Challenges in Trial Design for Psychedelic-Assisted Therapies:

Reflections from Two Trials of Psilocybin Therapy of Depression

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

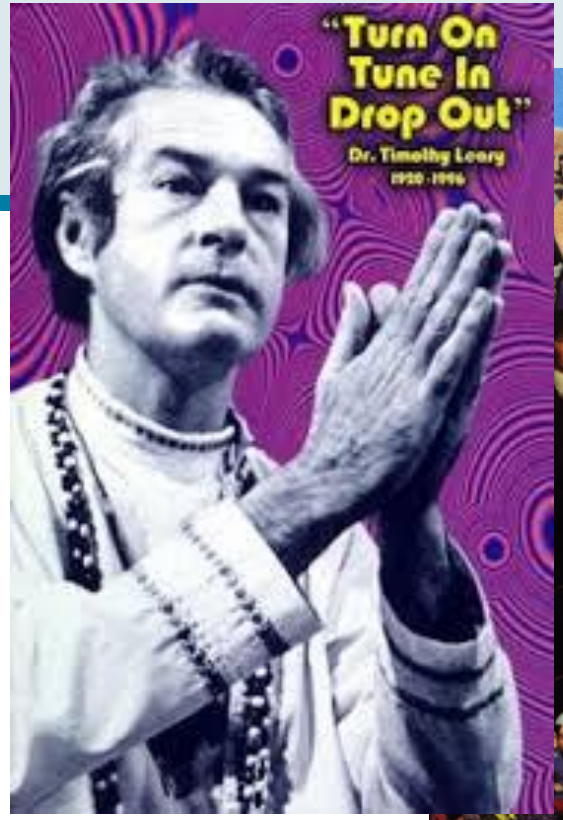
- Consultant with Usona Institute
- Clinical Supervisor with Cybin

Challenges in Psychedelic Trial Design

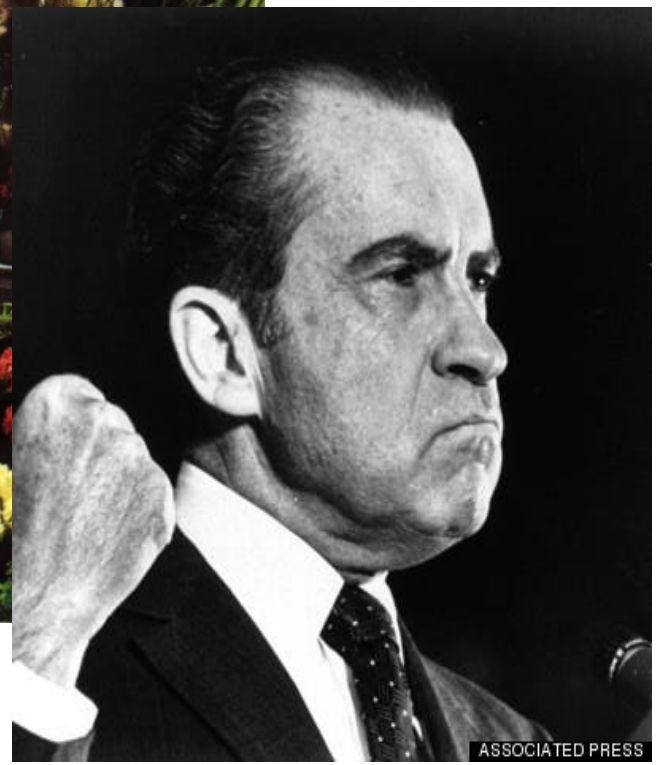
- Participant selection
- Consent process
- Antidepressant tapering
- Blinding
- Use of placebos
- Managing/Measuring Expectancy
- Standardizing set and setting
- How much / what kind of therapy
- Single vs multiple doses
- Open label crossovers
- Follow up periods and aftercare

Taking a Step Back

- How are psychedelic trials designed?
- What research questions and methods are privileged?
  - Which are marginalized?
- How do historical, political and economic factors inform or shape clinical trial design for psychedelics?


"Turn On
Tune In
Drop Out"
Dr. Timothy Leary
1920-1996


SGT PEPPERS
LONELY HEARTS
CLUB BAND
BEATLES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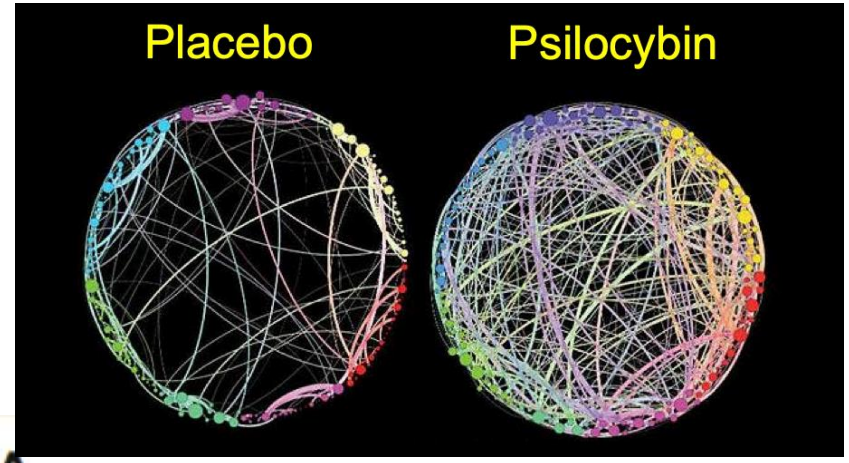
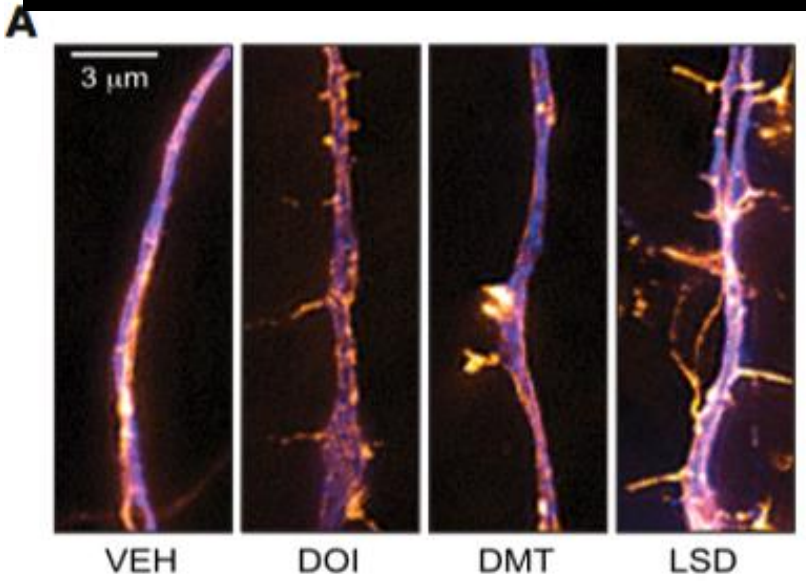
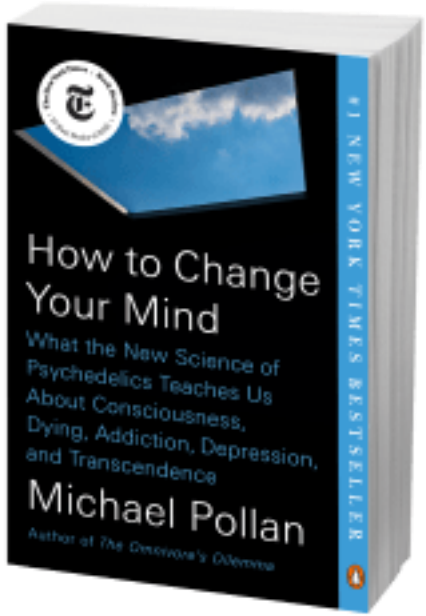
Psychedelic “Renaissance”

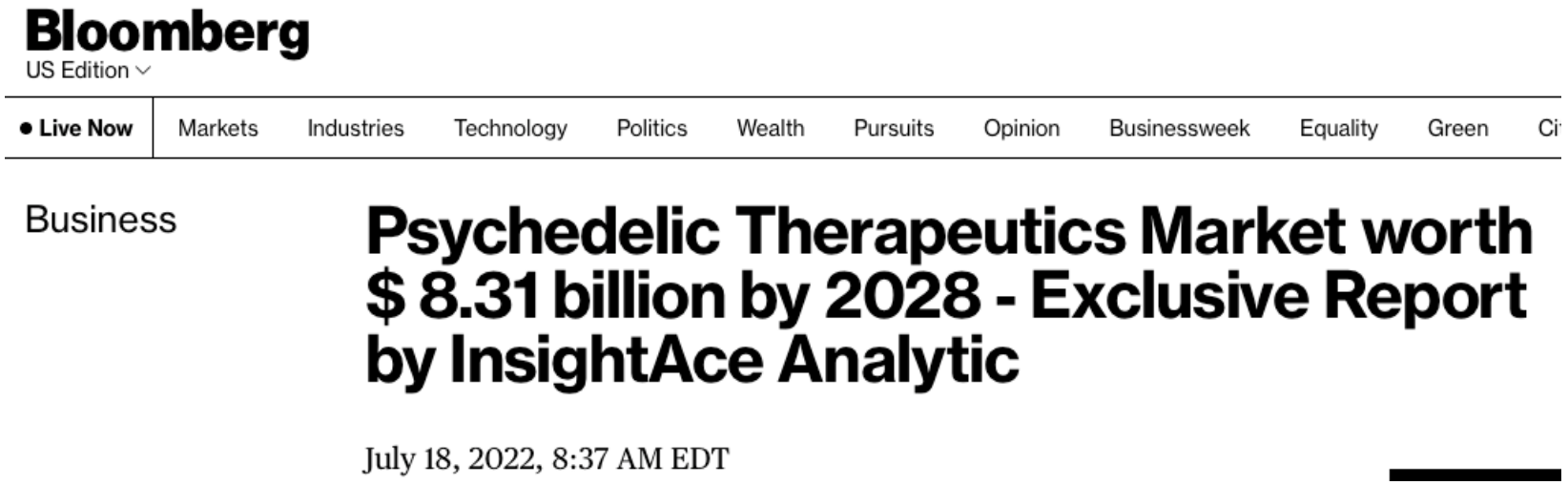






Psychedelic Medicalization

- Primary driving force behind trial design is to determine safety and efficacy of psychedelic **drugs** and **ultimately obtain FDA-approval.**



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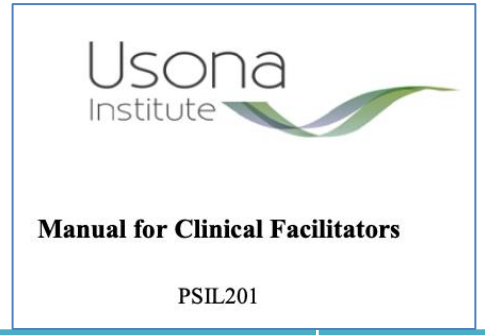
July 18, 2022, 8:37 AM EDT

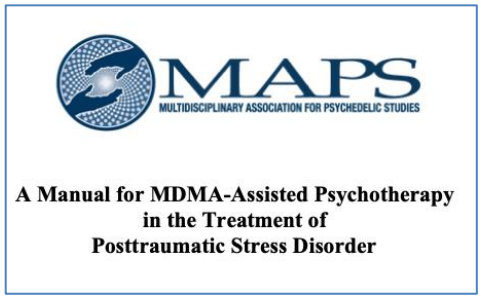
Impacts on Trial Design

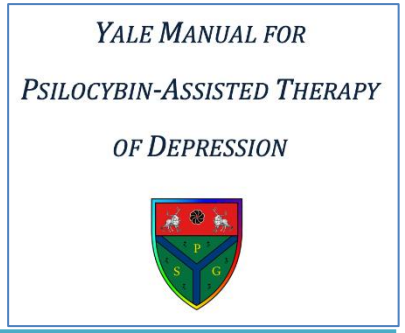
- Focus on the ‘drug’ as variable of interest / need to isolate ‘drug effects’
- Two primary strategies
  - Control ‘set’ and ‘setting’ variables, including psychotherapy
  - Blind the study drug, minimize expectancy effects
- Argument: need to isolate drug effects creates certain tensions between methodological and ethical/patient-centered concerns

Controlling Therapy: Minimize or Manualize?

"Psychological Support"
(Imperial, NYU, JHU)

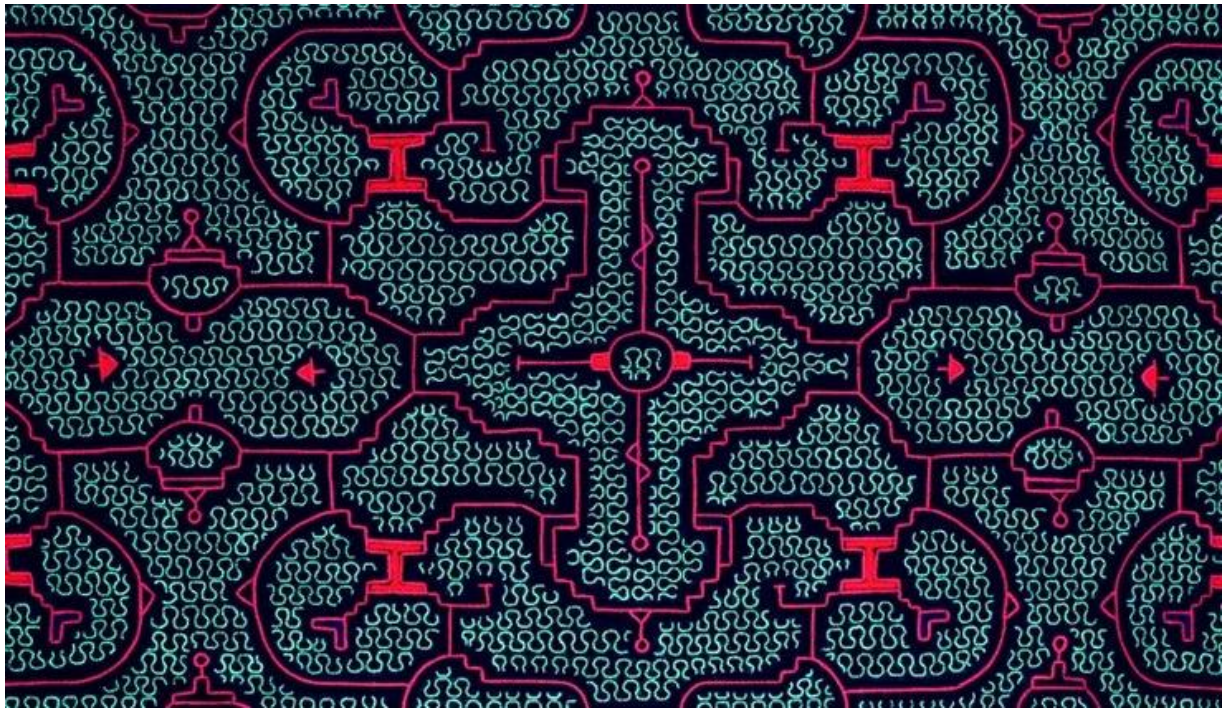






Minimize	Manualize
Non-specific Therapy	Specific or non-specific
Minimize Placebo/Therapy Effects; Focus on Drug Effects	Drug-Therapy Treatment
Focus on Safety	Focus on Effectiveness
Less Replicable	More replicable

Drug effects vs expanded states of consciousness



Blinding & Expectancy

- Many papers addressing this topic (e.g. Aday et al., 2022; Butler et al., 2022; Muthukumaraswamy et al., 2021).
- Variety of approaches
  - inert and active placebos (i.e. niacin)
  - Low dose psilocybin
  - instructions during consent process to increase uncertainty (i.e. more drug/dose combinations than are actually given)
- Limited success to date

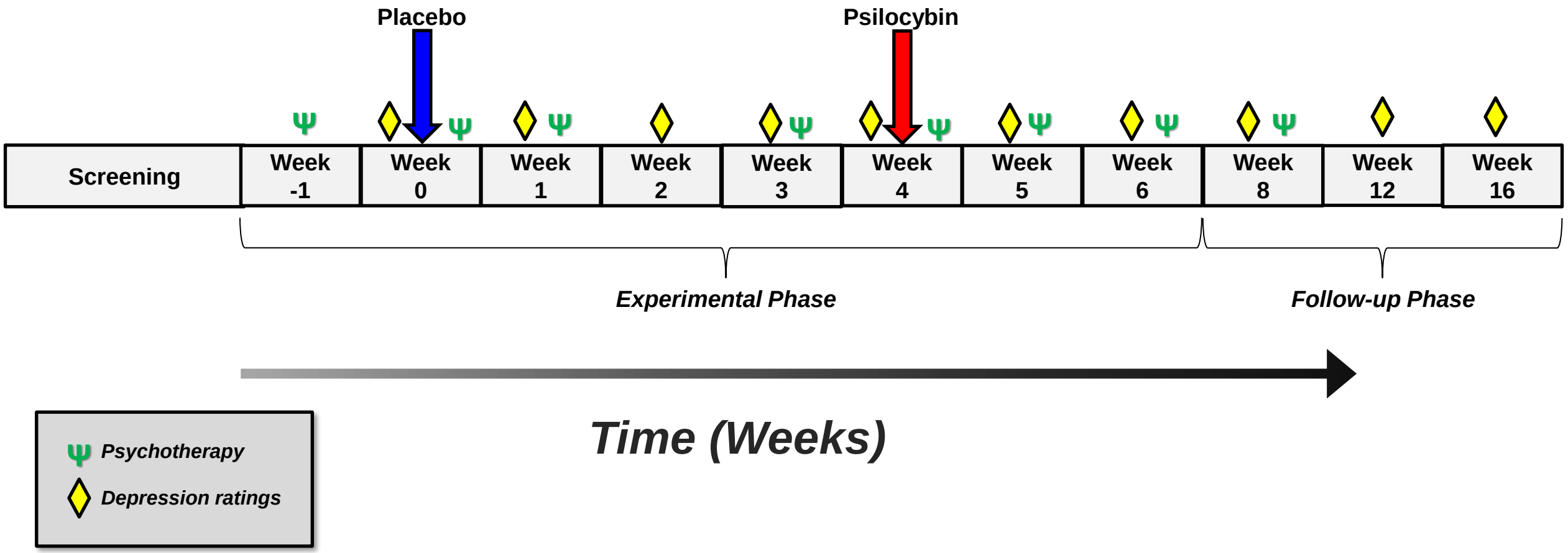
Psilocybin-induced Neuroplasticity in the Treatment of MDD

Yale Manual for Psilocybin-Assisted Therapy of Depression

Methods

- Inclusion: Adults with moderate to severe MDD (HAM-D≥17), one or more treatment failure, off antidepressants
- Target enrollment: n=18
- Placebo-controlled, within subject, fixed order design with enhanced blinding procedures

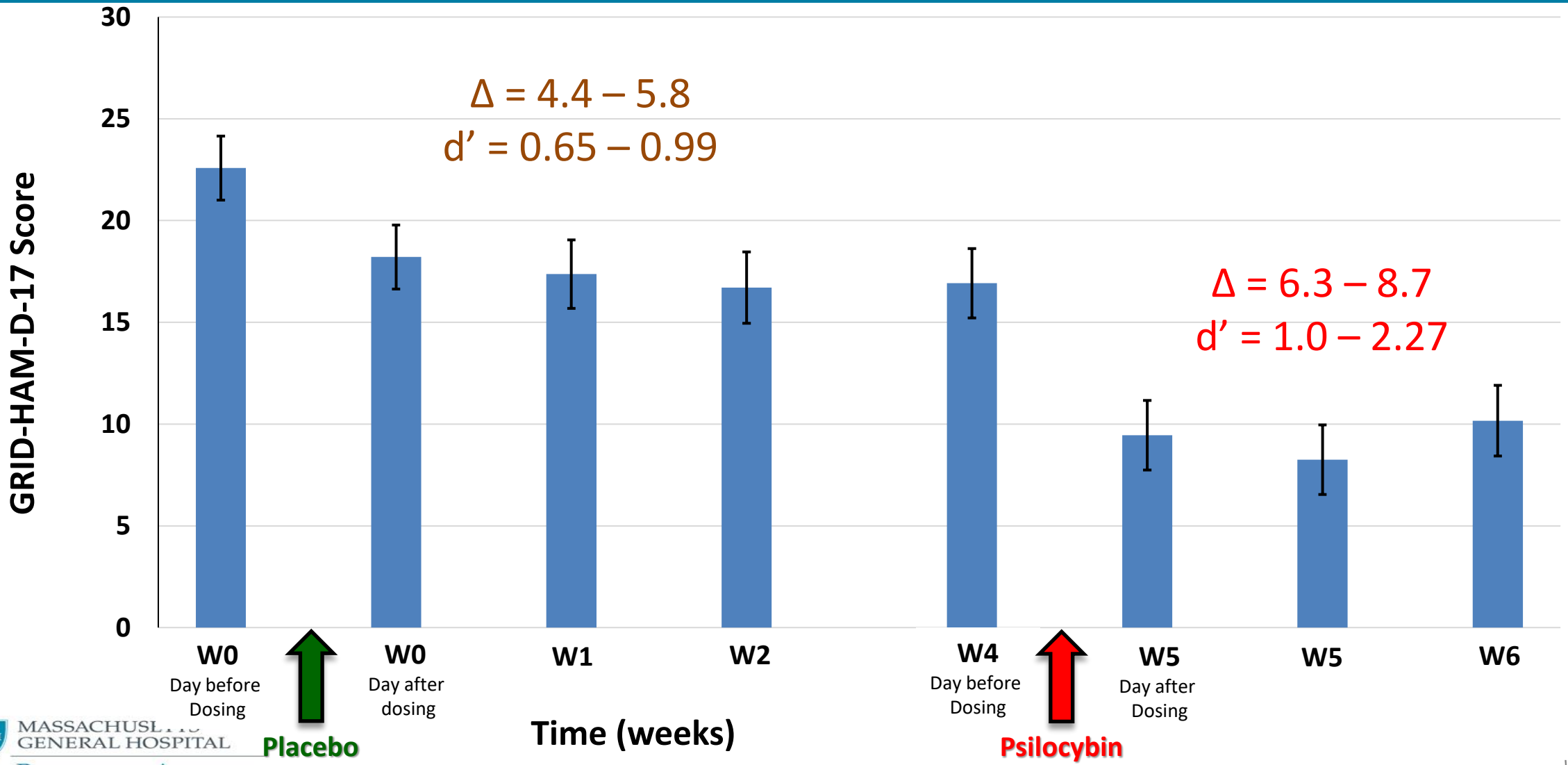
Study Design



Blinding Efficacy

- Placebo session
  - 15/19 (78.9%) participants correctly guessed they had received placebo
  - 4/19 guessed low dose psilocybin (0.1mg/kg)
- Psilocybin Session (0.3mg/kg)
  - 12/15 (80%) participants correctly guessed they had received this dose
  - 3/15 guessed low dose psilocybin (0.1mg/kg)

Change in Depression (HAM-D-17, n=19)



Usona PSIL201: Single-Dose Psilocybin for MDD

Usona Institute

Methods

- Inclusion: Adults with moderate to **severe** MDD (MADRS≥28), off antidepressants
- Target enrollment: n=100
- Randomized, parallel group design, placebo-controlled (niacin), single dose with no crossover

Considerations on Single Dose Design

- Study enrolled very ill patients, some of whom tapered in order to enter the trial
- 50/50 chance during single dosing session to receive active treatment
  - Significant disappointment and despair among participants who did not experience drug effects
  - Significant pressure on participants who did experience drug effects to ‘get it right’ as this was their one and only chance

Considerations

- Ethics of single dose studies and open-label crossovers
  - Aday et al. 2002
  - Is this a realistic treatment paradigm?
- Study facilitator challenges
  - Equipoise
  - Adhering to set/setting or supportive only approach

Study Proposals

- Noninferiority studies with other approved treatments for depression (esketamine)
- 2-3 dose paradigm for MDD/TRD (similar to MAPS studies)
  - Dose escalation option in subsequent sessions
  - Crossover at end of study for placebo group
- Psilocybin + support only vs psilocybin + therapy

Study Proposals

- How can traditional / indigenous uses of plant medicine inform trial design?
  - Not testing a dose but a given level or quality of ASC?
  - Not standardizing setting, music, and therapy but standardizing processes for adjusting these variables in a person-centered fashion

Conclusions

- Critically examine study designs from interdisciplinary perspectives
- Consider ethical challenges related to methodologies that focus on ‘drug effects/efficacy’
  - To what extent do we prioritize methods over ethics?
  - What may be the real world clinical implications of doing so?

References

- Aday, J. S. *et al.* Great Expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. *Psychopharmacology* 1–22 (2022).
- Butler, M., Jelen, L. & Rucker, J. Expectancy in placebo-controlled trials of psychedelics: if so, so what? *Psychopharmacology* 1–9 (2022).
- Gukasyan, N. & Nayak, S. M. Psychedelics, placebo effects, and set and setting: Insights from common factors theory of psychotherapy. *Transcult Psychiatry* (2021).
- Mertens, L. J. *et al.* Methodological challenges in psychedelic drug trials: Efficacy and safety of psilocybin in treatment-resistant major depression (EPIsoDE) – Rationale and study design. *Neurosci Appl* **1** (2022).
- Muthukumaraswamy, S., Forsyth, A. & Lumley, T. Blinding and expectancy confounds in psychedelic randomised controlled trials. *Expert Rev Clin Phar* (2021).
- O'Donnell, K. C., Mennenga, S. E. & Bogenschutz, M. P. Psilocybin for depression: Considerations for clinical trial design. *Journal of Psychedelic Studies* **3**, 269–279 (2019).

Thank you!

Any questions?

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