

# Psychedelics and Mood Disorders

August 20, 2022

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Mood Disorder Day

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## Conflict of Interest 2021-2022

- Conducting Investigator Initiated study with Compass Pathways on severe treatment-resistant depression
- Zylorion serves on Scientific Advisory Board, (Stock Options)

Special thanks to Giani Glick, MD., Founder of the Stanford Psychedelic Science Group for his slides showing the history of psychedelics and chemical formulation.

Thanks to Boris Heifets, MDPhD., for slides showing recent clinical studies .

# Today

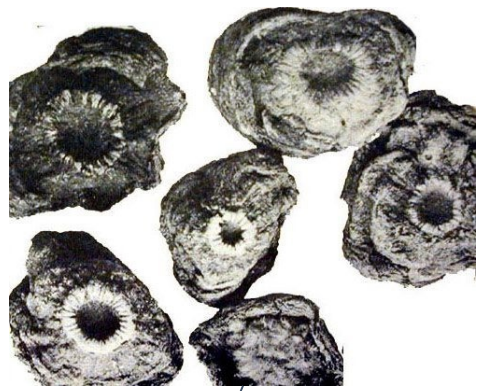
History of psychedelics

Use of psilocybin in patients with terminal illness

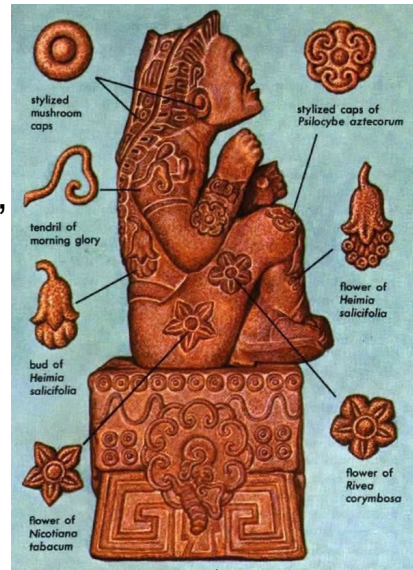
Recent Findings in depression

Stanford – VA Collaboration studies

Questions

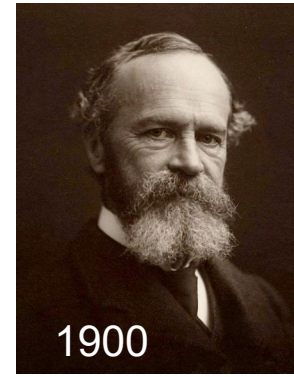


Aztec  
'Teonanacatl'  
~1400



~3700 BC

Peyote,  
Shumla Caves  
Texas



"Our normal waking consciousness, rational consciousness as we call it, is but one special type of consciousness, whilst all about it, parted from it by the filmiest of screens, there lie potential forms of consciousness entirely different" William James

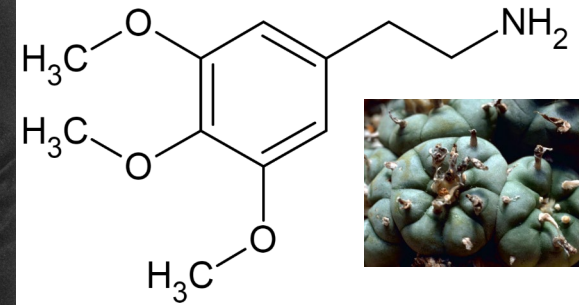


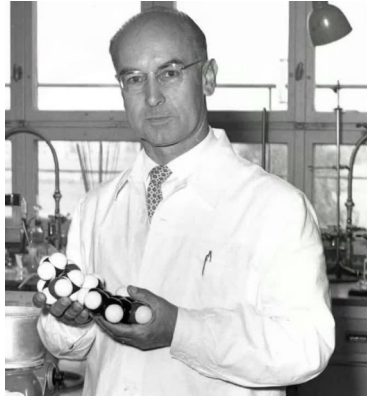
Kykeon  
Eleusinian  
Mysteries

Mayan  
mushroom  
stones  
~1000 BC



Arthur Heffter chemist





The Veterans Administration hospital in Palo Alto

# THE STANFORD DAILY

BUSINESS, DA 7-4150

STANFORD, CALIFORNIA, TUESDAY, JANUARY 31, 1967

## LSD And Creativity

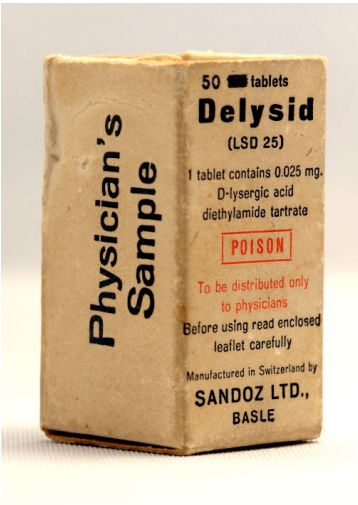
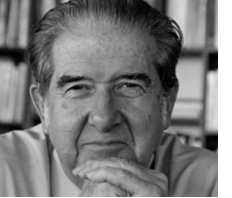
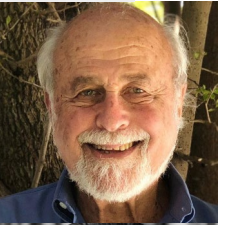
"Given appropriate conditions, the psychedelic agents can be employed to enhance any aspect of mental performance." — Dr. Alexander Leary

### We Need 'Hippies'

"When you realize that the other person is you, you don't kill him or even mistreat him. The Golden Rule works that way, not through enforcing it. It just happens." — Dr. Alexander Leary

Herbert and James Fadiman as a result of a study of psychedelic drugs and problem solving. The study involved experiments with professional people who worked various complicated problems after having taken a psychedelic drug (mescaline and psilocybin). "While this research was not related to intellectual and artistic activity, we believe the relaxation built into the other mental, perceptual or emotional process. The psychedelic agent acts as a facilitator... by itself neither good nor evil, relaxation for persuasion is not dangerous." The subjects of the experiment produced, among other things, a new conceptual model of a bicycle, a design of a laser spectrum analyzer from scratch, a new mathematical theorem regarding finite game circuits, and several innovations in architecture and design. Most of the subjects reported that their problem-solving and creative capabilities were relaxed and enhanced under the

influence of the psychedelic drug. The report of the study, soon to be published, explains: "The psychedelics appear to temporarily inhibit the mental elements coming into conscious awareness. Thus the subject may, for example, discover his latent ability to form colored images, to hallucinate, to recall forgotten experiences of early childhood, to generate musical and symbolic representations, etc." In work performance areas the subjects have shown significant or marked improvement in problem-solving capability. "Among consequences of this line of exploration, the most significant of all in our estimation is the gaining of new knowledge of the capacities higher processes of the human mind, the founding of new and more productive research questions, and the crucial effect on our sense of man—of what he can be, and what he is; of the vast possibilities which he has actually only begun to tap."



# ERA of Psychopharmacology!

- Humphry Osmond - idea of LSD therapy thinking could simulate Delerium Tremens - “rock bottom” (after which some alcoholics get better) - but found that the patients had deeply positive experiences instead,
- Thorazine discovered 1952, first trial in the 60s; imipramine (first antidepressant) also discovered 1952
- Tremendous breakthrough at the time

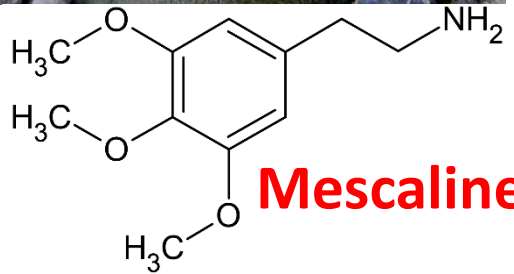
# What are Psychedelics?

- Psychedelics - class of psychoactive drugs that trigger non-ordinary states of consciousness (psilocybin, LSD, peyote)
- Primary mode of action - via serotonin 2A receptor agonism
- The psychedelic experience - compared to altered states of consciousness: meditation, mystical or near-death experiences
- A sense of ego dissolution may be key to treatment response
- Considered to be non addictive and physiologically safe

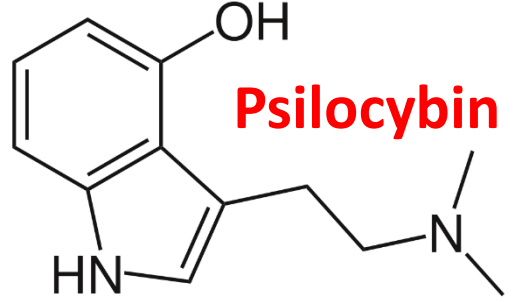




**Phenethylamine**



**Mescaline**

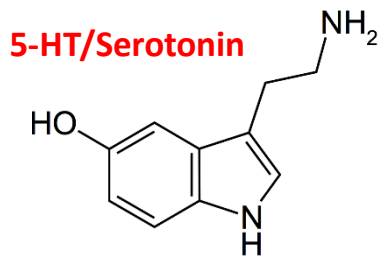


**Psilocybin**

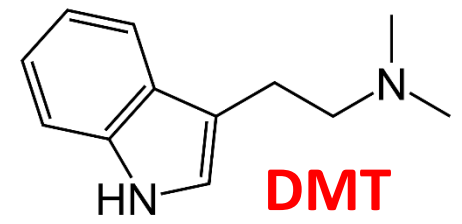


**Tryptamines**

# CLASSICAL PSYCHEDELICS



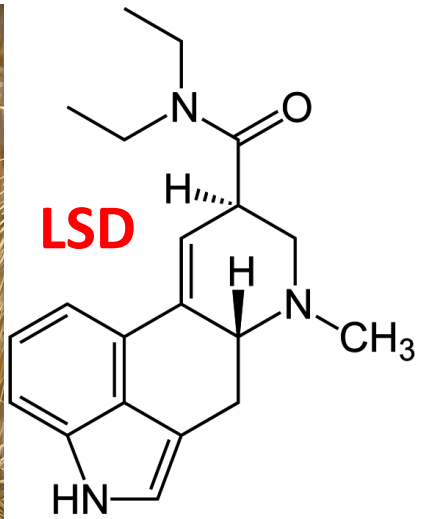
**5-HT/Serotonin**



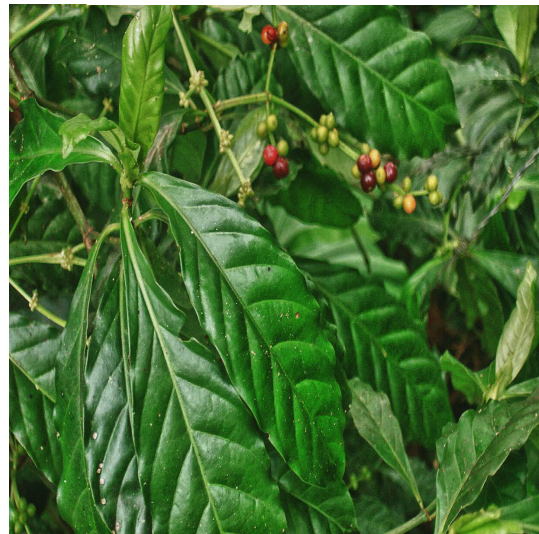
**DMT**



**Ergolide**



**LSD**



# Timing is everything!

- Why now?
- Field stalled
- Despair up
- Hope matters

2017 - 2021

- Breakthrough status by FDA for MDMA (“ecstasy”) treatment of PTSD
  - Both Phase 3 studies completed
  - Next step apply for FDA Indication
  
- Breakthrough status granted by FDA for psilocybin treatment of Depression
  - First Phase 2 study completed
  - Phase 3 starting in 2023

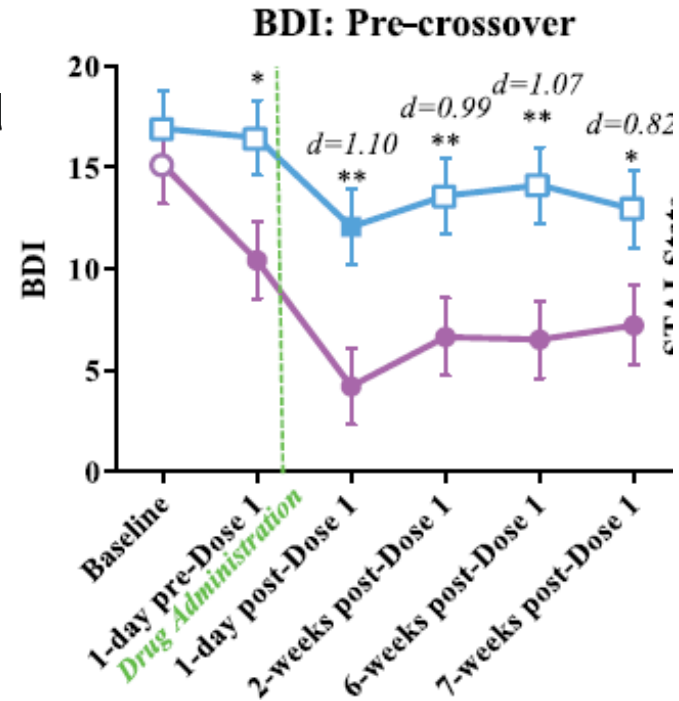
# Psilocybin studies in terminal illness

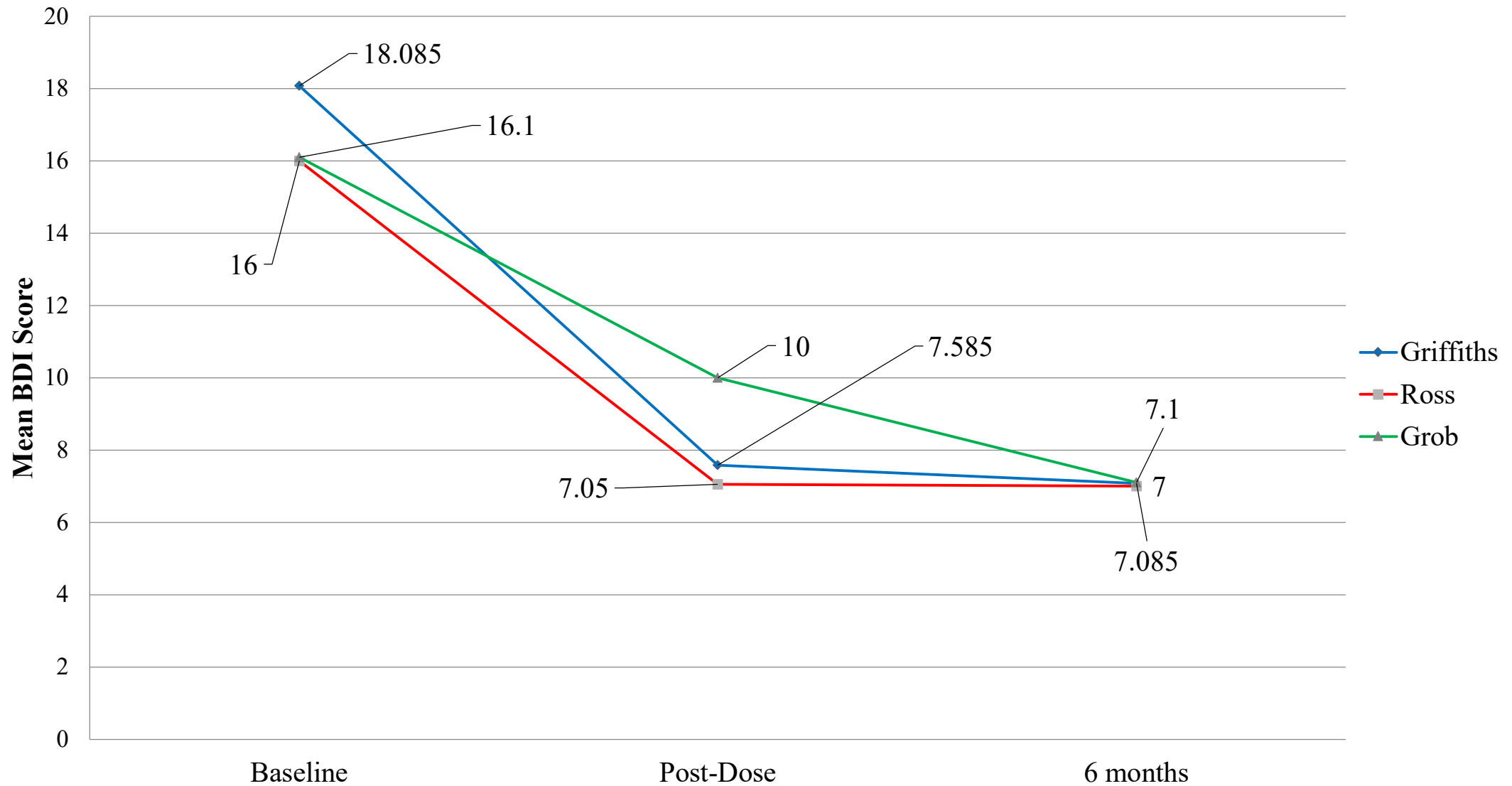
- Earliest modern use
- Target existential depression and anxiety associated with diagnosis
- Three randomized blinded trials: Grob et al 2011; Griffiths et al 2016; Davis et al 2016

## Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial

Stephen Ross<sup>1,2,3,4,5,6</sup>, Anthony Bossis<sup>1,2,4</sup>, Jeffrey Guss<sup>1,2,4</sup>, Gabrielle Agin-Liebes<sup>10</sup>, Tara Malone<sup>1</sup>, Barry Cohen<sup>7</sup>, Sarah E Mennenga<sup>1</sup>, Alexander Belser<sup>8</sup>, Krystallia Kalliontzi<sup>2</sup>, James Babb<sup>9</sup>, Zhe Su<sup>3</sup>, Patricia Corby<sup>2</sup> and Brian L Schmidt<sup>2</sup>

*Journal of Psychopharmacology*  
2016, Vol. 30(12) 1165–1180



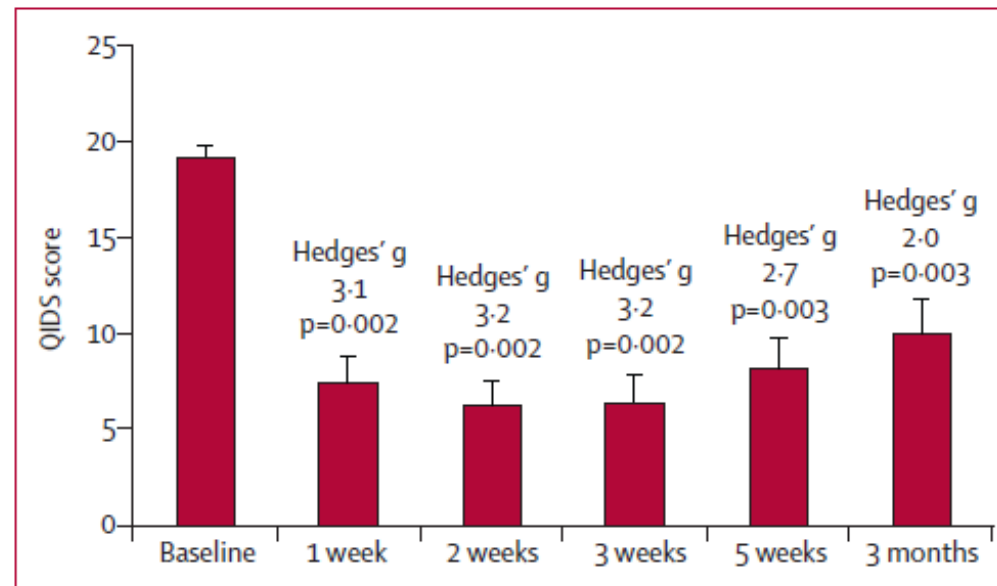


**Figure 3: Beck Depression Inventory scores across three studies.** BDI scores are shown at baseline, 1 day post the first dosing session, and 6 months following the first dosing session. Data is from the Griffiths et al. (2016), Ross et al. (2016), and Grob et al. (2016).

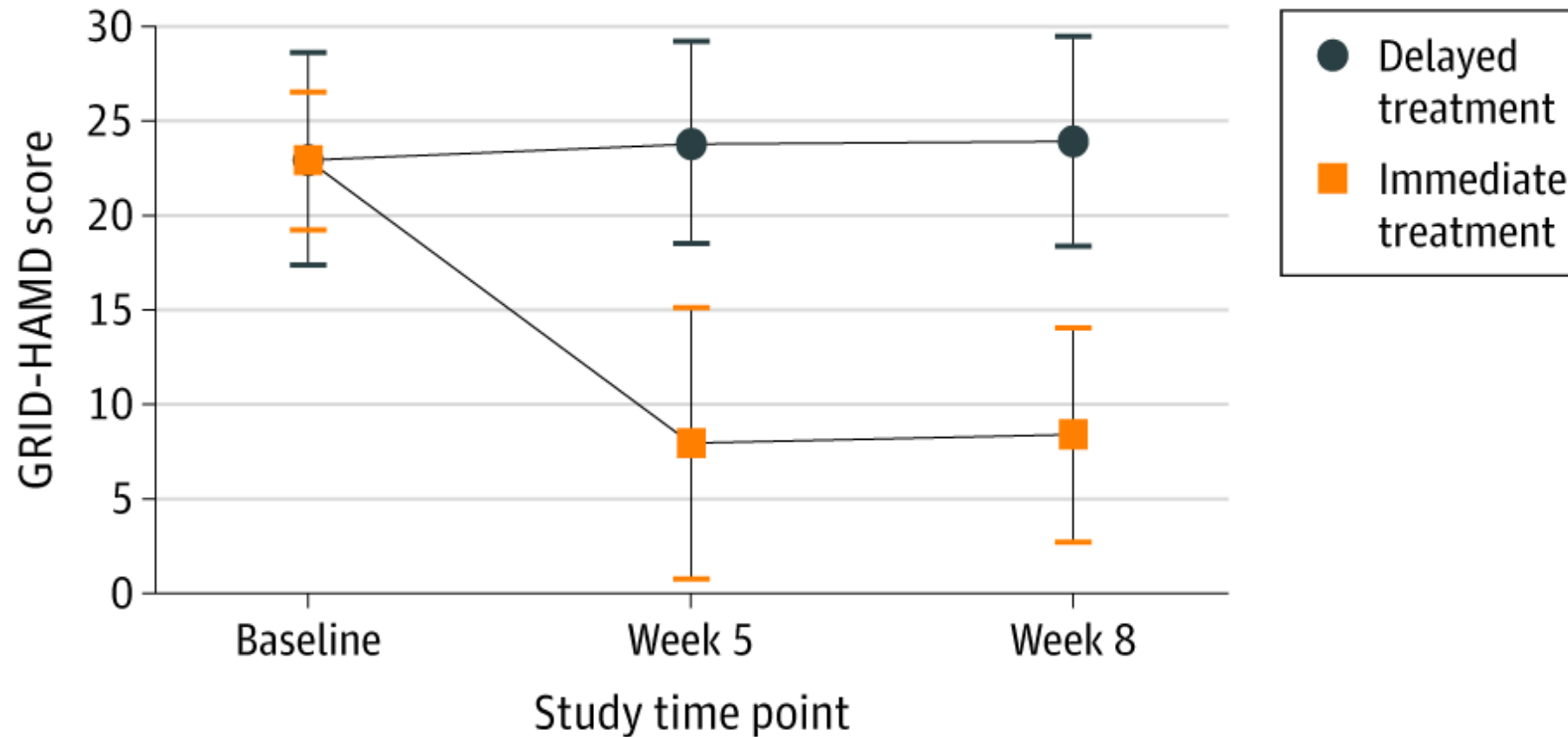
# Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study

Robin L Carhart-Harris, Mark Bolstridge, James Rucker\*, Camilla M J Day\*, David Erritzoe, Mendel Kaelen, Michael Bloomfield, James A Rickard, Ben Forbes, Amanda Feilding, David Taylor, Steve Pilling, Valerie H Curran, David J Nutt

[www.thelancet.com/psychiatry](http://www.thelancet.com/psychiatry) Vol 3 July 2016



# Psilocybin in TRD Davis, JAMA Psychiatry (2021) n=24

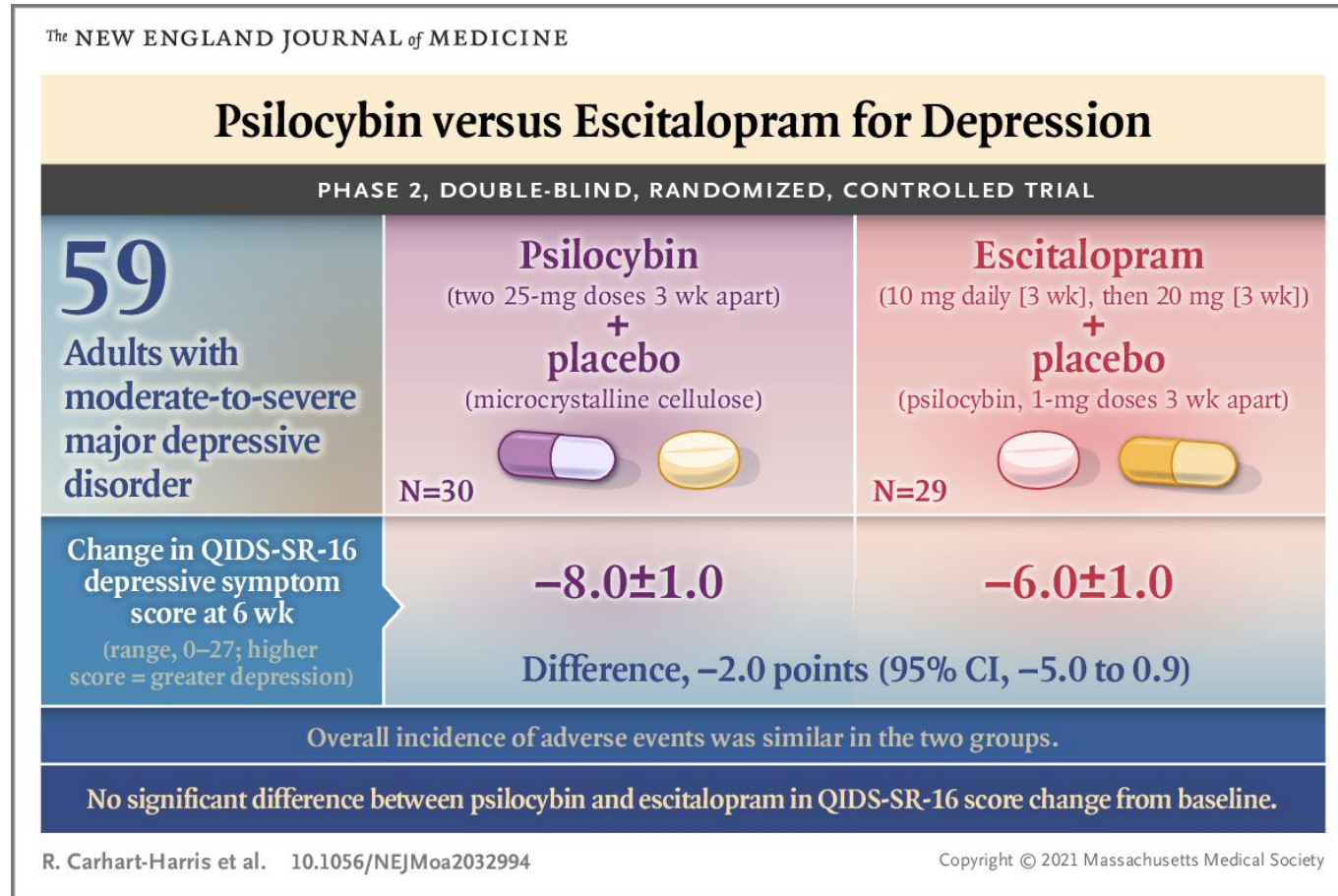




# Psilocybin vs. Escitalopram in MDD (Carhart-Harris 2021 NEJM)

- Randomized comparison of 59 patients randomized 1:1 to either 10, then 20 mg of escitalopram vs **two** 25 mg doses of psilocybin over 6 weeks
- Not a treatment resistant population
- Primary outcome measure was QIDS-SR score at 6 weeks post first dose.
- **No statistically significant difference between the two groups though psilocybin group had an arithmetically greater decrease in score compared to baseline**
- Secondary measures separated, but not adjusted for multiple comparisons

# Carhart Harris et al 2021 NEJM



# What Are We Doing with Psychedelics

- Psilocybin seems to enhance the brain's capacity for change or neuroplasticity (which is diminished across most psychiatric illnesses)
- We are making the brain more receptive to change
- People leave their usual well trod thoughts for a period
- A psychotherapeutic interaction to foster that process may be critical

Largest study to date – results available soon

- Compass Phase 2 study: Double-blinded randomized 1 mg, 10 mg, and 25 mg for moderate Treatment resistant depression
  - Dr. Debattista was a PI for this study

# Safety and Efficacy of Psilocybin in Participants with Severe Treatment-resistant Depression (TRD)

- *Principal Investigators:*
  - Scott Aaronson, MD - Sheppard Pratt Health System, Maryland and
  - Trisha Suppes, MD, Ph.D. - VA Palo Alto Health Care System, Stanford University
- *Rationale:* A recent open-label study of the effects of psilocybin in participants with treatment-resistant depression (TRD) showed rapid significant decrease of depressive symptoms after treatment with psilocybin coupled with psychological support.
- *Participants:* Maryland: TRD n=12 and Palo Alto US Veterans n=15

## Study Definition of TRD

- Participants with TRD are defined as those who meet the DSM-5 diagnostic criteria for single or recurrent episode of major depressive disorder (MDD) **without** psychotic features which have
- **EITHER**
- 1) failed to respond to an adequate dose and duration of **>4 pharmacological treatments for the current episode ;**
- **OR**
- 2) the **duration of the current episode is > 2 years.**

# Investigator Initiated Trial in Severe Treatment Resistant Depression (>4 treatment failures) - *Shepard Pratt*

- 12 patients, open label, single dose study.
- Participants tapered off all psychotropic medication and med free for two weeks before dosing
- Standard dosing prep, dosing session, 2 to 4 integration session

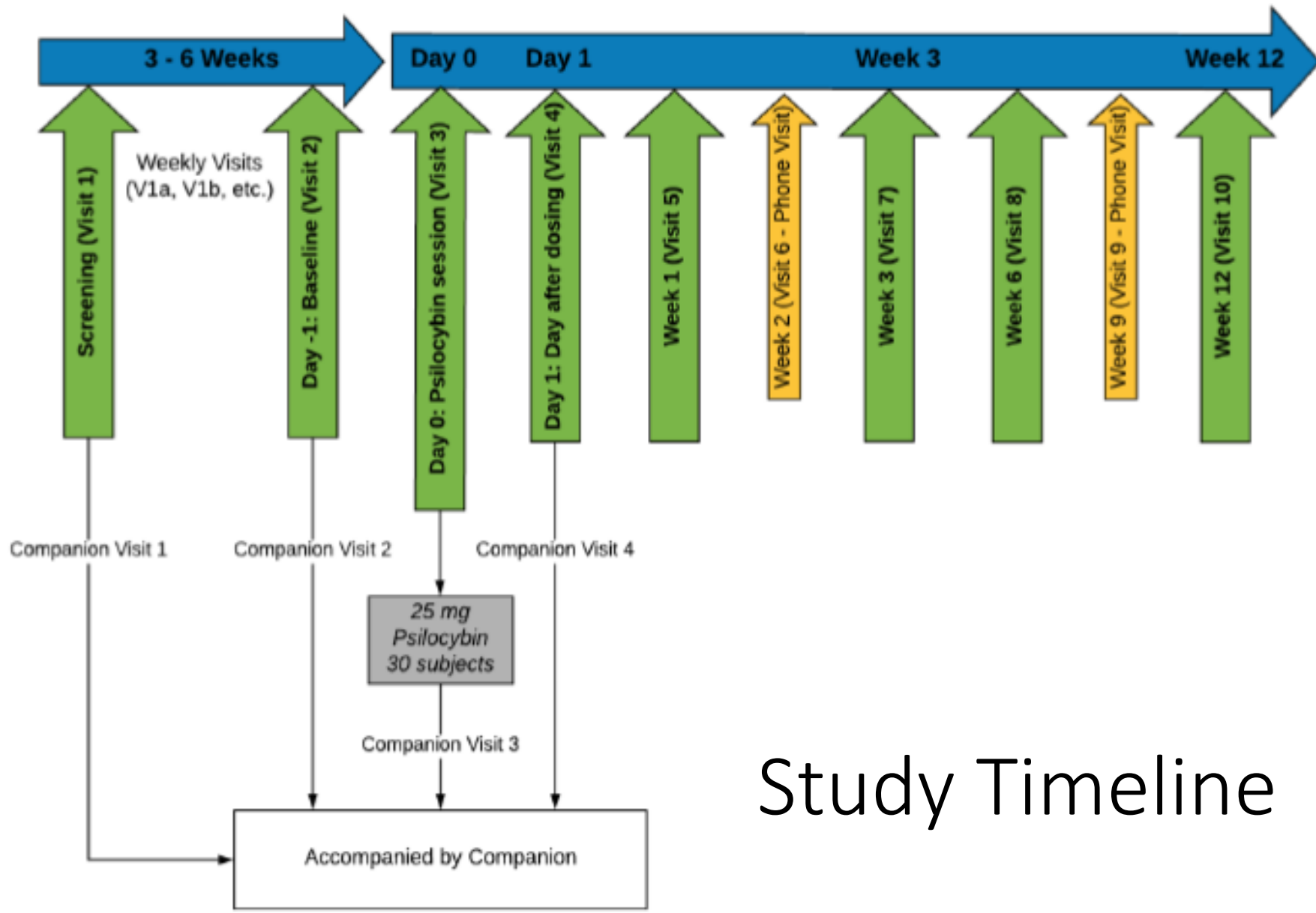
## *Shepard Pratt - Aaronson*

- Following results are from the completed sample of 12 TRD participants
- 75% remission rate 1 week post dose, also 75% response rate
- 25% remission rate 12 weeks post dose, 58% response rate at 12 weeks
- Presented at SOBP, 2022



## *Palo Alto: VA and Stanford - Suppes*

- Start-up time extensive due to creating new processes and obtaining all needed regulatory documents
- Currently only VA in the country carrying out a treatment study in depression for Veterans
- Enrolling and will complete 33% of sample by end of August, 2022



# Study Timeline

# Dosing Room



# What Does Psilocybin Assisted **Psychotherapy** Look Like – Palo Alto VA and Stanford

- Careful screening of potential subjects
- Three sessions with the therapist prior to dosing
- Dosing session—assume 8-9 hours from arrival to departure, two experienced therapists available for the entire session
- Check in with psychiatrist after dosing
- Integration therapy session #1 one day after dosing
- Integration therapy session #2 one week after dosing
- Further sessions as needed

# Psilocybin impact and potential side effects

- Sensory awareness is heightened
  - Within the context of psilocybin administration in a controlled setting, a participant may report transient visual or auditory disturbances, feelings of unreality, altered sense of time, and other changes in mood or affect
- transient anxiety during psilocybin onset
- transient confusion or thought disorder
- mild transient nausea
- transient headache

# Brain Imaging – Dr. Leanne Williams

- Functional MRI with neurocognitive testing
- Offered 1-day pre and post dose
- May be able to also study at 12 weeks post dose in patients
- Optional for participants

# What Does Improvement Look Like in Psychedelic Therapy – Shepard Pratt

- Study subject comments:
  - Nine months after dosing—“before life was in black and white and now it is in color,” “before I felt I was sucking air through a straw, now I can take deep breaths” “I have more compassion for myself.” Chronic vivid intrusive imagery of horrible deaths before dosing is now “more of a detached glimmer which feels like remembering a previous part of myself that I no longer identify with”
  - Nine weeks after dosing—“meditation finally works, it can put me at peace when I get anxious”

# What have we seen so far – VA and Stanford

- This is not the same as the 60's
- The focus is on healing and addresses deep seated pain
- Expectation and setting are critical
  - Goals and the focus of the dosing established before the dosing day



## Questions in the field

- Is a 'mystical' and/or ego dissolving experience needed for the therapeutic effect of psilocybin?
- Can the impact of psilocybin be enhanced – through setting or therapy?
- What is the ideal dosing regimen? What about second dosing and/or algorithms involving other treatments?



# ERA of Rapid Acting Therapeutics!

- Rapid acting therapeutics: Ketamine, Electrical stimulation, psychedelics and MDMA
- Inflection point with greater focus on rapid, enduring, and brain neuroplasticity aka brain changes
- Psychedelics are likely to change the landscape of psychiatric diagnosis and treatment

## In summary

- Psychedelics have been used throughout human history.
- The therapeutic potential is being explored for many conditions including depression, anxiety, eating disorders, and substance abuse.
- There are currently more unanswered questions than studies.
- Public media FAR exceeds scientific work.
- Lots going on at Stanford – more studies on the way!



**Exploratory  
Therapeutics  
Laboratory**

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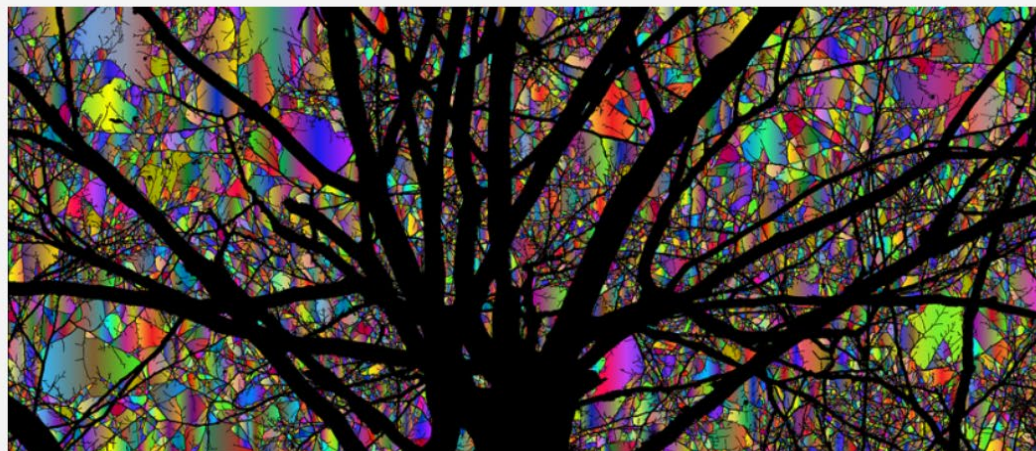
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**Our Vision**

To explore the potential of psychedelic compounds and other rapidly-acting therapies to minimize human suffering and enhance lives.





Trisha Suppes, MD, PhD

Michael Ostacher, MD, MHP



Wendy Feng, MD

Laura Hack, MD, PhD



ET Laboratory — Doctors + Boris Heifets, MD, PhD

# Staff and students



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Study Coordinator



Sara Ellis  
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Melanie Lean, PsyD



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Please feel free to call, email, or Teams message us!

Thank you!



- <https://med.stanford.edu/exploratorytherapeutics.html>
- Stanford Exploratory Therapeutics Lab