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Psilocybin-Assisted Therapy for Depression

A Critical Look at the Evidence

Kelley O'Donnell, MD, PhD
Assistant Professor of Psychiatry, NYU Grossman School of Medicine
Director of Clinical Training, NYU Langone Center for Psychedelic Medicine

Disclosures

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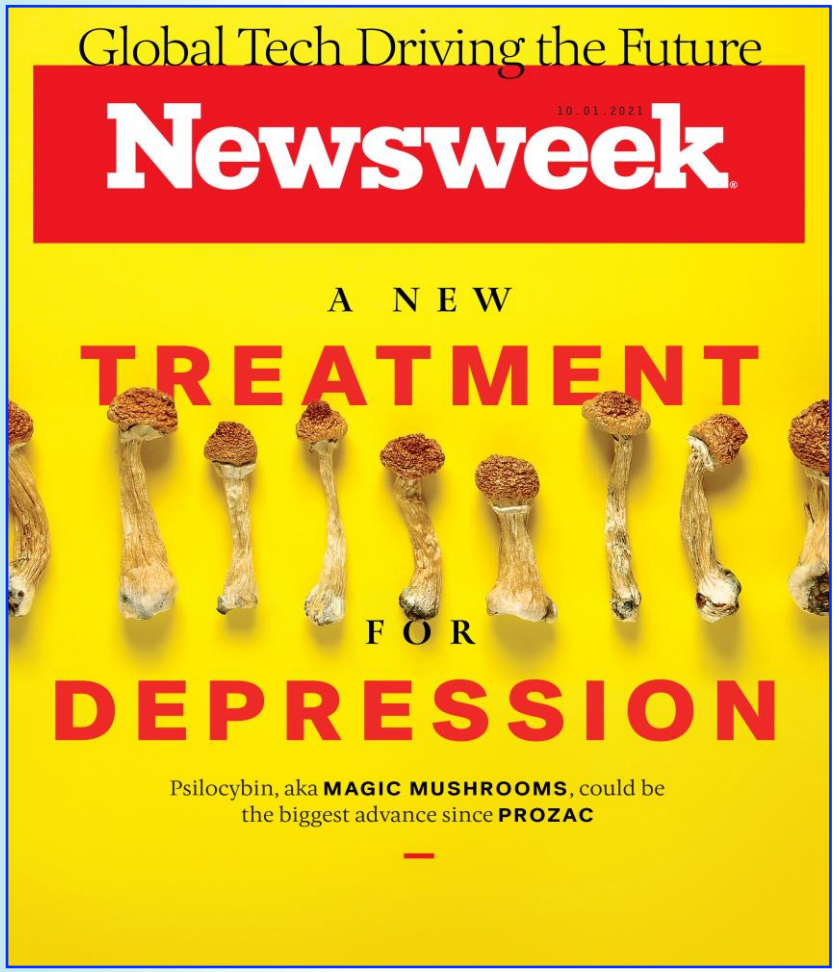
I have received payments from Lykos Therapeutics (formerly MAPS-Public Benefit Corporation) as a consultant and for training and supervising research therapists.

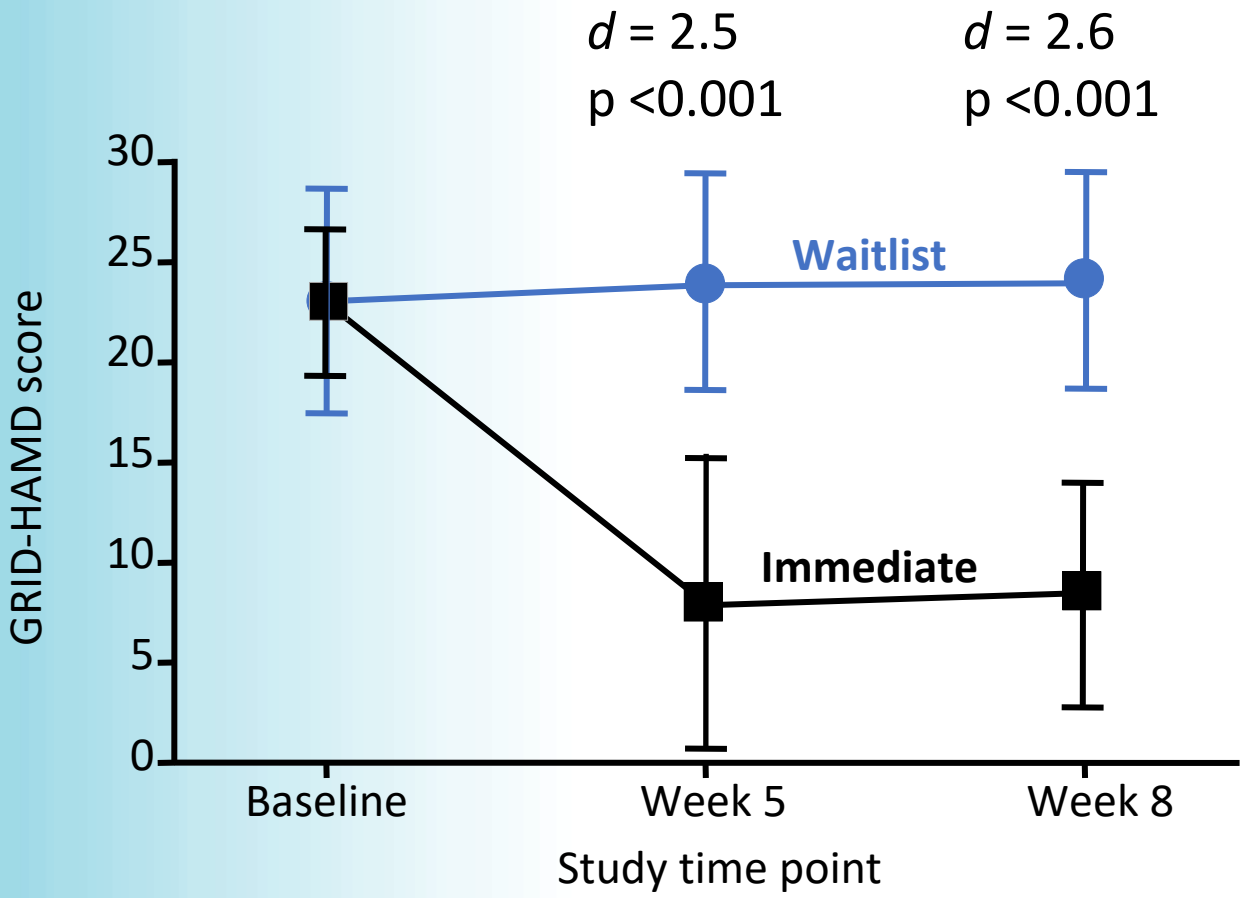
Depression

- Impairs quality of life and increases risk of suicide
- Significant social and economic repercussions
- Treatment options are inadequate, with no recent pharmacologic innovations



Hopkins: Psilocybin vs. Waitlist Control

- N = 27
- Control: 8 week delayed start
- 2 doses, ~1-3 weeks apart
- Dose 1: 20mg/70kg
- Dose 2: 30mg/70kg
- 11 total hr of therapy (2 therapists) during prep and follow-up visits
- QIDS-SR: Decrease at day 1 post-session 1, maintained at week 4
- Overall sample: 71% response rate at Weeks 1 and 4; 58% remission rate (≤7 GRID-HAMD) 54% at week 1, 54% at Week 4



Davis et al. *JAMA Psychiatry*. 2021;78:481.

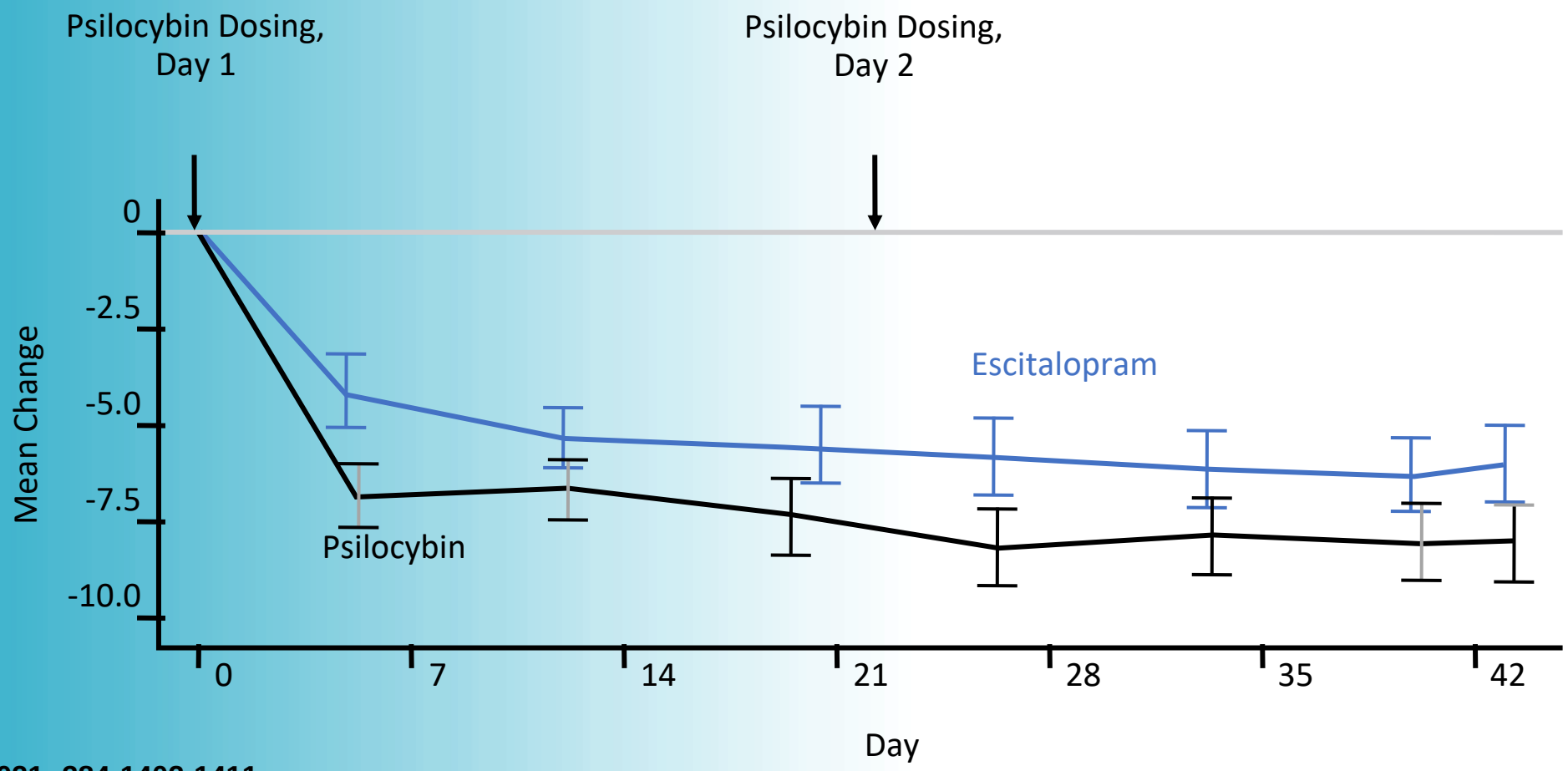
Imperial: Psilocybin vs. Escitalopram for TRD

- N = 59
- Psilocybin group: 25 mg x2 (3 weeks apart) + 6 weeks placebo
- Active control: 1 mg psilocybin + 6 weeks escitalopram
- Prep and integration with 2 therapists
- QIDS-SR measured weekly
- Primary outcome: change in QIDS-SR at 6 weeks

Carhart-Harris et al, *NEJM* 2021; 384:1402-1411

Imperial: Change in QIDS-SR

- No statistically significant difference between groups at Week 6: -2 (95% CI: -5 to 0.9; P = .17)
- Significant changes in MADRS, HAM-D, BDI at Week 6



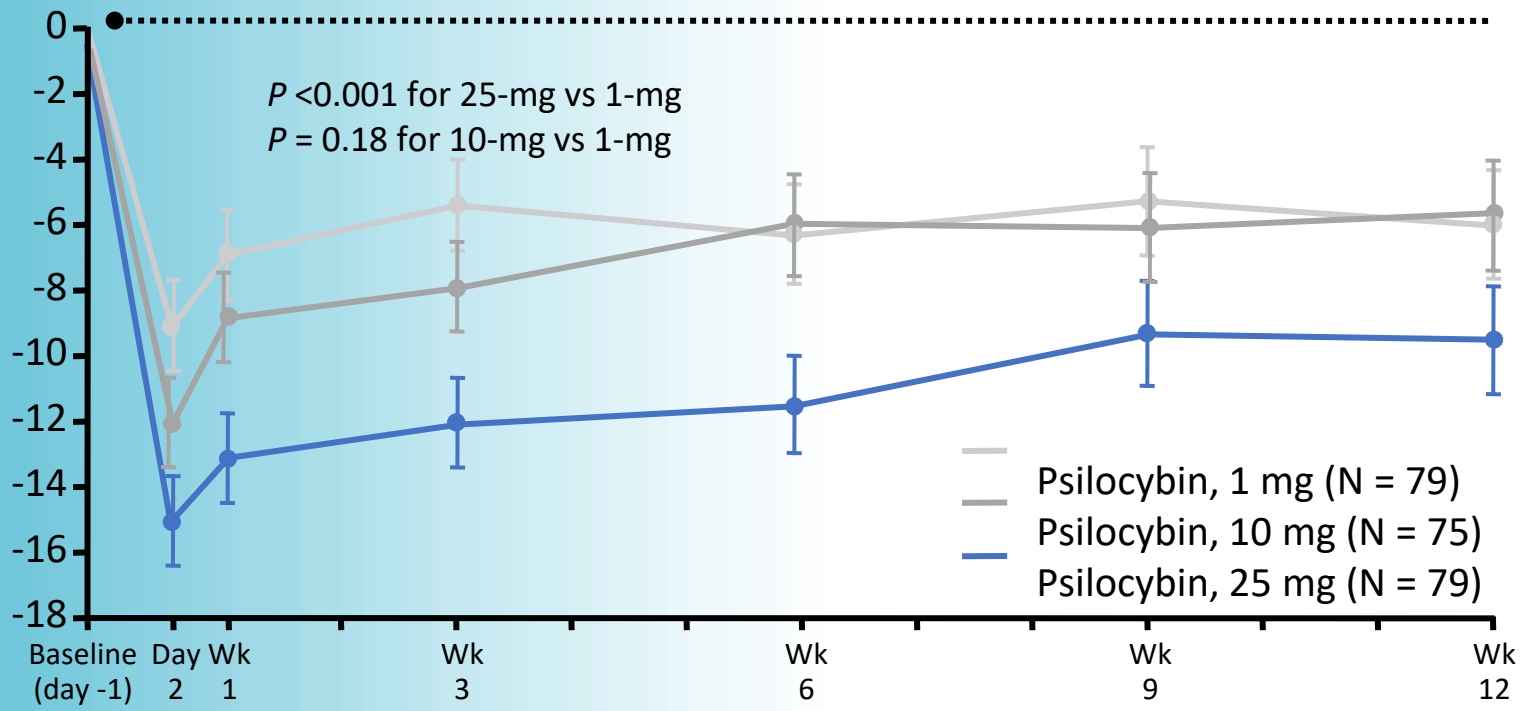
Carhart-Harris et al, *NEJM* 2021; 384:1402-1411

COMPASS: Proprietary psilocybin for TRD

- N = 233
- “Dose-finding” study: 1 mg, 10 mg, or 25mg psilocybin
- 3 prep sessions, 2 integration sessions (1 day and 1 week post-psilocybin) with 1 therapist; assistant therapist also present for dosing day
- MADRS measured at baseline, 1 day post-dose, and weeks 1, 3, 6, 9, 12 post-dose
- Primary outcome measure: change in MADRS from baseline to Week 3

COMPASS: change in MADRS

- Least-squares mean change: −12.0 for 25 mg, −7.9 for 10 mg, and −5.4 for 1 mg
- Difference between the 25-mg group and 1-mg group: -6.6 (95% CI: −10.2 to −2.9; P<0.001)
- Difference between 10mg and 1mg group: −2.5 (95% CI, −6.2 to 1.2; P=0.18).



Goodwin et al. *NEJM*. 2022;387:1637.

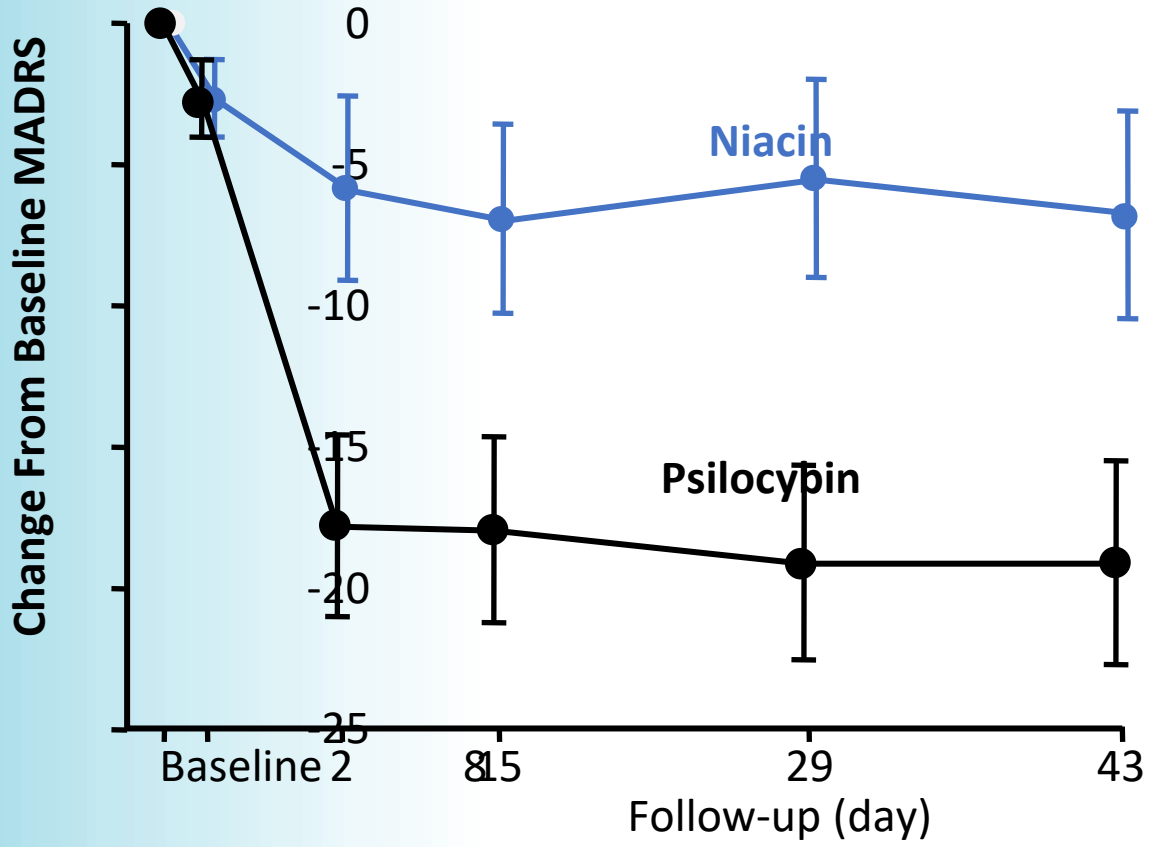
Usona: Psilocybin vs. Niacin for MDD

- N = 104 patients with major depressive disorder
- 2 therapists, 6-8h for preparatory sessions, 4h for integration
- Single dosing session: psilocybin 25mg vs. niacin 100mg
- Primary outcome: change in MADRS score between baseline and Day 43

Raison et al. *JAMA.* 2023;330(9):843-853.

Usona: Change in MADRS

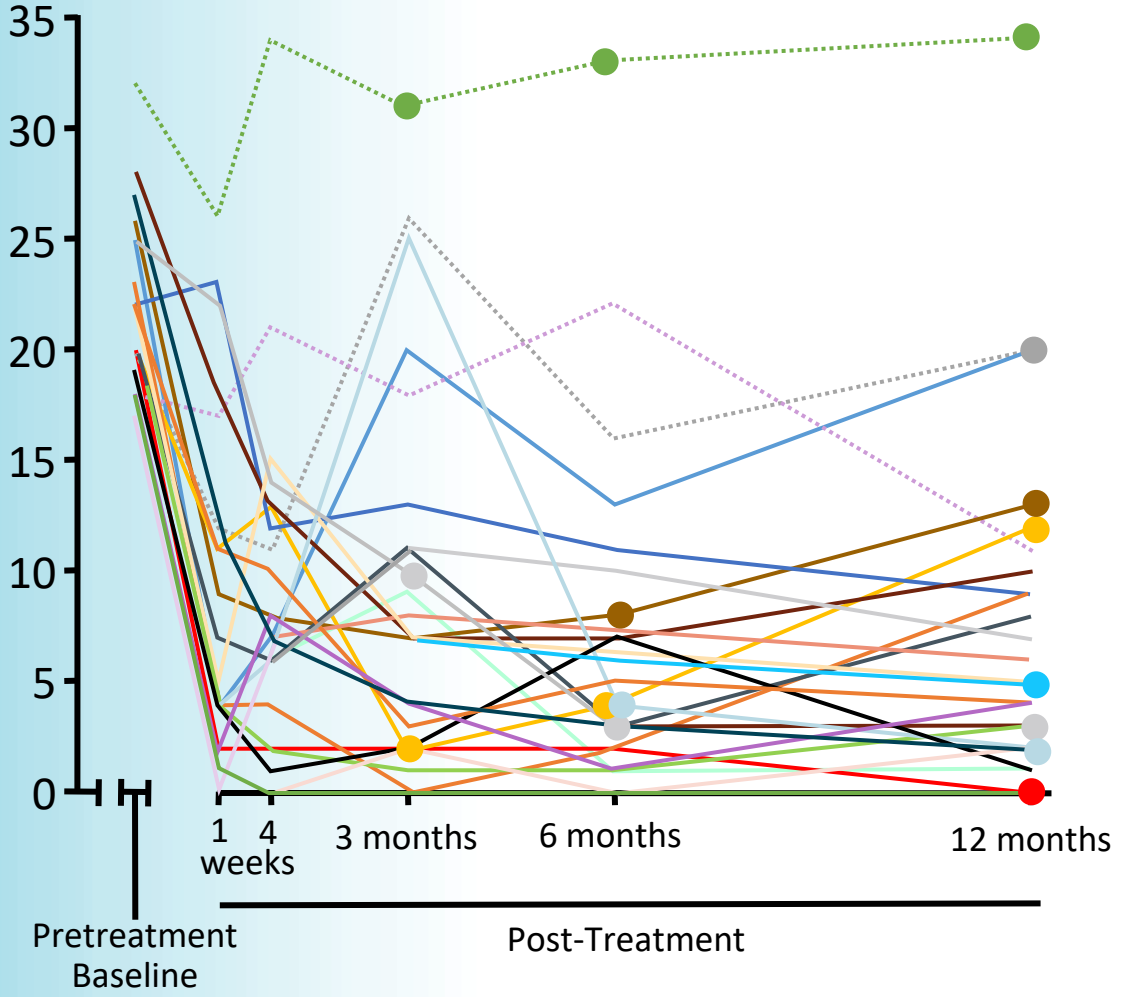
- Rapid and sustained decrease in MADRS score in psilocybin group at all time points
- Mean between-group differences:
  - Day 8: -12.0 (95% CI, -16.6 to -7.4 *P* < .001)
  - Day 42: -12.3 (95% CI, -17.5 to -7.2 *P* <.001)



Raison et al. *JAMA.* 2023;330(9):843-853.

“Sustained” response?

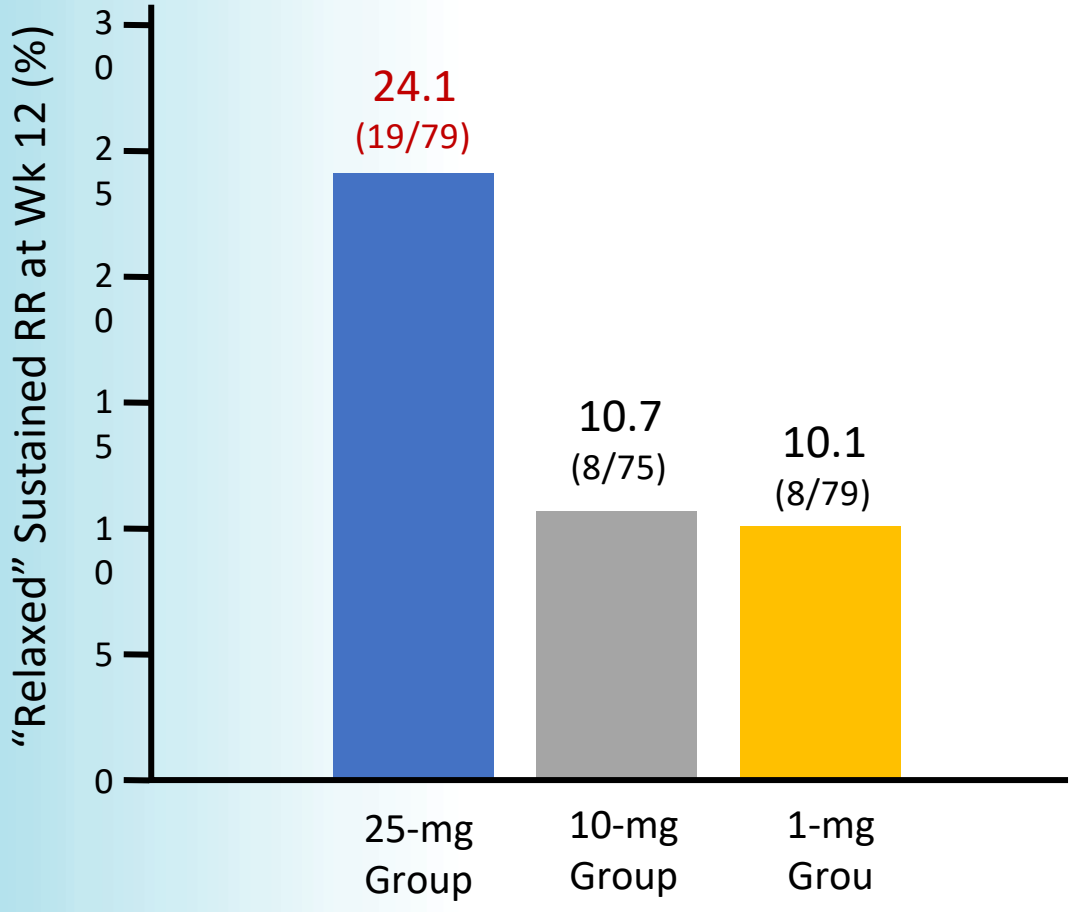
- Follow-up from Hopkins trial (Davis et al., 2021)
- General upward trend over 12 months Still 75% response and 58% remission at 12 months…
- …but 8 participants started an antidepressant during the follow-up period



Gukasyan et al. *J Psychopharmacol*. 2022;36:151.

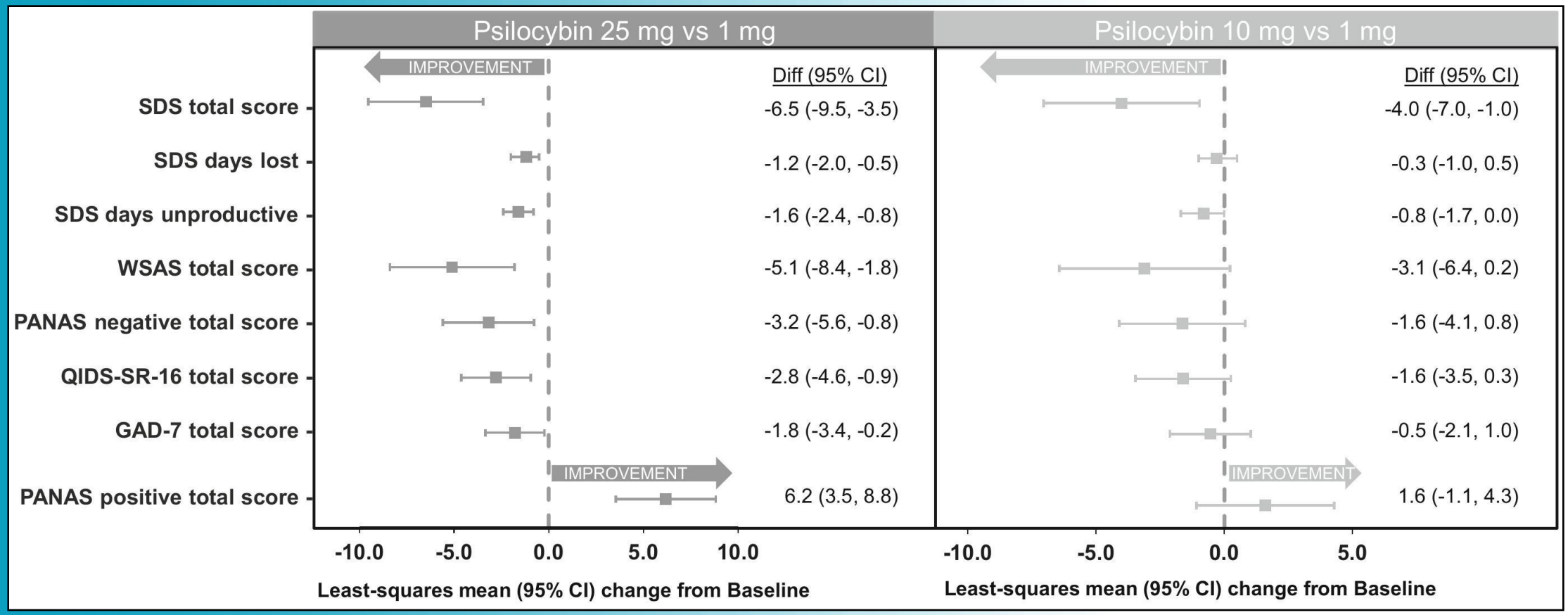
Response and risks during follow-up

- COMPASS trial follow-up
- 24.1% response rate at Week 12…but only with “relaxed” criteria, including 1 deviation (at Week 6 or Week 9)
- Suicidal ideation in all groups during f/u, but only in 10 and 25mg groups between Day 2 and Week 3
- 3 instances of suicidal behavior in the 25mg psilocybin group between Week 3 and Week 12
- Note that this is despite the fact that **all 4 trials excluded patients with history of serious suicidality**



Goodwin et al.. *NEJM*. 2022;387:1637.

Improved functioning & quality of life



Goodwin et al.. 2023. *J Affect Disord*. 327:120-127

Therapeutic alliance predicts benefit

- In the Imperial College study, strength of therapeutic alliance before the 1st session predicted:
  - Greater emotional breakthroughs
  - Mystical-type experiences
- Weaker alliance ahead of 2nd session predicted higher depression scores at Week 6
- In the Hopkins study, stronger alliance at final preparation session (pre-dosing) predicted lower depression scores, psychological insight scores, and mystical experience ratings

Murphy et al. *Front Pharmacol*. 2022 Mar 31;12:788155
Levin et al. *PLOS One*. 2024 Mar 14;19(3):e0300501

Psilocybin-*assisted* therapy

- Underreporting the content and extent of psychotherapy is common
- Idealization of the drug experience
  - Do underwhelming experiences → disappointment, resignation, despair?
  - Incomplete/idealized reporting of the *content* of the acute experience is common
- Insufficient support for integration of intense experiences during and after the trial

"What I have learned in the last five years is that the greatest threat to a healthy psychedelic future is the fetishising of just the drug alone."

Rosalind Watts, PhD

Medium, 2022

Describing the intervention

- **Usona study** (Raison et al., 2023)
  - Therapists described as “facilitators,” “supervising” the dosing session, “discussing” it with the participant during integration sessions
- **Imperial College study** (Carhart-Harris et al., 2021)
  - Framework “involves being physically and emotionally **present** for the patient before, during and after the acute drug session. It may incorporate empathetic listening and reassurance, for example.”
  - Integration “involves **non-judgmental listening** to the patient’s testimony … and may occasionally feature some **interpretation** regarding the content of the experience and its potential meaning, as well as **advice** regarding maintaining and cultivating positive changes in outlook and lifestyle.”

Murphy et al. *Front Pharmacol*. 2022 Mar 31;12:788155
Levin et al. *PLOS One*. 2024 Mar 14;19(3):e0300501

"[The] psilocybin for depression work at Imperial was done in the context of a neuroscience lab, but **none of our team thought we were simply providing a drug to reset the brain**.

[…]

The therapeutic container was always painstakingly and lovingly curated; emphasis placed on the **interpersonal bond** between guides and participants, on creating a **nest of trust and safety** for the participant to unravel in, and an **understanding that the real work, the real healing, would occur only if the person felt able to 'let go' and surrender to the deepest layers of long-suppressed feelings**."

Rosalind Watts, PhD. Medium, 2022

Other limitations of psilocybin research

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- Different protocols across studies
- Hype may increase expectancy bias (i.e., expectation of favorable result) among participants and researchers
- Functional unblinding is unavoidable, and undermines the RCT fantasy…
- …though it's unclear how much that truly affects clinical outcomes

"The story I have told [regarding my first psilocybin experience] is one of transformation ….

The story I have told is not false; neither is it complete. It is incomplete because **I have never elaborated on my second experience in that same trial**, which impacted me in ways that I still grapple with. I understand, however, that some impacts were un-therapeutic. **Anti-therapeutic, even**."

Petersen, 2022. Harvard Divinity Bulletin.

Chisamore et al (2024). J Psychiatr Res Aug:176:77-84.
Goodwin et al. (2023) *J Affect Disord* May 1:328:1-5
Ledwos et al. (2022) *J Clin Psychopharmacol* 2022 Mar 42(6):581-588
Rosenbaum (2024) J Clin Psychiatry. 85(3):24com15504

Other limitations

Review > Neuropharmacology. 2022 Aug 15:214:109127.
doi: 10.1016/j.neuropharm.2022.109127. Epub 2022 May 13.

Special considerations for evaluating psilocybin-facilitated psychotherapy in vulnerable populations

Cynthia E Ortiz [1], Haley Maria Dourron [2], Noah W Sweat [2], Albert Garcia-Romeu [3], Sarah MacCarthy [2], Brian T Anderson [4], Peter S Hendricks [5]

Affiliations + expand

PMID: 35577136 DOI: 10.1016/j.neuropharm.2022.109127

- Low diversity affects generalizability of safety, as well as efficacy, data
- Low diversity (including among researchers?) also affects psychotherapy protocols

Summary

- 1-2 doses of psilocybin with “psychological support” may have a **rapid-acting** antidepressant effect in patients with depression
  - Effects seen as early as 1 day post-dose
  - Long-term effects of 1-2 doses are less convincing, and treatment is not risk-free
  - In general, participants have been medication-free and relatively **low-risk** (no serious prior suicide attempts, no major psychiatric comorbidities, able to tolerate being medication-free)
- No evidence that antidepressant findings are due to the drug effect alone
  - Therapy may be more extensive than what gets reported
  - Therapeutic alliance established in drug-free sessions correlates with short- and long-term efficacy
  - Participants may need (and seek out) more support than we think → implications for safe, efficacious, ethical, and equitable care
- Functional unblinding, expectancy bias (!!!), low diversity, and poor standardization are major limitations of psilocybin studies to date

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Thank You!