARCH SUMMARY

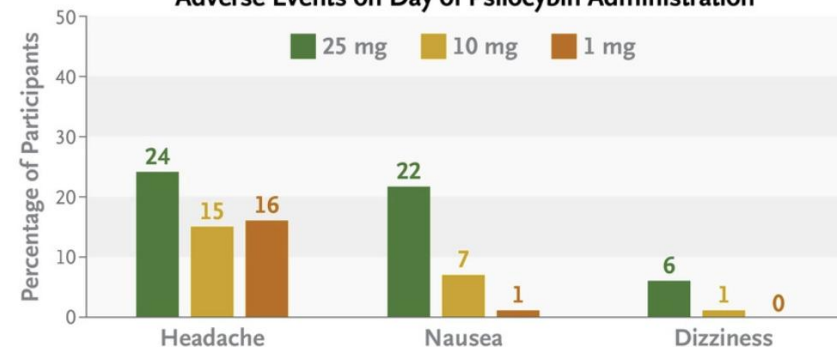
Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression

Goodwin GM et al. DOI: 10.1056/NEJMoa2206443

Change in MADRS Total Score
 From baseline to week 3



Adverse Events on Day of Psilocybin Administration



Suicidal Ideation or Behavior or Self-Injury (Serious Event)



CONCLUSIONS

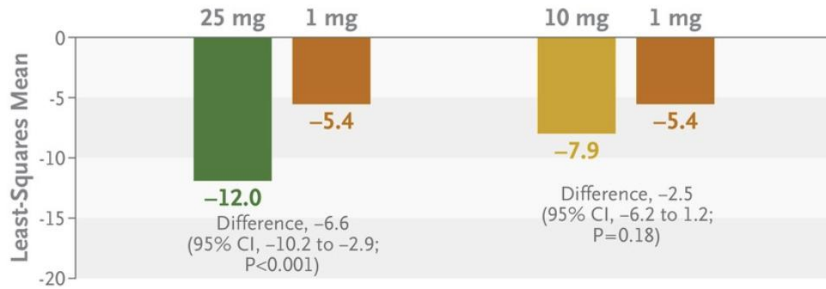
Among adults with treatment-resistant depression, a single dose of 25 mg of psilocybin — but not 10 mg — reduced depression severity significantly more than a 1-mg dose at 3 weeks.

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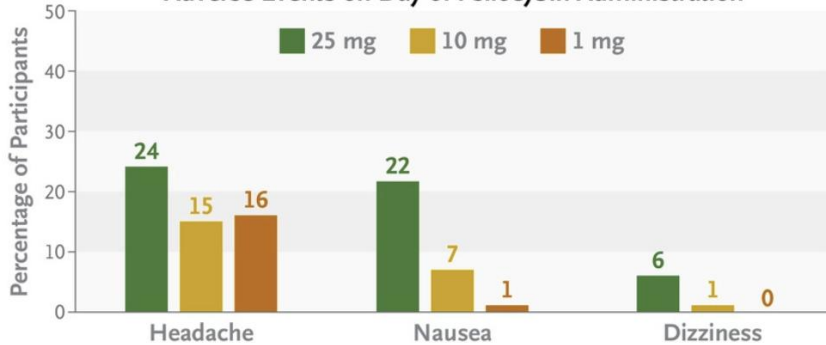
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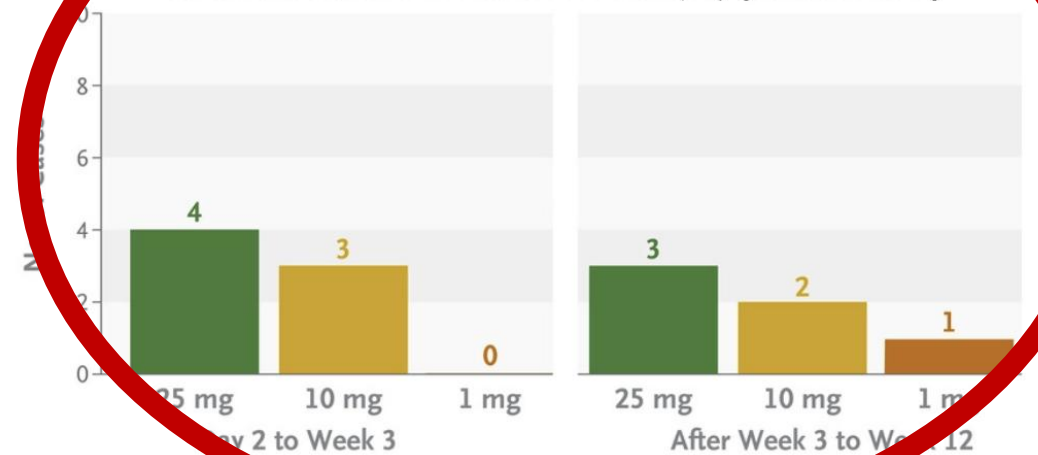
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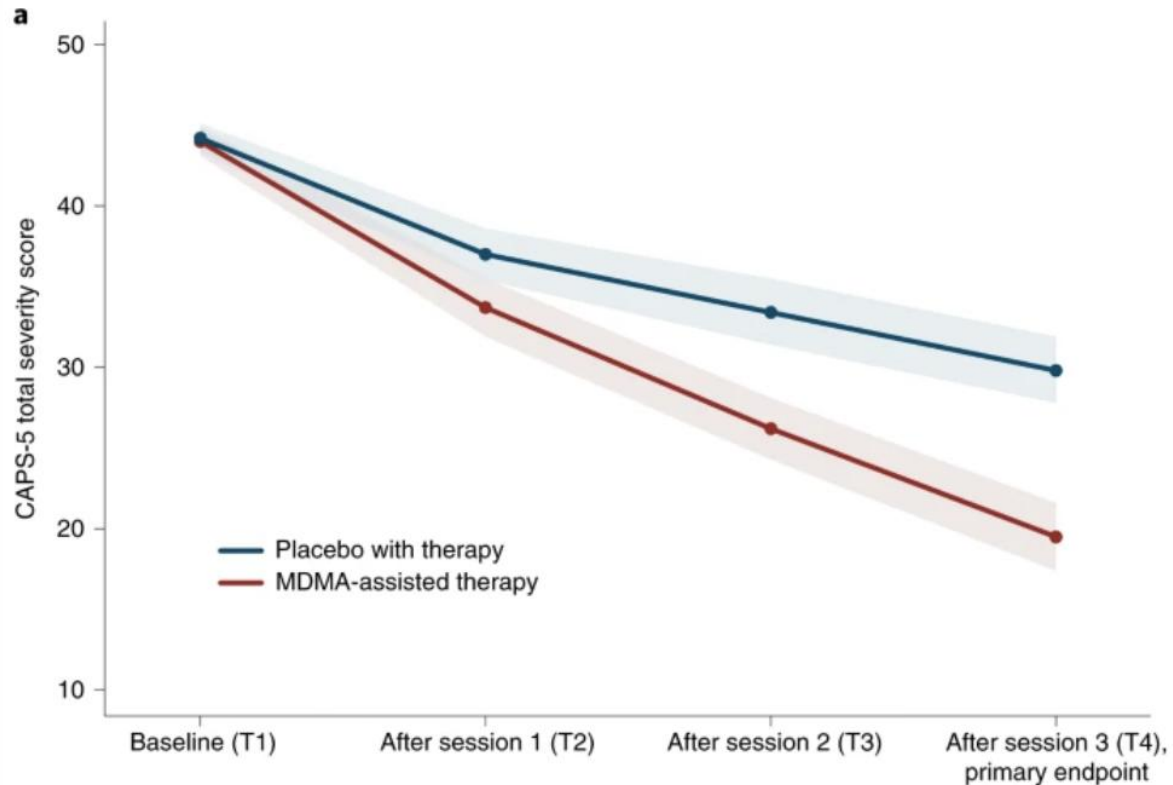
MDMA-AT for PTSD

- 2021: Mitchell et al, *Nature Medicine*
 - N=90 participants with PTSD randomized to MDMA-assisted therapy (3 MDMA sessions) or placebo + therapy
 - Primary outcome: CAPS at 18 weeks vs baseline
 - Results: MDMA -24.5; placebo -13.9
- 2023: Mitchell et al, *Nature Medicine*
 - N=104 participants, moderate-severe PTSD
 - Primary outcome: CAPS at 18 weeks vs baseline
 - Results: MDMA -23.7, placebo -14.8

MDMA-AT for PTSD

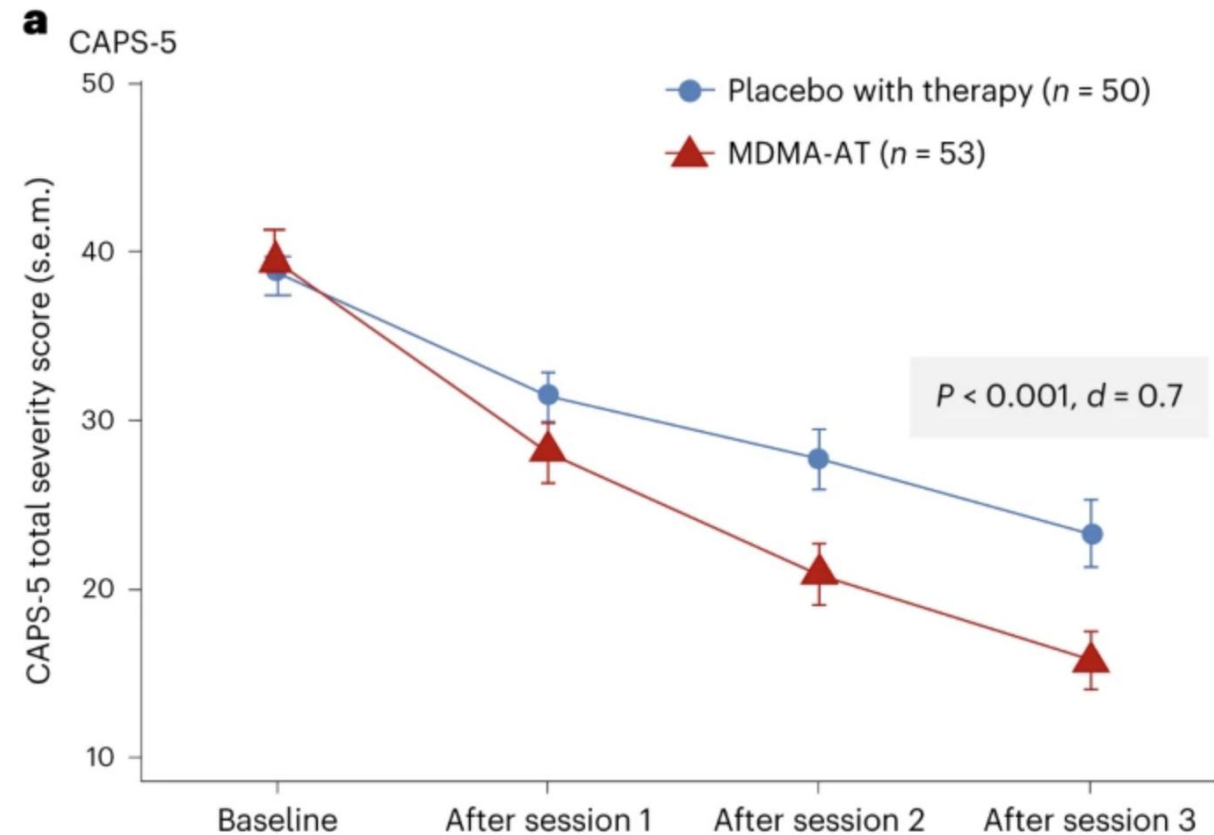
2021

Fig. 2: Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group.



2023

Fig. 2: Measures of efficacy in the MDMA-AT and placebo with therapy groups.



Psilocybin-AP for end of life depression & anxiety

- Promising area of research in the 1960s before work was curtailed
- Initial work with LSD for cancer-related pain led to findings that transcendent experiences led to reduced pain and improved mental well being
- Building on earlier work, pair of RCTs (Ross et al & Griffiths et al) in 2016 both found 60-80% reductions in sx in patients with depression and anxiety a/w advanced stage cancer, 6 months after single session of P-AP
- Degree of improvement associated with having a mystical experience

Mechanisms of psychedelic action

The 5HT-2A Receptor

- 5HT-2A agonists promote neuroplasticity (growth of dendritic spines, synaptic proteins)
 - Increase in BDNF (a marker of plasticity)
 - This effect is blocked by ketanserin
- Expressed throughout cortex but higher density in certain cortical areas involved in top down control of thought (claustrum, Layer V)
- Disruption of influence of high level priors, switching between external and internal focus

Carhart-Harris and Friston, 2019; Barrett et al 2020

Default mode network and psychedelics

- Most active during introspection, daydreaming, mind-wandering, and “self-referential thoughts”
- Associated with sense of self, memory retrieval, personal narratives
- Most active when individual is at rest or engaged in *internally-directed* thoughts
- Inactive when engaged in externally focused tasks
- Associated with rumination (negative, *self-directed* thoughts)

Default mode network and psychedelics

- Decreased or disrupted DMN activity found during psychedelics in multiple studies: LSD, ayahuasca, psilocybin
- Magnitude of DMN effects correlated with subjective experience
- A basis for “ego dissolution”?
- Reduced self-referential thinking/ruminating
- Reduced self-focus in other disorders, such as SUDs

Carhart Harris 2011 *PNAS*, Palhano-Fontes 2015 *PLOS ONE*, Carhart Harris 2017 *Sci Rep*, Müller Neuroimag Clin 2018, Zhang Neuroimag 2019

Psychological factors

Neuroticism: personality trait associated with increased susceptibility to stress, negative affect, anxiety, somatization

Decreased neuroticism found after psychedelic-assisted therapy (MDMA, psilocybin, LSD)

Psychedelics also shown to increase openness to experience and extraversion

Meditation, mindfulness, self-compassion

Psychological flexibility model (ACT) - defusion, present moment focus, committed action, acceptance, values, self as context

Challenges

Regulatory challenges — MDMA

- June 2024: FDA-appointed Advisory Committee recommended against MDMA's efficacy and safety
- Three types of concerns raised:
- Issues that had already been established by FDA during trial design (collection of LFTs, post-MDMA EKGs)
- Issues that raise question of double standards (functional unblinding; esketamine also causes functional unblinding; most trials do not report on unblinding)
- Issues that Lykos ignored (reporting on euphoria as AE)
- Note: claims of “research misconduct” reported by media and fomented by certain critics were not discussed by Ad Comm

Regulatory and scientific challenges

- FDA's statutory mandate is to evaluate and regulate drugs, not therapy
- RCT are not well-suited to study changes induced by drugs where *subjective experience* is both a consequence of the drug as well as a therapeutic mechanism: “drug + context”
- Pressures to devalue the role of the experience, devalue the therapy/psychological support will produce higher risk and avoid answering the critical epistemological question

Schenberg, Hauskeller, Schwarz, King, *Nat Mental Health* (in press), 2024

Challenges — sociocultural

- Issues of hype, reductionistic thinking, panacea claims, and stigma
- Epistemic injustice: psychedelics-as-therapeutics rest on millennia of Indigenous knowledge
- Generalizability: 85% of participants in modern psychedelic trials identified as non-Hispanic white
- Accessibility: PAT is time-consuming and resource intensive

Schenberg and Gerber, *Transcultural Psychiatry*, 2021;
Hughes and Garcia-Romeu, *eClinicalMedicine*, 2024

Thank you!

