Magic Mushrooms and Mental Health:
Exploring Psilocybin for Depression

- Introduction to psychedelics.
- Our research experience with OCD
- Current trials at UA for Depression
- Discussion

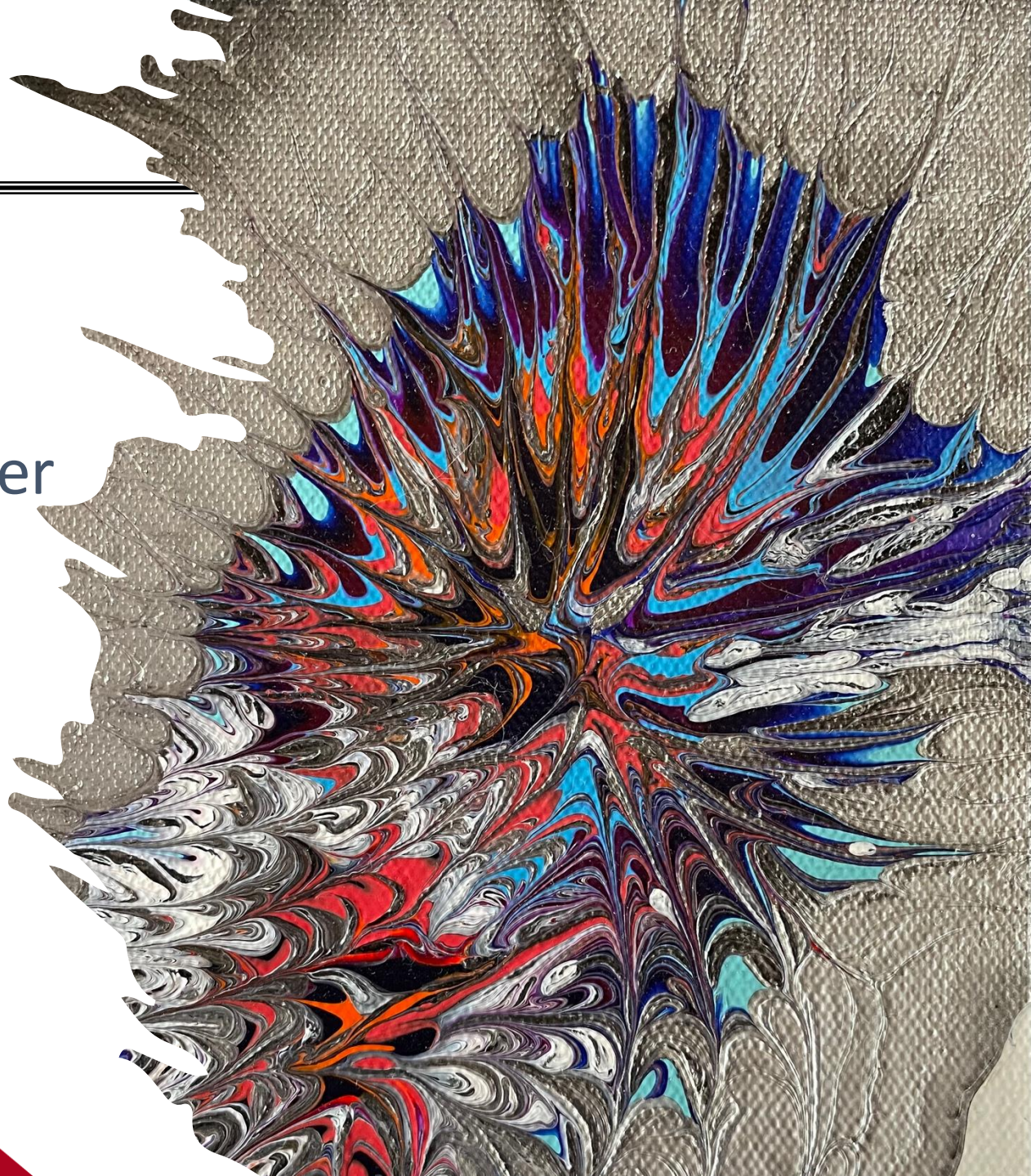
What are psychedelics?

Any agent that causes alterations in perception, cognition, and mood as its primary psychobiological actions in the presence of an otherwise clear sensorium

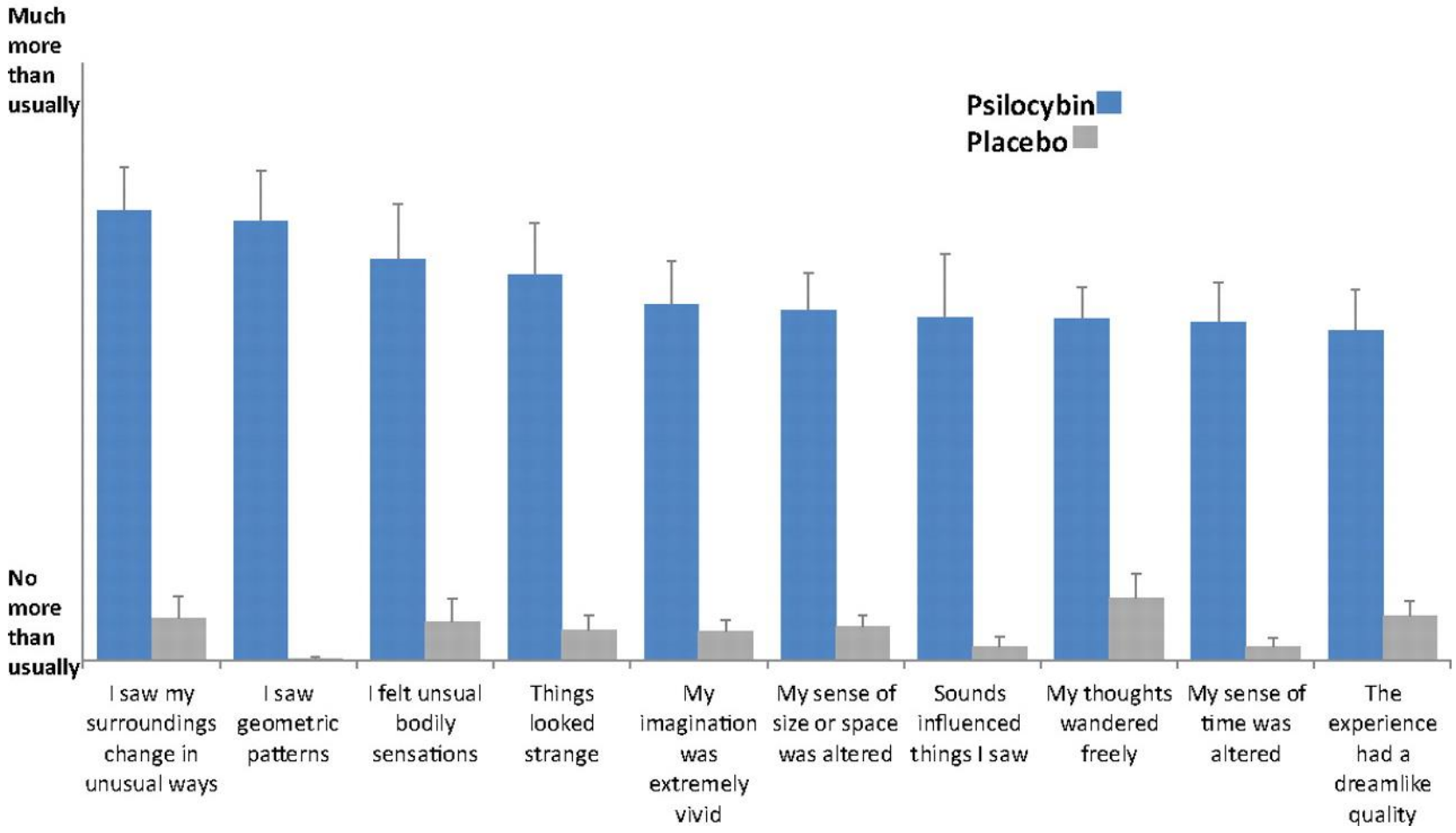
- Greek: “mind-manifesting”
- OED: “…producing an expansion of consciousness through greater awareness of the senses and emotional feelings and the revealing of unconscious motivations...”
- a.k.a. hallucinogens, psycholytics, psychotomimetics, entheogens, empathogens, entactogens

Psychedelic Experience

- Complex interaction of the drug, psychological and physical environment, personality and expectations of the user and his/her company
- Description of effects:
  1) mood and affect
  2) interpersonal behavior
  3) sensory and perceptual effects
  4) intellectual function and reality testing
  5) intuitive effects



Subjective Psilocybin ratings (n = 30)
Top 10 rated items

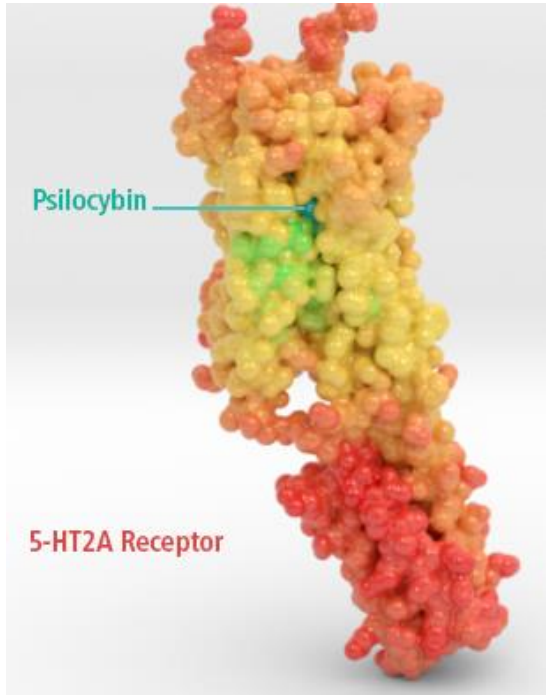


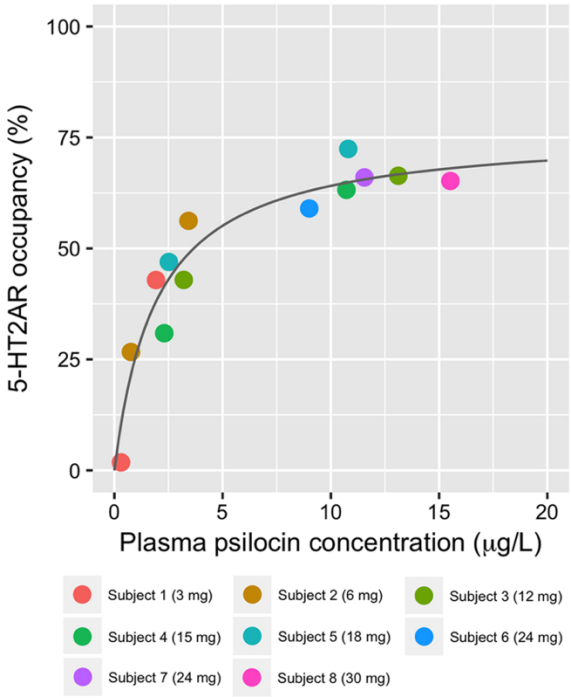
Robin L. Carhart-Harris et al. PNAS 2012;109:2138-2143

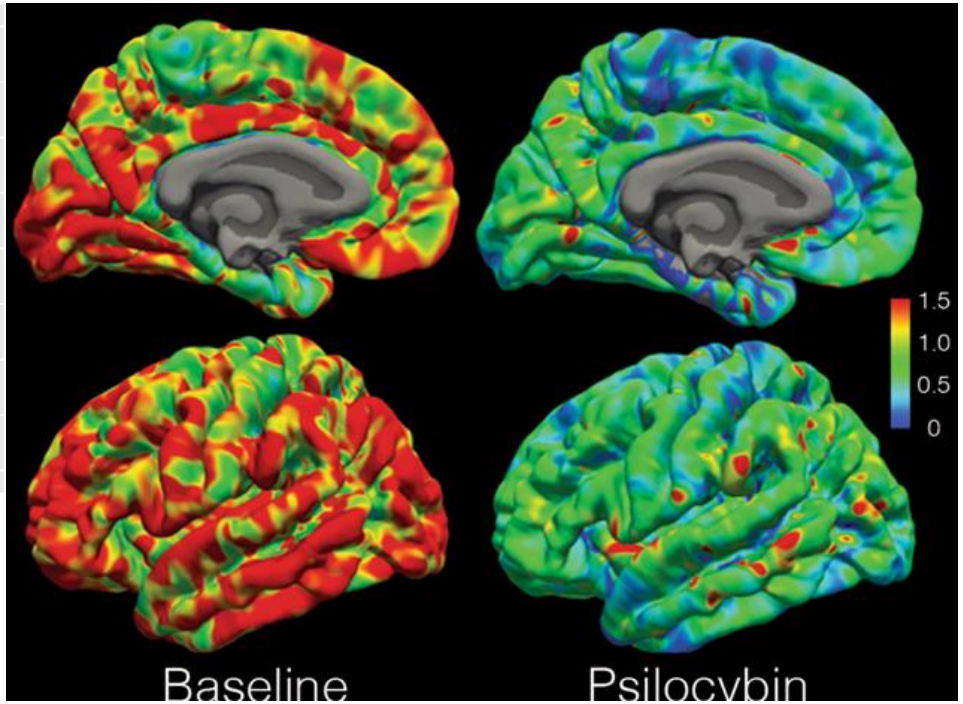
Pharmacology of Psychedelic Drugs

- Potent agonist activity @ **5HT-2a/2c** receptors
- Initial sympathetic arousal, followed by the psychedelic experience
- Effects last 4 to 12 hrs for most (DMT 30 min)
- Exhibit tolerance & cross tolerance
- No withdrawal symptoms, no physical dependence
- No deaths (due to direct physiological effects) even in accidental overdoses
- Chronic use of some antidepressants (SSRI's, TCA's) reduces the psychedelic experience (Strassman, Bonson)

Psilocybin 5HT2 Occupancy

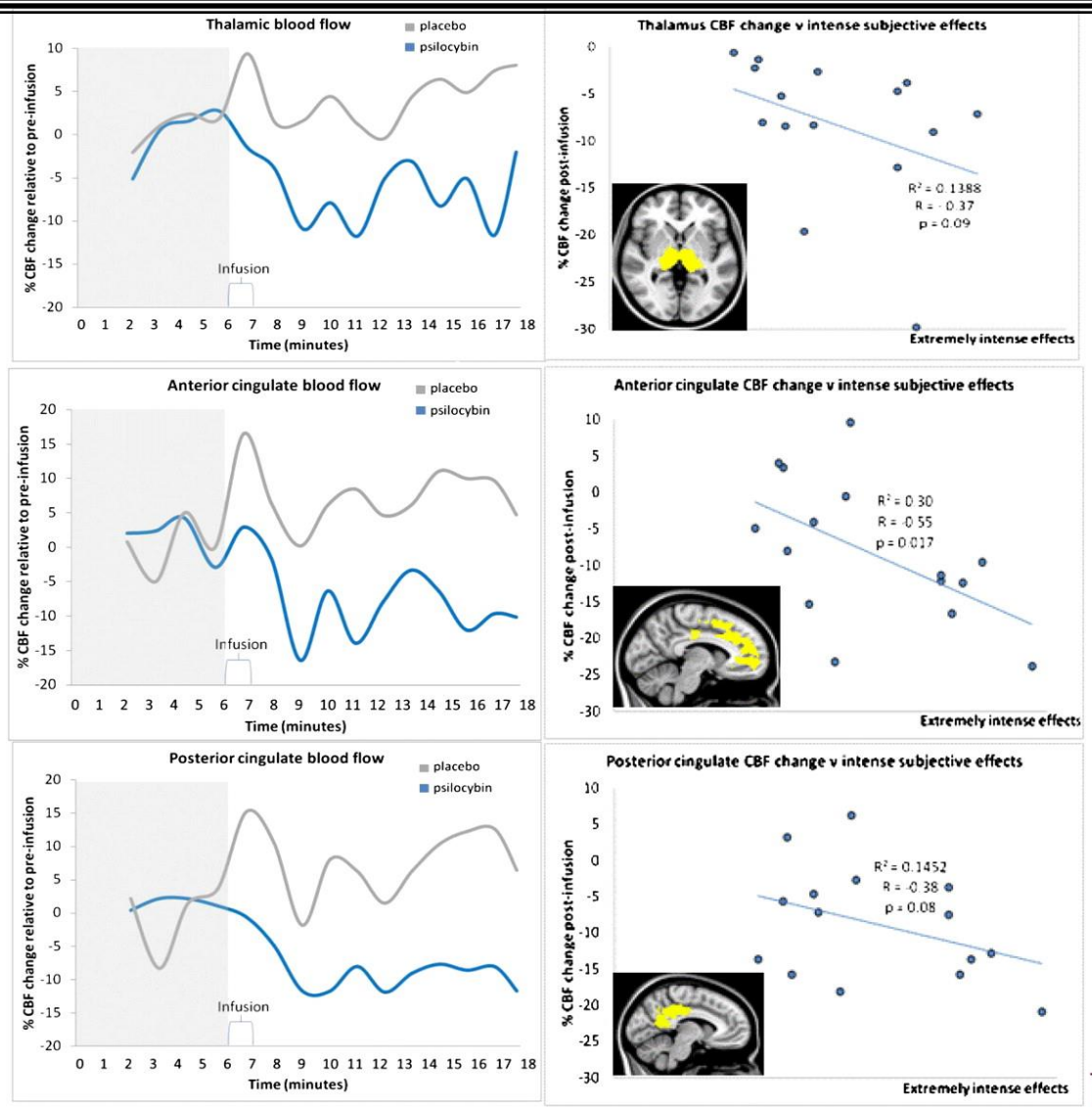






Madsen MK, Fisher PM, Burmester D, et al. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacology. January 2019:1 Correction March 2019 https://doi.org/10.1038/s41386-019-0324-9,

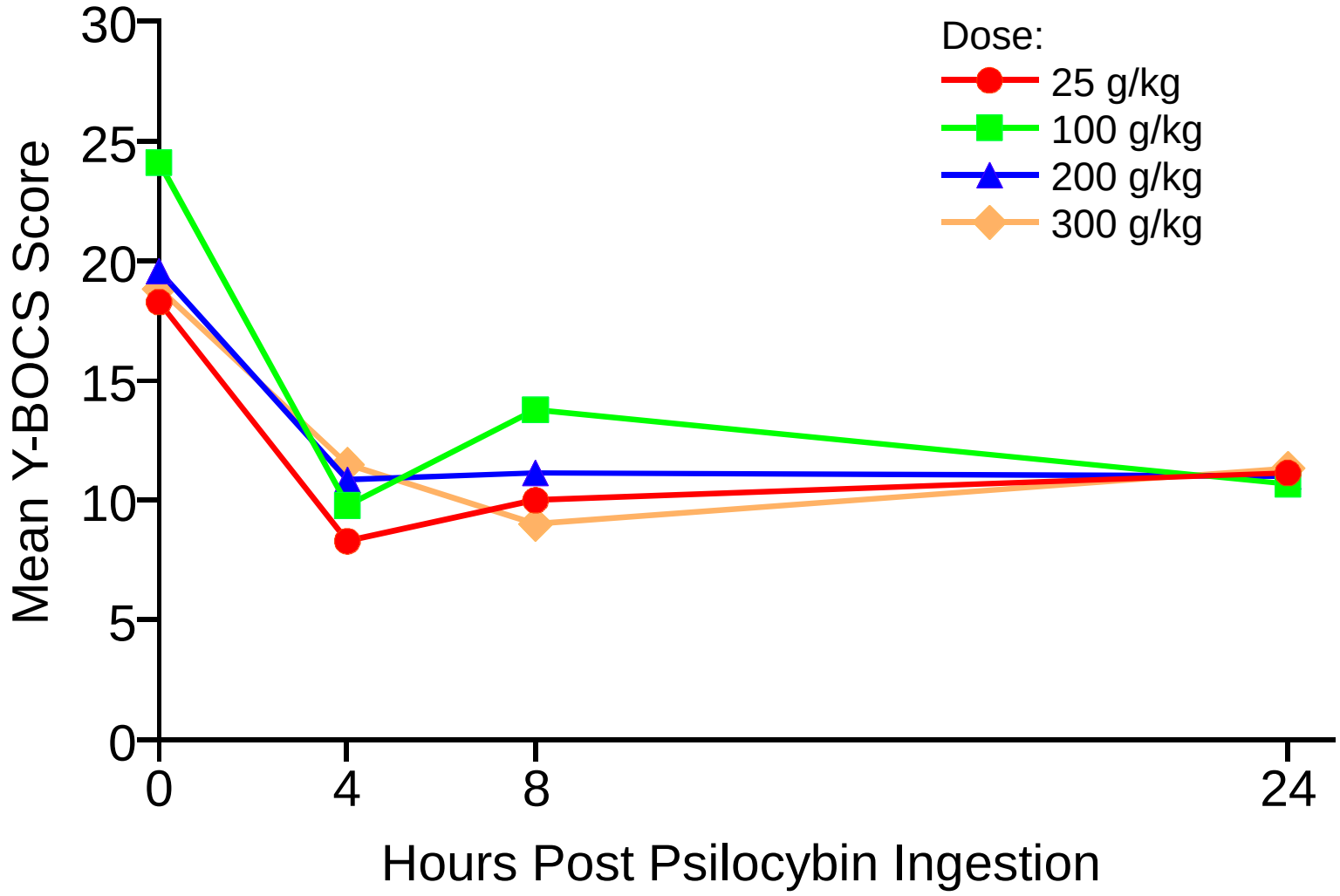
Group CBF changes over time (Left) and CBF vs. subjective effects (Right)

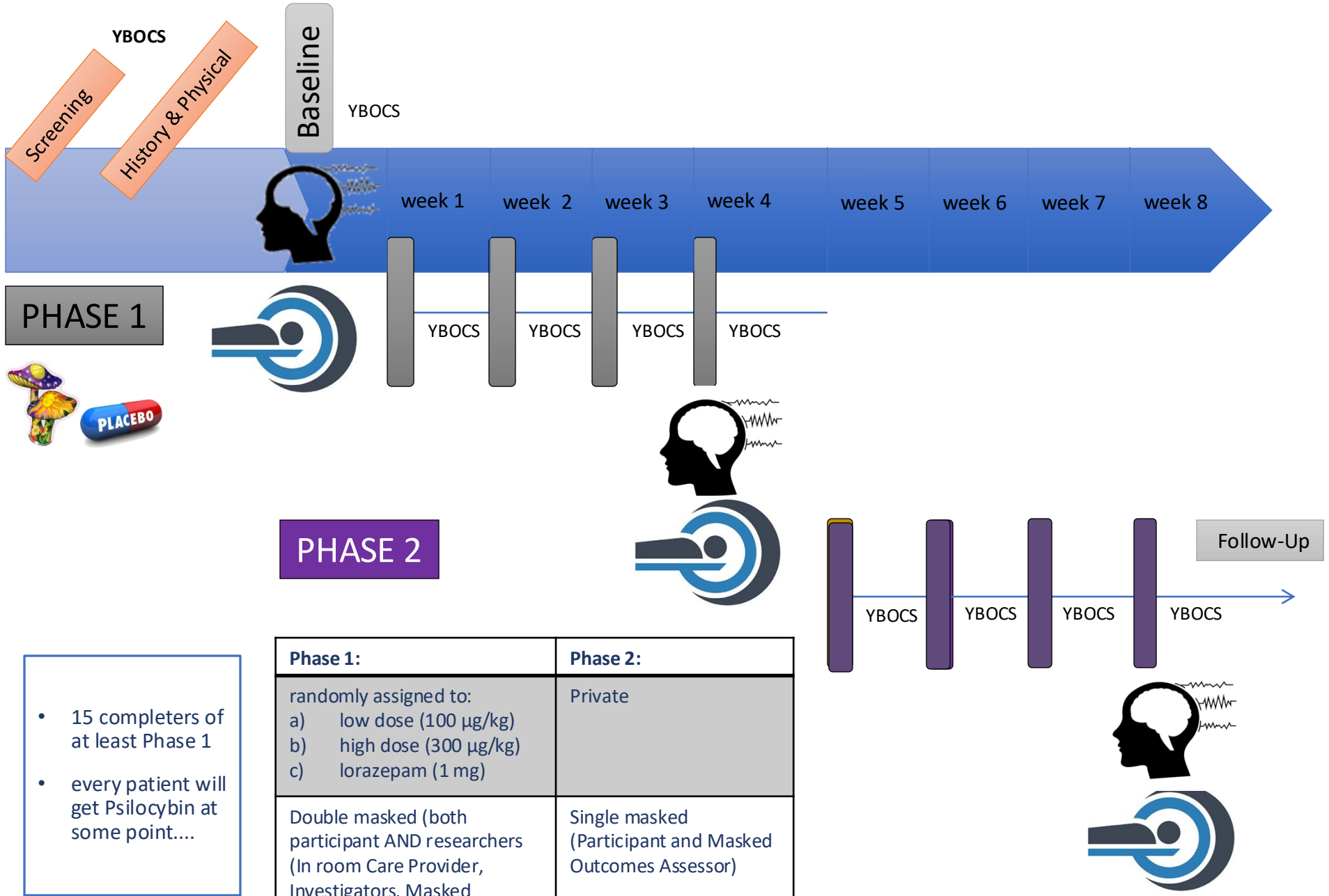


Potential Psychiatric Complications

- Challenging experiences
- Brief psychotic experiences
- DTS / DTO
- Insomnia when used at night, and REM rebound.
- Flashbacks
- Depressive mood swings after exposure
- Prolonged psychotic reactions

Effects of Psilocybin on Symptom Severity





- 15 completers of at least Phase 1
- every patient will get Psilocybin at some point....

Phase 1:	Phase 2:
randomly assigned to: a) low dose (100 µg/kg) b) high dose (300 µg/kg) c) lorazepam (1 mg)	Private
Double masked (both participant AND researchers (In room Care Provider, Investigators, Masked Outcomes Assessor)	Single masked (Participant and Masked Outcomes Assessor)

Safety and Tolerability

- Psychotic Symptoms
  - SCID Psychotic Screen: Baseline vs. after each Session (24h): NONE

- Suicidality
  - CSSRS: Baseline vs. End of each Session: NO increase

Baseline	13.3%
Placebo Sessions	5%
Low-Dose Sessions	5%
High-Dose Sessions	5%

- Bloodwork
  - complete blood count (CBC) and Comprehensive Metabolic Panel (CMP): Baseline vs. Session 4 and Session 8: NO significant change in any variable

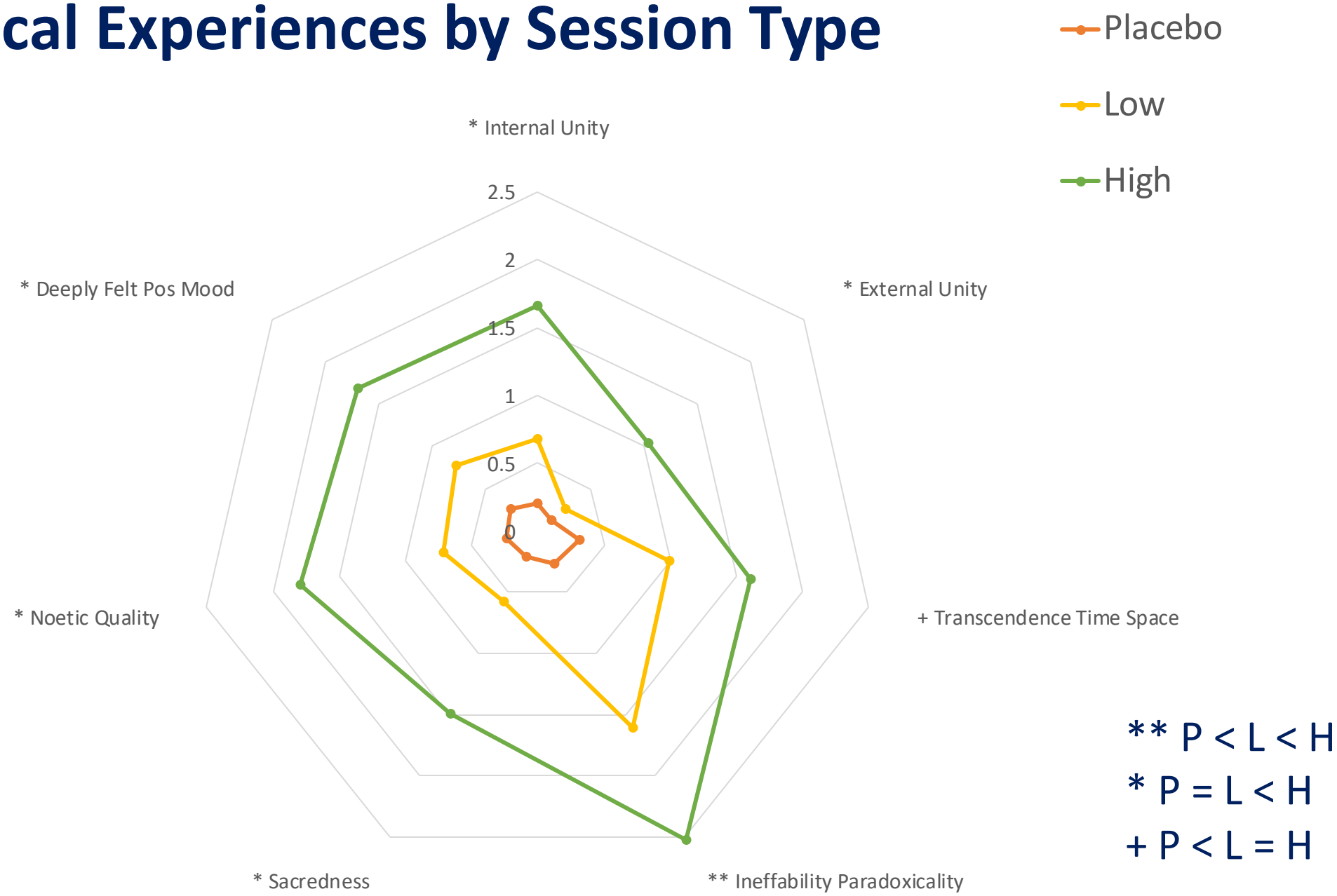
Safety and Tolerability

Adverse Events (SAFTEE)

	High Dose	Low Dose	Placebo
GI symptoms:			
Abdominal Pain	3	1	1
Diarrhea	2	1	1
Nausea	3	2	2
Vomiting	1	0	0
Decreased appetite	4	2	1
Increased appetite	2	1	2
Non-specific symptoms:			
Headache	3	1	4
Itching	2	0	1
Rash	0	0	1
Decreased libido	0	0	1
Missed menses	1	0	0
Muscle tension (neck)	1	0	0
Photophobia & Hyperacusis	1	0	0

	High Dose	Low Dose	Placebo
CNS symptoms:			
Dizziness	2	2	1
Fatigue	5	4	3
Somnolence	1	0	0
Impaired attention	0	1	1
Nervousness/Anxiety	5	1	2
Aggression	1	0	0
Depression	4	3	2
Insomnia	4	2	2
Elevated Mood	1	2	1
Euphoric Mood	1	0	0
Feeling Drunk	1	0	1
Feeling Hungover	1	1	2
Feeling of Relaxation	3	2	1

Mystical Experiences by Session Type

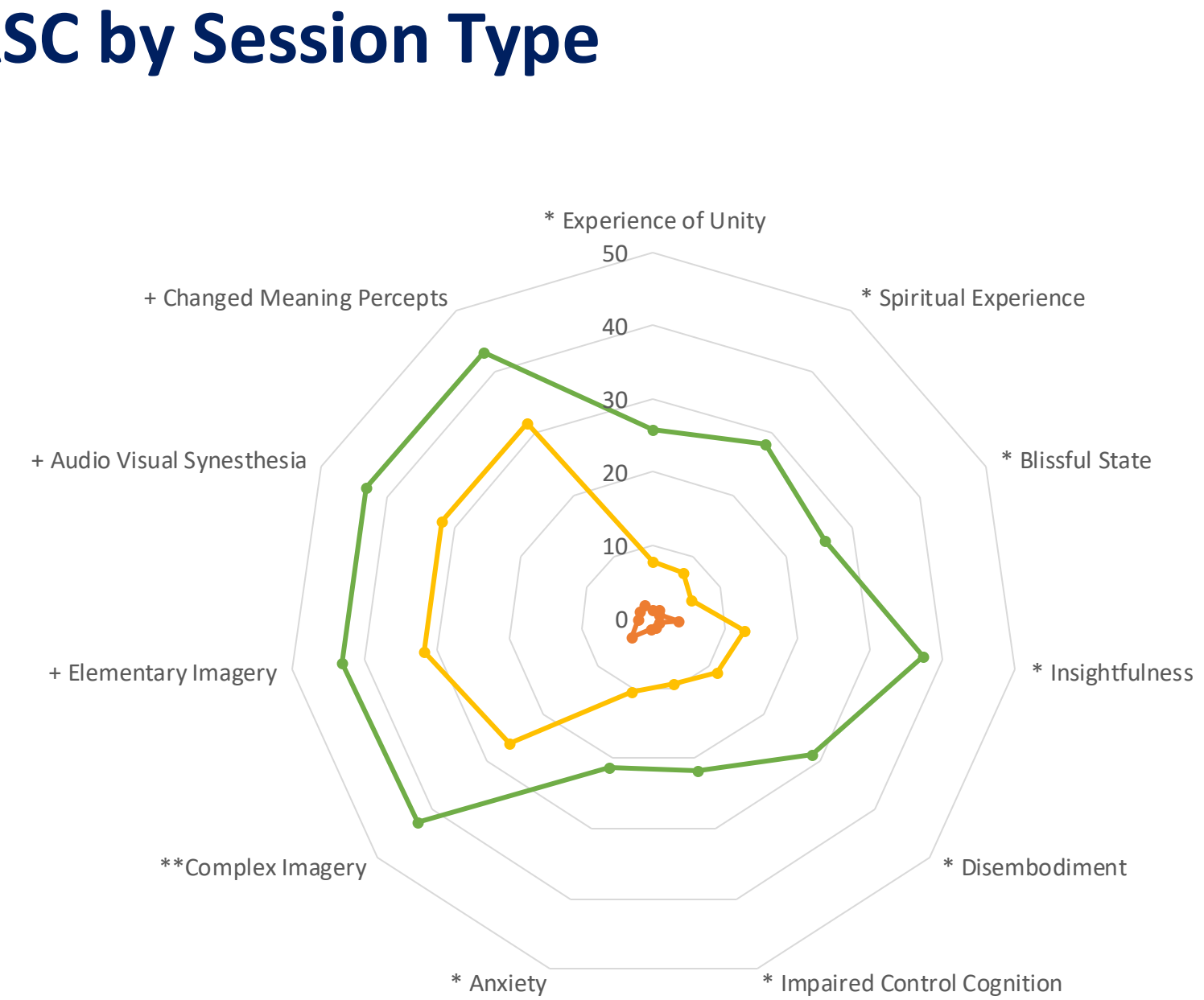


** P < L < H

* P = L < H

+ P < L = H

5D-ASC by Session Type

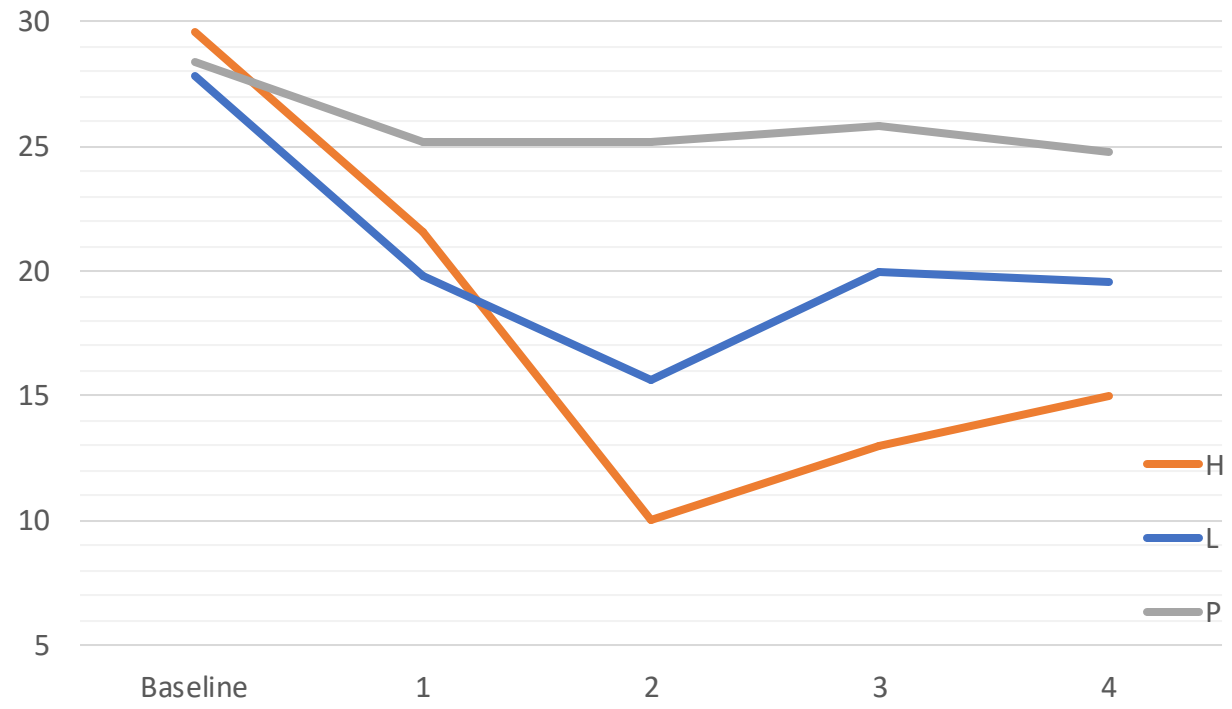


** P < L < H

* P = L < H

+ P < L = H

YBOCS Scores by Condition
Day After Session

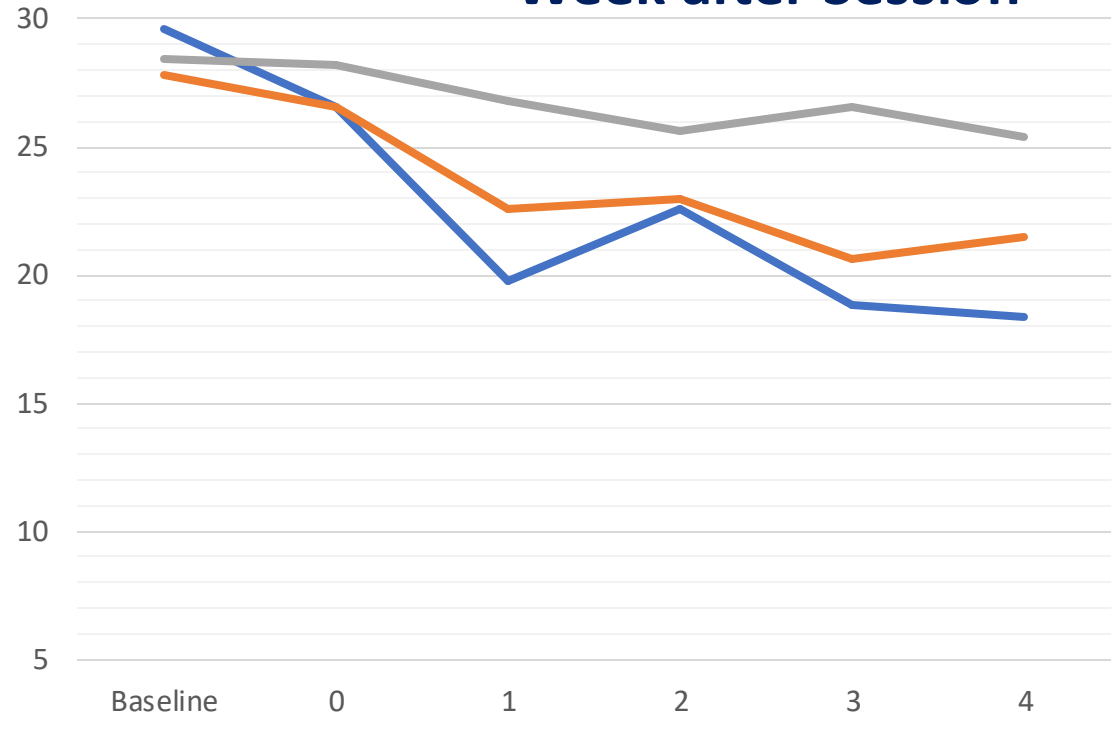


Baseline, and Morning after each session corresponding to Phase 1 (RCT). No interaction (p=.37) low power), but…

Group effect p = .007 : High = Low < Placebo

Effect of time within group
High: *p* = .030
Low: *p* = .206
Placebo: *p* = .582

YBOCS Scores by Condition
Week after Session

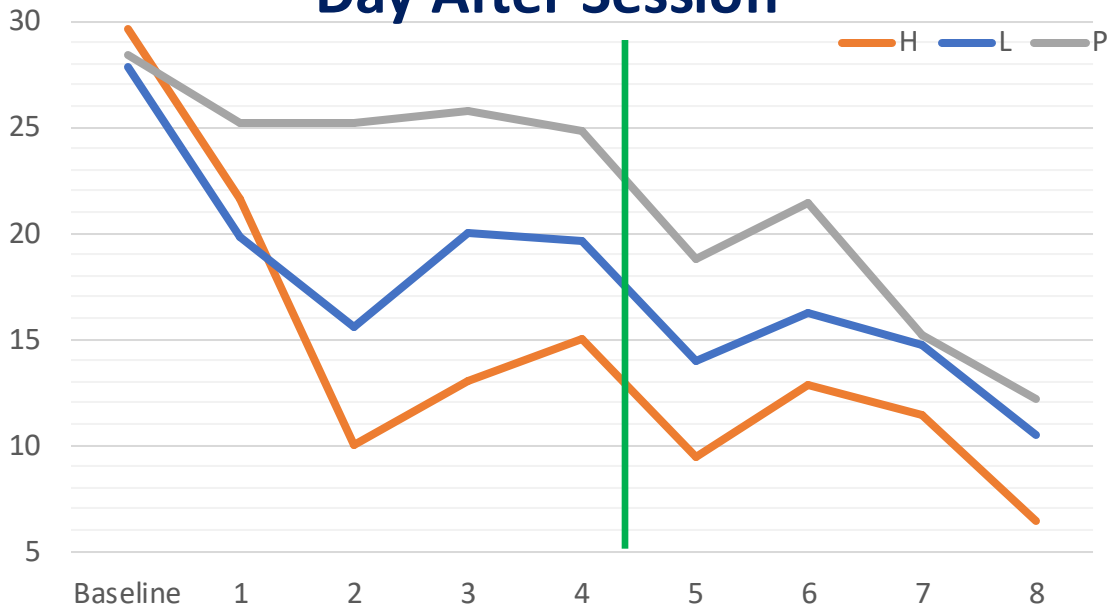


Baseline, and start of each week corresponding to Phase 1 (RCT)

No interaction (low power), but…

Effect of time within each group
High: *p* = .064
Low: *p* = .427
Placebo: *p* = .303
Pooled high and low: *p* = .044

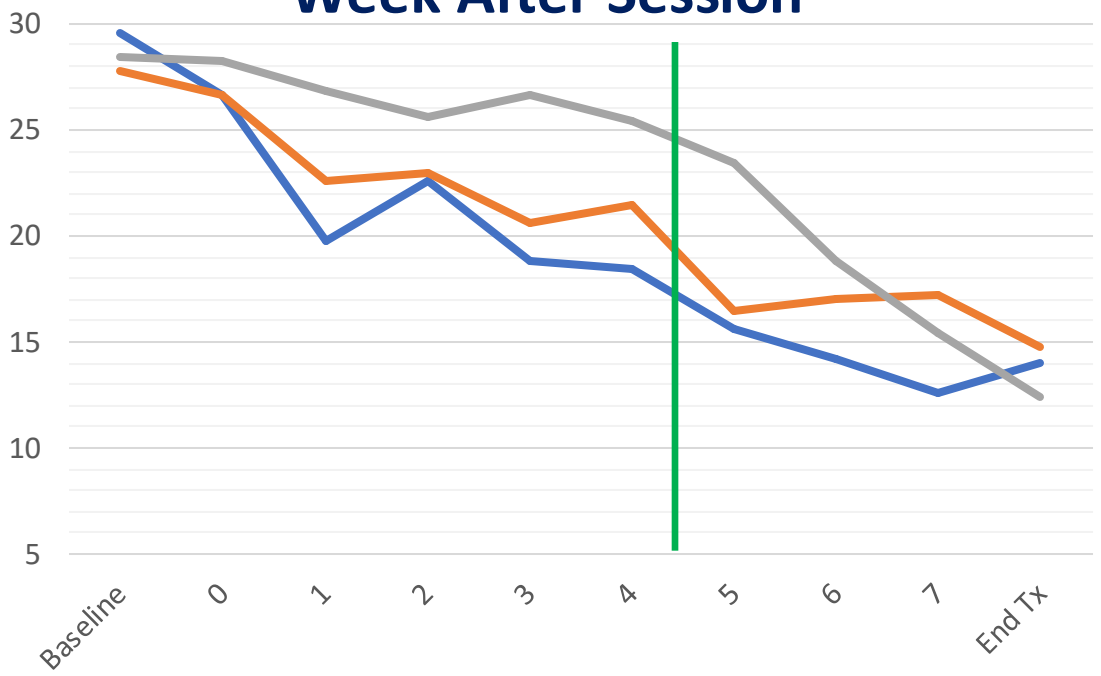
YBOCS Scores by Condition
Day After Session



Baseline, and Morning after each session

Significant change over time $p < .001$
Group effect $p < .001$)
Interaction ns ($p = .811$)

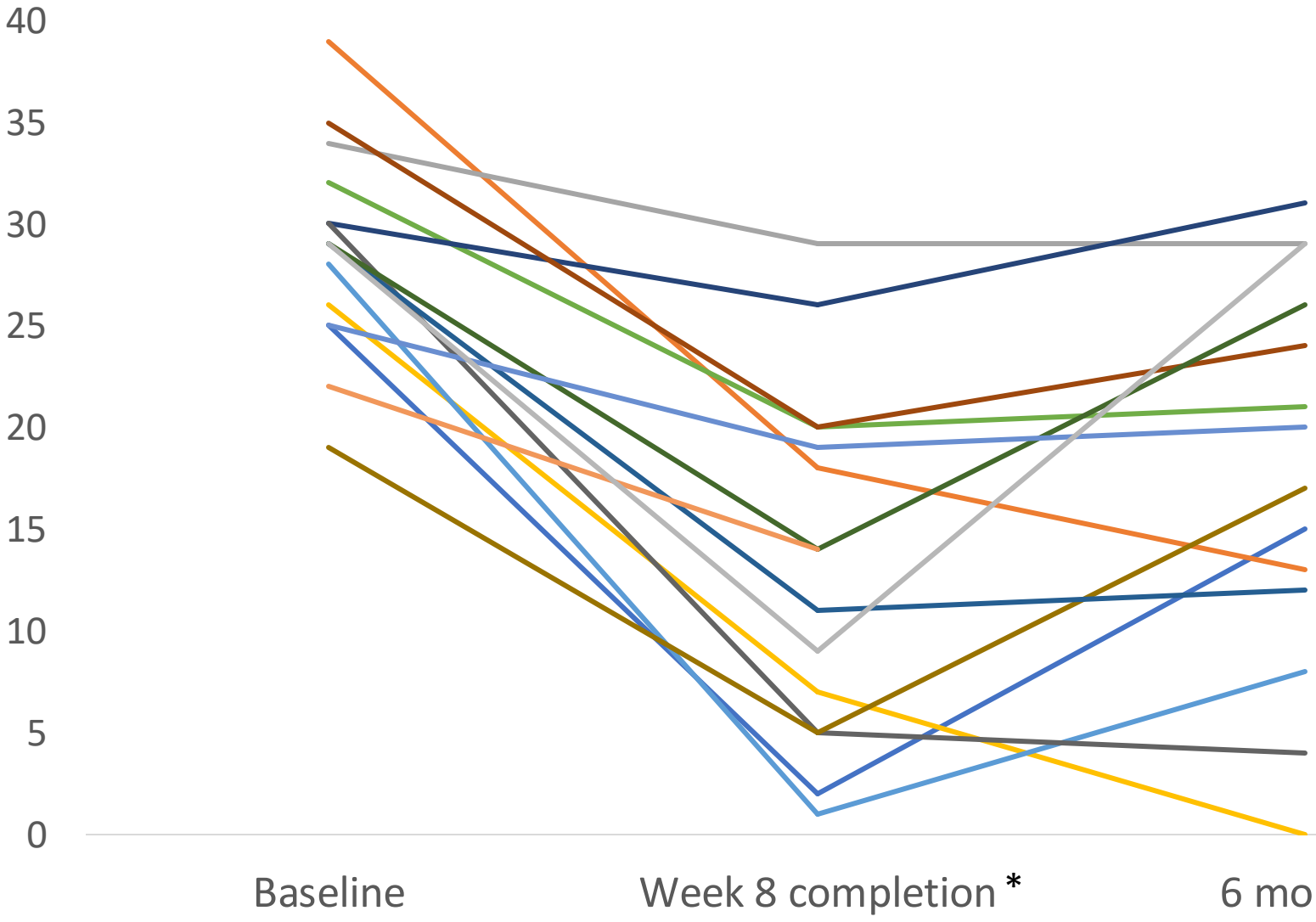
YBOCS Scores by Condition
Week After Session

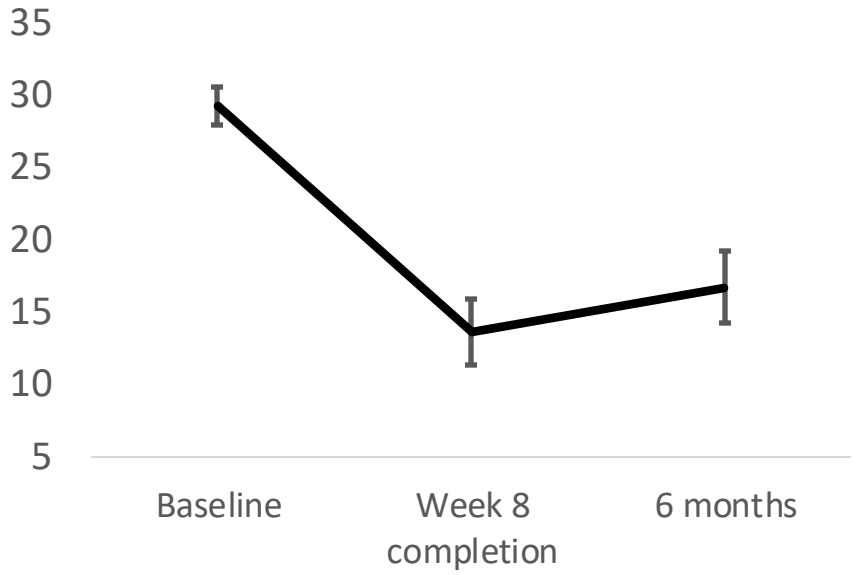


Baseline and Week after each session

Significant change over time $p < .001$
Group effect ns ($p = .084$)
Interaction ns ($p = .99$)

YBOCS Severity Scores by time





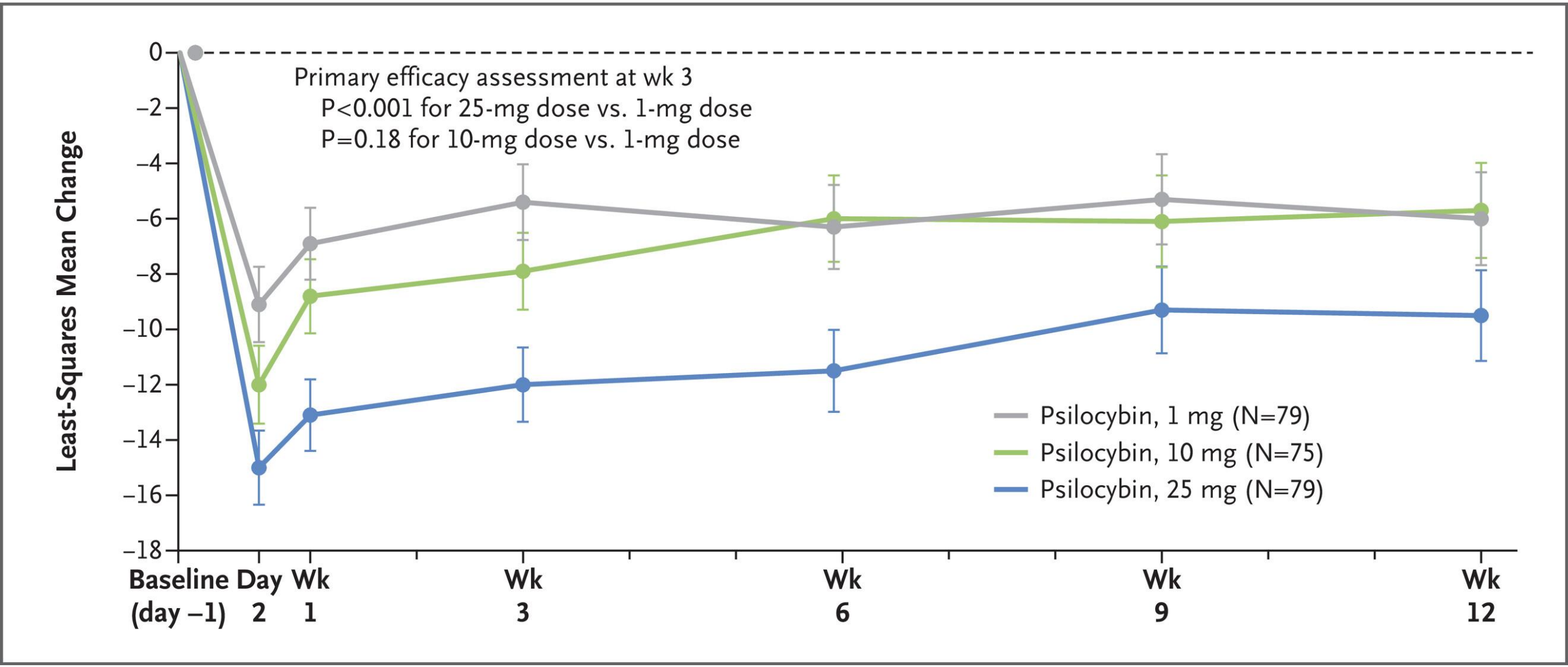
	Remission YBOCS < 12	Response > 35% Reduction	Response > 25% Reduction
End of Treatment	40.0%	73.3%	80.0%
6-month follow-up	20.0%	53.3%	66.7%

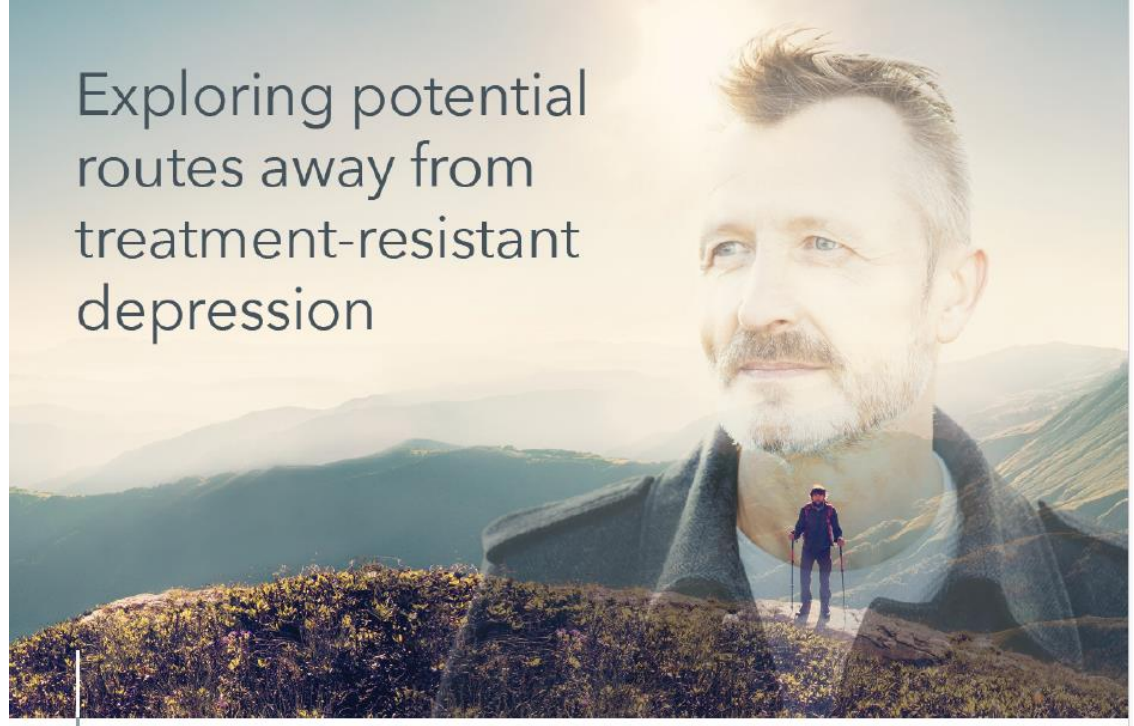
*YBOCS Scores taken 1 week after each session

Summary of Outcomes at 8 Weeks

- 9 subjects who completed 8 weeks of study achieved categorical remission (YBOCS < 12)
- 11 participants who completed 8 weeks of study achieved a response of 35% or greater drop in YBOCS.
- 12 subjects who completed 8 weeks of study achieved a response of 25% of greater drop in YBOCS.

Psilocybin for Treatment of Depression
Change from Baseline in MADRS Total Score
(Modified Intention-to-Treat Population). Goodwin et al., 2022 NEJM





Exploring potential routes away from treatment-resistant depression

Introducing the COMP 005 Study

Learn more about a study looking at a new investigational treatment approach for treatment-resistant depression using an investigational medicine alongside psychological support.

You may be able to join the study if you:

- Are 18 years of age or older
- Have been diagnosed with major depression and have not responded to antidepressants

Other criteria will need to be met to confirm your eligibility for this study, which will last up to 62 weeks.

Study participants receive investigational treatment and follow-up care at no cost. Travel and study-related costs may be reimbursed.

You can find out more by talking to your local study center or visiting www.compasspathfinderstudies.com.

Contact us to find out more:

(520) 626-8000

COMP 005

COMP 005 Flyer_V3.0_17NOV2023

COMPASS

From: **Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial**

JAMA. 2023;330(9):843-853. doi:10.1001/jama.2023.14530

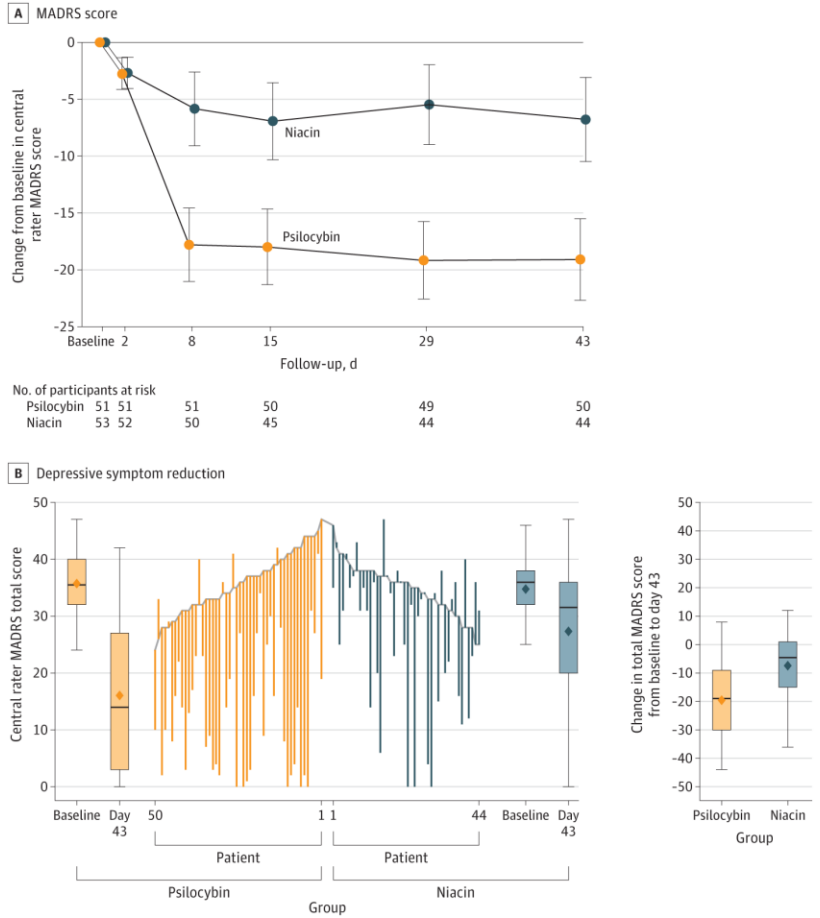
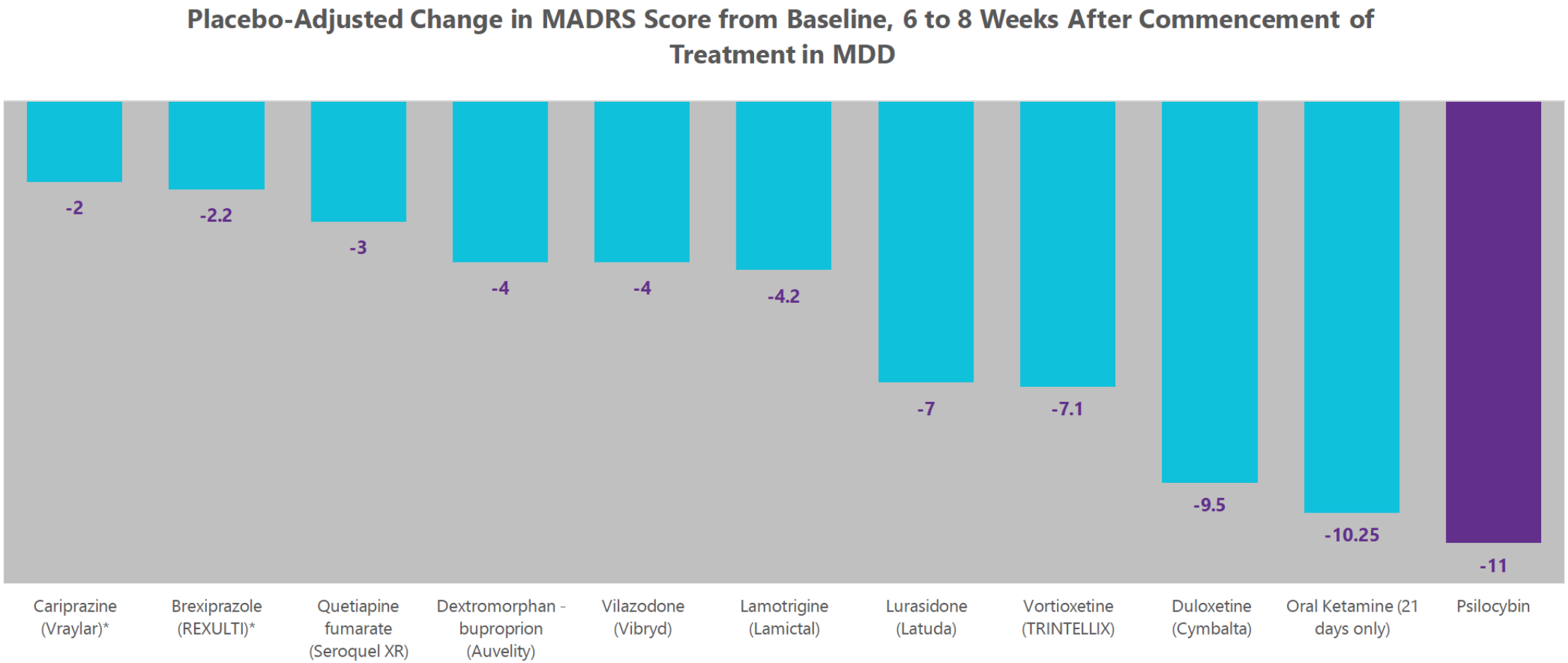


Figure Legend:

Change in Montgomery-Asberg Depression Rating Scale (MADRS) Score by Treatment Group A, Results from mixed model for repeated measures adjusted for baseline score, site, sex, and treatment-resistant depression. Error bars represent 95% CIs; point labels are P values for treatment difference for primary (day 43) and key (day 8) secondary end points in the intent-to-treat population. B, Raw value participant change values with means indicated with diamonds and medians indicated by the bar in the boxes. The boxes show the IQR and the whiskers extend from the boxes to indicate the most extreme point that is less than or equal to 1.5 times the IQR. See eFigure 2 in Supplement 3 for additional details.

Psilocybin has been shown to produce durable and unprecedented rapid efficacy in a single dose outperforming currently approved chronic treatments



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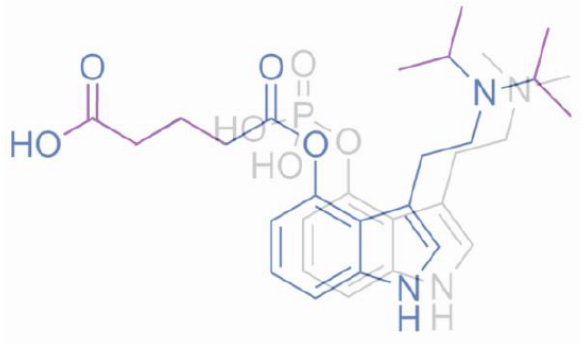
Sources: https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.20220504, https://www.sciencedirect.com/science/article/pii/S0165032717307942, https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.21080800, https://www.psychiatrist.com/jcp/depression/efficacy-safety- vilazodone-major-depressive-disorder/, https://www.researchgate.net/figure/MADRS-total-score-over-8-weeks-of-double-blind-treatment-with-lamotrigine-titrated-to_fig2_342047532, https://www.medscape.org/viewarticle/864387_transcript_2, https://pubmed.ncbi.nlm.nih.gov/24257717/, https://pubmed.ncbi.nlm.nih.gov/30246667/, https://jamanetwork.com/journals/jama/fullarticle/2808950

RE104's Structure and Pharmacological Profile is Similar to Psilocybin

Chemical Structure



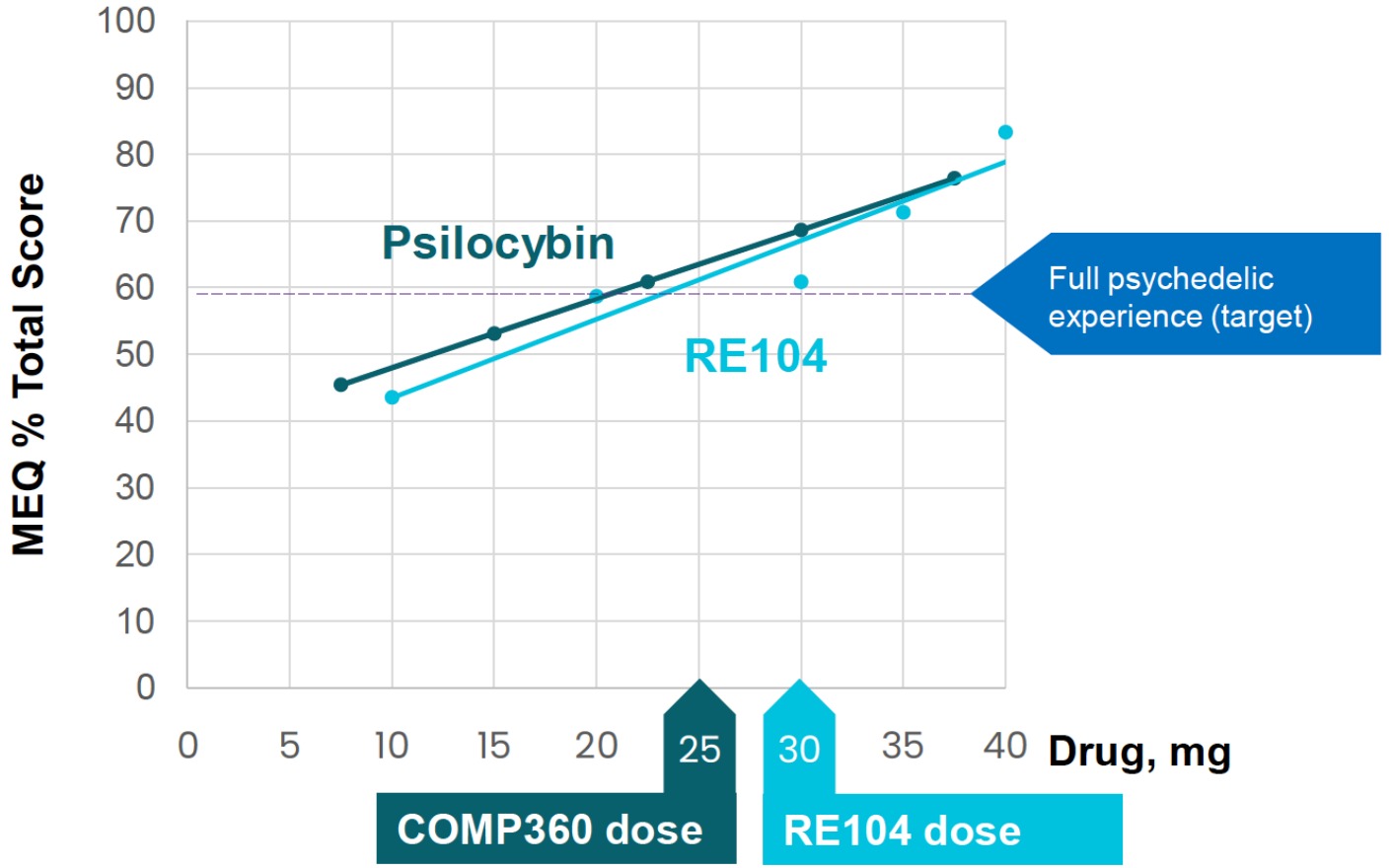
Psilocybin	RE104
110 nM 4-OH-DMT	**120 nM** 4-OH-DiPT

Relative Binding Constants*

nM, nanomolar

* Relative binding 2A normalized, produced internally from various sources, including PDPS (B Roth), Klein 2020 *ACS Pharmacol* and Rickli 2016 *Eur Neuropharmacol*

RE104 MEQ Dose Response Parallels Psilocybin



RE104 achieves target MEQ response (>60%) in a majority of subjects at a tolerable dose of 30mg

Removed 0 and 5mg doses because of sigmodal nature at low dose/low plasma levels (see slide 24)

Minimum Requirements to Participate

You may be eligible to join this study if:

- You are a female 18 to 45 years of age
- You had your baby sometime in the last 12 months
- You are experiencing signs of depression
- You have a caretaker who can look after your baby during the Dosing Session and for 24 hours after dosing

This is not a complete list of study requirements. The study staff will explain the complete list of requirements.

Costs and Expenses

There is no charge to participate in the research study. Participants who satisfy applicable requirements will be compensated for study-related time and expenses. Please ask the study staff for details.

Risks and Benefit

All drugs and medical procedures carry a risk of side effects. Therefore, it is possible that participants may experience some discomfort or other reactions from the use of RE104 (the study drug) or from the study procedures or tests. The study staff will explain these risks before potential participants decide whether to participate in the study. The safety of participants will be closely monitored throughout the study.

The information learned from this study may help find treatment options in the future for women suffering from postpartum depression. Participants will help contribute to the research of RE104. There is no guarantee that study participants will receive any direct benefit from their participation.

Next Steps

If you are interested to learn more about this study, please contact us using the information on the back of this brochure. If you contact us, you will not be obligated to participate in this study. Participation is entirely voluntary. Should you qualify for participation and decide to participate in the study, you may stop your participation at any time with no adverse impact to the care you receive outside of the study.

For more information about this research study, please contact:

HAVE YOU HAD A **BABY** IN THE LAST **12 MONTHS**?

Are you experiencing symptoms of **depression** such as **sadness**, **anxiety**, or feelings of being **overwhelmed**?

If so, you may have **postpartum depression**. Find out if participating in our medical research study of a new single-dose investigational drug for postpartum depression may be an option for you.

RECONNECT | Phase 2 Clinical Trial

Version: 06-06-24-v2

Summary

- Findings suggest promise of Psilocybin for the acute and durable treatment of certain mental health conditions
- In the context of supervised clinical research, psilocybin appears to be well-tolerated
- Results support the merit of larger clinical trials


THANK YOU