Sheppard Pratt

Psychedelics: A Paradigm Shift for Psychiatry?

Scott T. Aaronson, MD

Chief Science Officer, Institute for Advanced Diagnostics and Therapeutics

Sheppard Pratt

Adjunct Professor of Psychiatry

University of Maryland Medical School

Baltimore, Maryland

Disclosures

Research Support

Neuronetics

Compass Pathways

Consulting and Advisory Boards

LivaNova

Neuronetics

Janssen

Genomind

Sage Therapeutics

Sheppard Pratt

Audience Response Question 1

My interest level in the use of psychedelics for psychiatric illness is:

a. highly skeptical

b. interested but cautious

c. excited by the possibilities

d. where do I sign up?

How are we doing with Major Depression

- The standard monoamines and evidence-based psychotherapies are better than placebo, but…
- The time is long overdue for treatments that are better tolerated, work more often for more people with MDD, more quickly, and more enduring.

- MDD, major depressive disorder.

Where Is Psychiatric Treatment at Present?

Treatment of depression has been limited for 6 decades to the monoamine hypothesis targeting serotonin, norepinephrine, and dopamine

Novel treatments are now able to act on NMDA[a] (esketamine) and GABA-A[b] (brexanolone) receptors

Neurostimulation by TMS, VNS, and/or ECT may treat patients with inadequate response to medications[c]

Biological therapies and psychological treatments are largely separate in most research as well as clinical care

- ECT, electroconvulsive therapy; GABA, gamma aminobutyric acid; NMDA, N-methyl-D-aspartate; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.
- [a] Caliman-Fontes AT, et al. Trends Psychiatry Psychother. 2021;6; [b] Meltzer-Brody S, et al. Lancet. 2018;392:1058-1070; [c] Perrin AJ, et al. Brain Behav Immun. 2020;87:910-920.

Reintegration of Psychotherapy and Somatic Therapies in the Research Paradigm

- Important wave of the future is the re-integration of biological and psychotherapies -- more protocols with meds, neurostimulation, and NMDA antagonists or psychedelics used in combination with a particular therapy

- The overarching notion is that many biologic therapies -- some meds and some forms of neurostimulation -- can increase neuronal plasticity, making the brain more receptive to change which can then be fostered by some psychotherapy modality geared toward the particular underlying illness (depression, substance use disorder, PTSD, etc)

- PTSD, post-traumatic stress disorder.
  Daws RE, et al. Nat Med. 2022;28:844-851.

History of Psychedelics 1

- Long history of use in traditional medicine and religion to promote well-being as well as evidence of treating alcoholism
- Peyote contains mescaline
- Ayahuasca contains DMT
- Psilocybin found in certain mushroom
- LSD derived from natural ergotamines first discovered in 1943
- Rich history of use of LSD for alcoholism in the 1950s and 1960s with some signal for efficacy but "almost completely obscured by media sensationalism, unsupervised self-experimentation, poorly designed research, and misinformation." Mangini, *Journal of Psychoactive Drugs* (1998)

- Mangini M. J Psychoactive Drugs. 1998;30:381-418.

History of Psychedelics 2

- **1970s to 1990s:** Psychedelics go largely underground after the Controlled Substances Act in 1970 with some recreational and fringe psychotherapeutic use with MDMA gaining popularity and notoriety
- **1986:** MAPS founded to develop a pathways for the use of MDMA in PTSD
- **2000s:** Re-emergence of serious scientific interest with a start to loosening government restrictions. Small studies looking at psychedelic assisted psychotherapy in OCD,
  personality disorder
- **2010s:** Major advances with articles on psilocybin in terminal cancer patients and first efforts looking at MDMA in PTSD
- **2021:** First government funding for psychedelic research in 50 years awarded to Matt Johnson at JHU for smoking cessation
- Excellent article by Ben Sessa -- "The History of Psychedelics in Medicine" -- from 2016

- JHU, Johns Hopkins University; MAPS, Multidisciplinary Association for Psychedelic Studies; MDMA, 3,4-Methylenedioxymethamphetamine.
  Sessa B. The History of Psychedelics in Medicine. Handbuch Psychoaktive Substanzen. 2016:1-26.

What Does Psilocybin Do?

- It seems to enhance the brain's capacity for change or neuroplasticity, which is diminished across most psychiatric illnesses
- The chemical structure of psychedelics is similar to serotonin and bind to several serotonin receptors
- The mind-altering effects are presumed to be agonist or partial agonist activity at the 5HT-2A receptor
- Co-administration of a serotonergic antidepressant can block this activity (unclear how much of an issue)

- Vollenweider FX, et al. Nat Rev Neurosci. 2010;11:642-51; Banks MI, et al. Mol Biol Cell. 2021;32:1135-1144; Daws RE, et al. Nat Med. 2022;28:844-851.

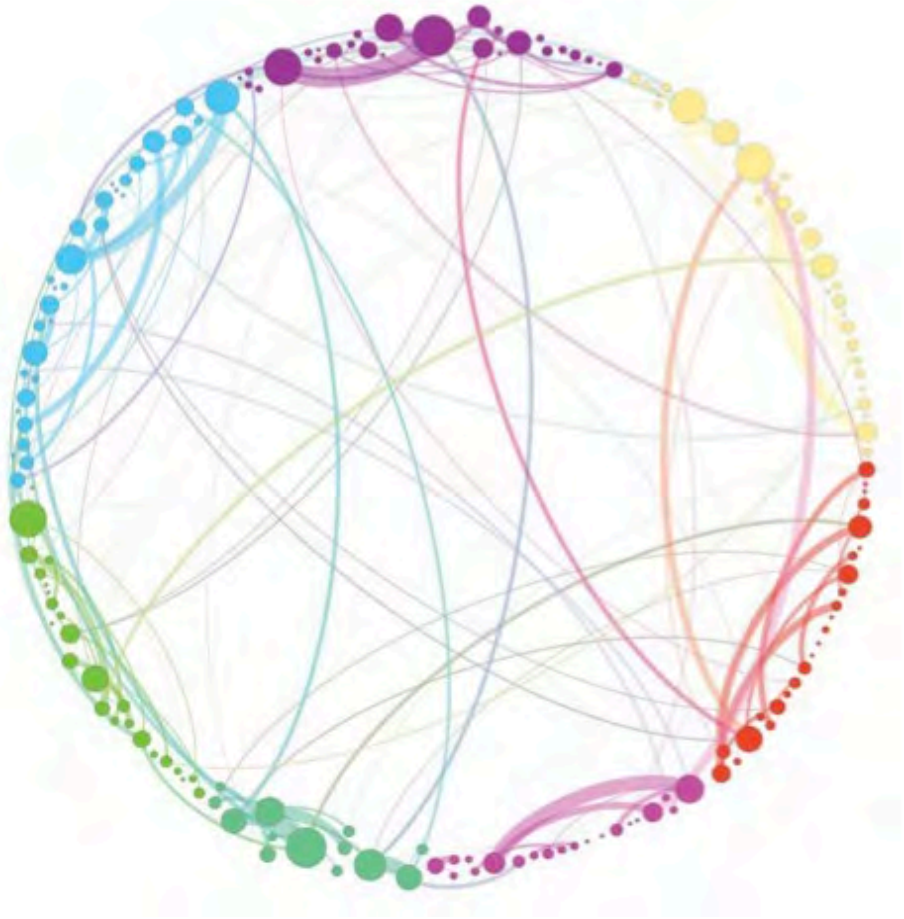
Changes in the Default Mode Network

- DMN is a large-scale brain network which includes the medial frontal cortex, posterior cingulate cortex, and the angular gyrus
- Active when a person is not focused on the outside world, brain is at wakeful rest such as daydreaming or mind wandering
- In major depression there is hyperconnectivity in the DMN and increased activity during rumination
- Psychedelics acutely decrease resting-state connectivity in the DMN

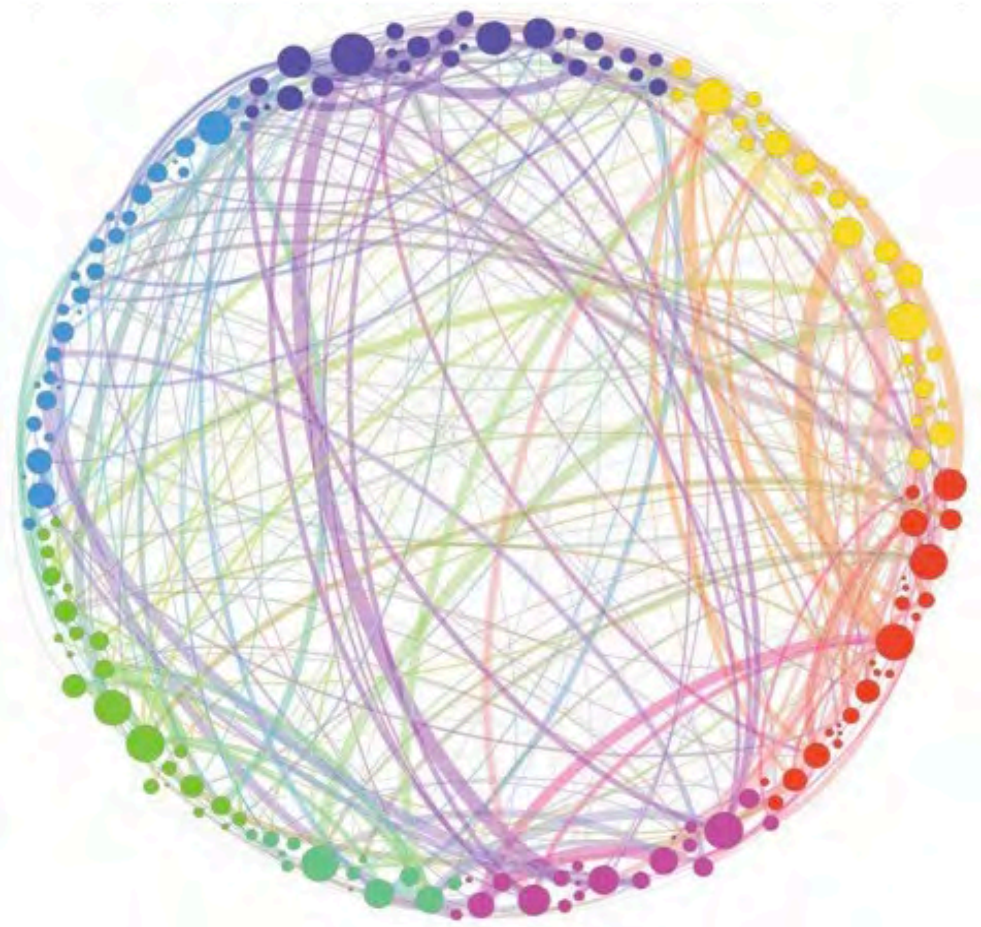
- DMN, default mode network.

- Vollenweider FX, et al. Nat Rev Neurosci. 2010;11:642-51; Banks MI, et al. Mol Biol Cell. 2021;32:1135-1144; Daws RE, et al. Nat Med. 2022;28:844-851.

Connectome Post Dose Placebo/Psilocybin From Imperial College, Carhart-Harris



Placebo



Psilocybin

- Petri G, et al. J Royal Soc Interface. 2014;11:20140873-20140873.

So, What Are We Doing With Psychedelics?

We are making the brain more receptive to change

We are turning down the DMN which has evidence of hyperconnectivity in MDD, OCD, and PTSD

At the same time, they increase dendritic arbor complexity, promote dendritic spine growth, and stimulate synapse formation

A possible viewpoint is we may be able to open a door toward psychological growth or change, but we need a psychotherapeutic interaction to foster that process

What Illnesses Should We Target?

- Illnesses that constrict one's thinking, provoke excessive internal rumination, and might benefit from an expanded perspective:

- Major depression
- Obsessive compulsive disorder
- Post-traumatic stress disorder
- Substance abuse
- Eating disorders
- Autism
- ? Dementing illnesses
- ? Persistent grief disorder

- Notice the dramatically transdiagnostic nature of this list

Phase I and II Studies on Psilocybin

- **Select Studies on ClinicalTrials.gov**

	Study Phase	
Condition	**Phase II**	**Phase I**
MDD/BP II depression	16	3
Substance use disorder	8	2
Cancer/palliative	5	4
Eating disorders/BDD	4	2
OCD + PTSD	3	3
Other anxiety/mood disorders	3	0
Fibromyalgia/headache/ migraine/pain	2	7
Frontline HCP - burnout	1	1
Spiritual/religious	0	3
Comparative hallucinogenic	0	3

- BDD, body dysmorphic disorder; BP, bipolar; HCP, healthcare provider.
ClinicalTrials.gov. Accessed May 10, 2022. https://clinicaltrials.gov/ct2/results?cond=&term=Psilocybin&cntry=&state=&city=&dist=m

- Primarily
  - Depression; unipolar and bipolar II
- Secondarily
  - Substance use disorders
  - Cancer/palliative care
  - Pain disorders

Current Situation

- Lots of active investigations with both non-profit and commercial entities with the goal of getting FDA clearance for MDMA and psilocybin for treatment resistant depression
- MDMA is in a Phase 3 trial (first phase 3 was completed) now for PTSD supported by a non-profit Multidisciplinary Association for Psychedelic Studies (MAPS)
- Usona and other non-profits are working with psilocybin and other psychedelics
- Many for profit companies, led by Compass Pathways have major funding for multiple indications largely for psilocybin

Current Landscape

- Lots of interested parties including:
  - Spiritual advisors and shamans
  - Basic and clinical scientists
  - Profiteers
  - Carnival barkers
  - Visionary leaders (who may fall in one or more of the first three categories)

  Be wary of self proclaimed experts. The available data is still relatively small. Some folks who do one course in psychedelics start showing up in news broadcasts as experts. Some journalists try to be part of the story.

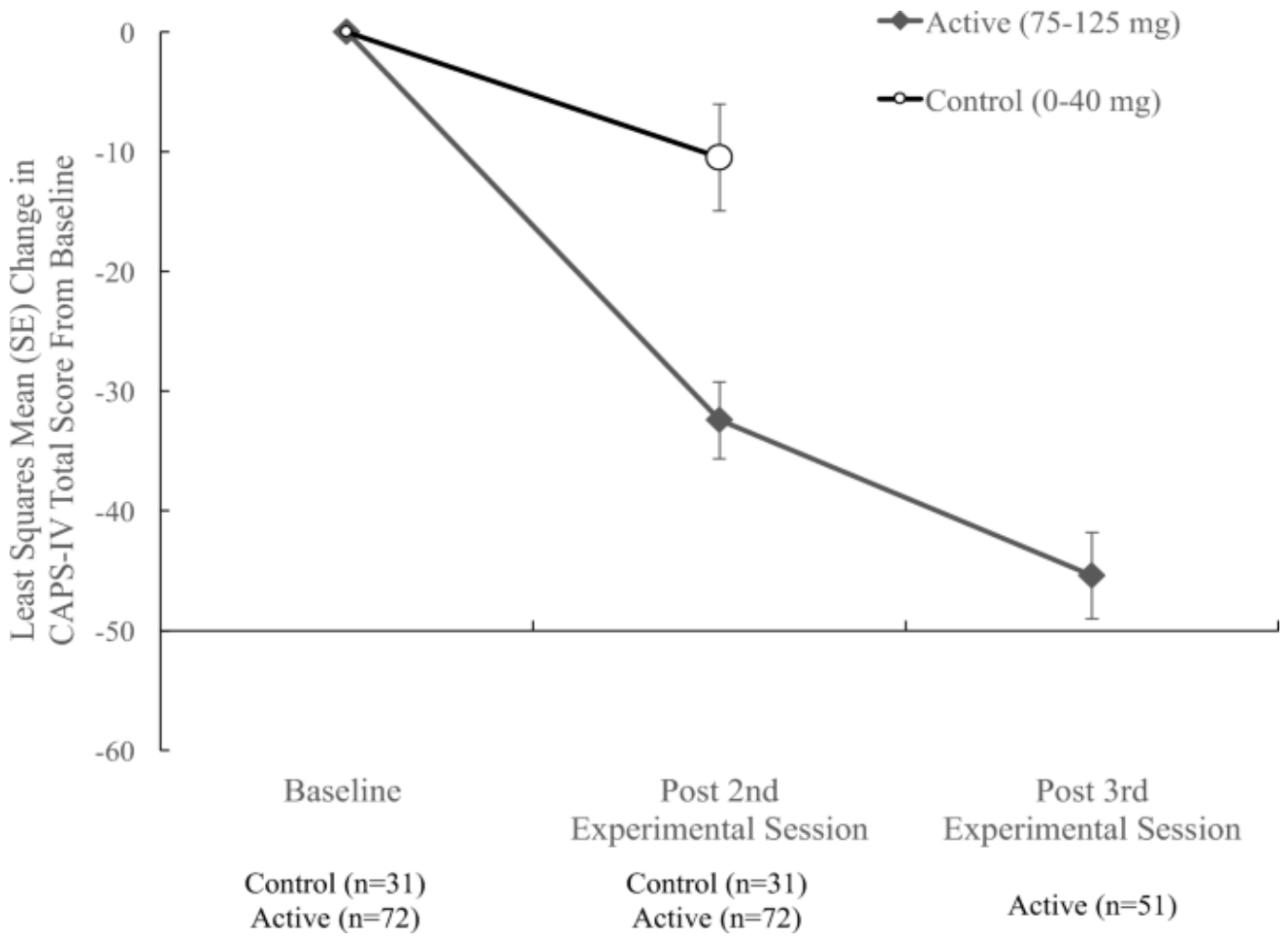
Treatment Concept

- The aim is to allow a unique, often profound subjective experience to unfold through *self-directed inquiry* and *experiential processing*
- Session is supported by 2 specially trained therapists
- Treatment rooms are designed for a non-clinical calming environment
- Patients listen to a specially designed music playlist that follows pharmacokinetics of psilocybin through high-fidelity sound system
- As a result of the session, patients often experience sense of connectedness, emotional catharsis, and acceptance and gain new perspectives

Sheppard Pratt Dosing Room

- Photo courtesy of Scott Aaronson, MD.

Phase 2 MDMA for PTSD (Mithoeffer, Psychopharmacology, 2019)

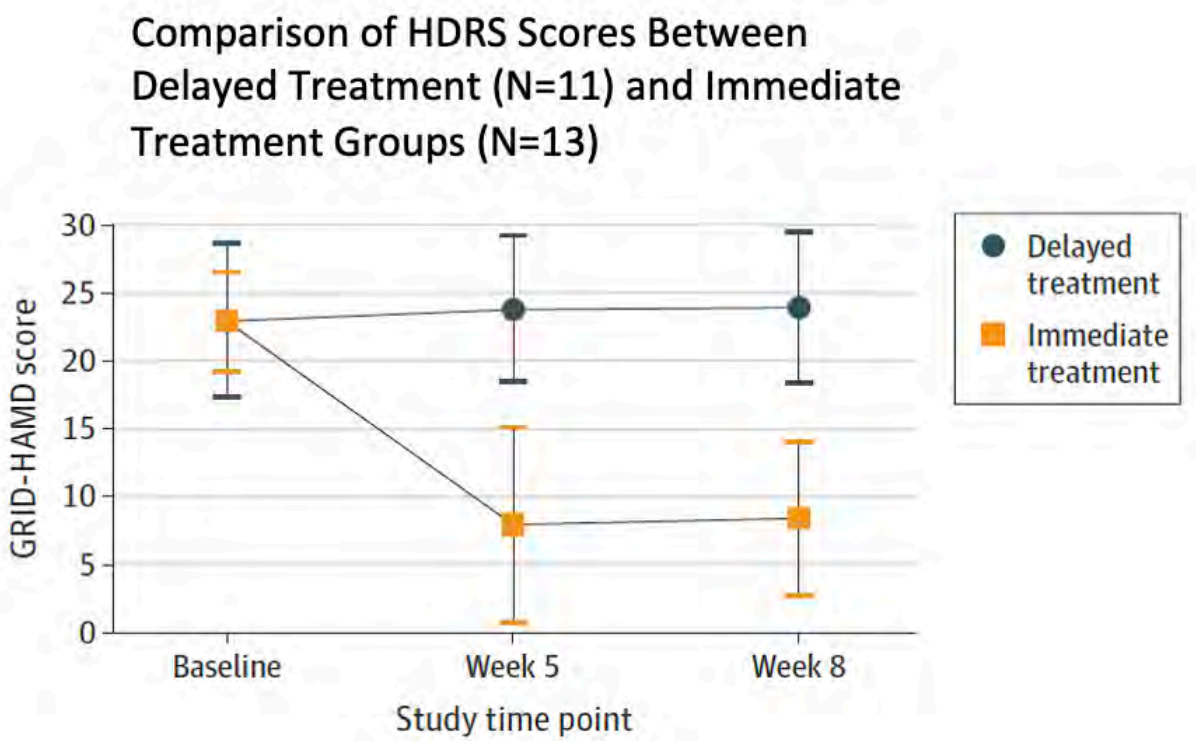


Phase 3 MDMA for PTSD Trial (Mitchell JM et al 2021 Nature Medicine)

- 90 participants 1:1 randomized to either MDMA or placebo
- Three preparatory sessions followed by three dosing sessions along with nine integrative therapy sessions over nine weeks.
- Primary outcome measure was Clinician Administered PTSD Scale for DSM-5 (CAPS-5)along with Sheehan Disability Scale at 2 months after last dosing
- Excellent statistically significant separation on both scales
- 24.4 mean drop in CAPS-5 in MDMA group vs. 13.9 in placebo $p<0.0001$
- No evidence of abuse potential, suicidality or QT prolongation

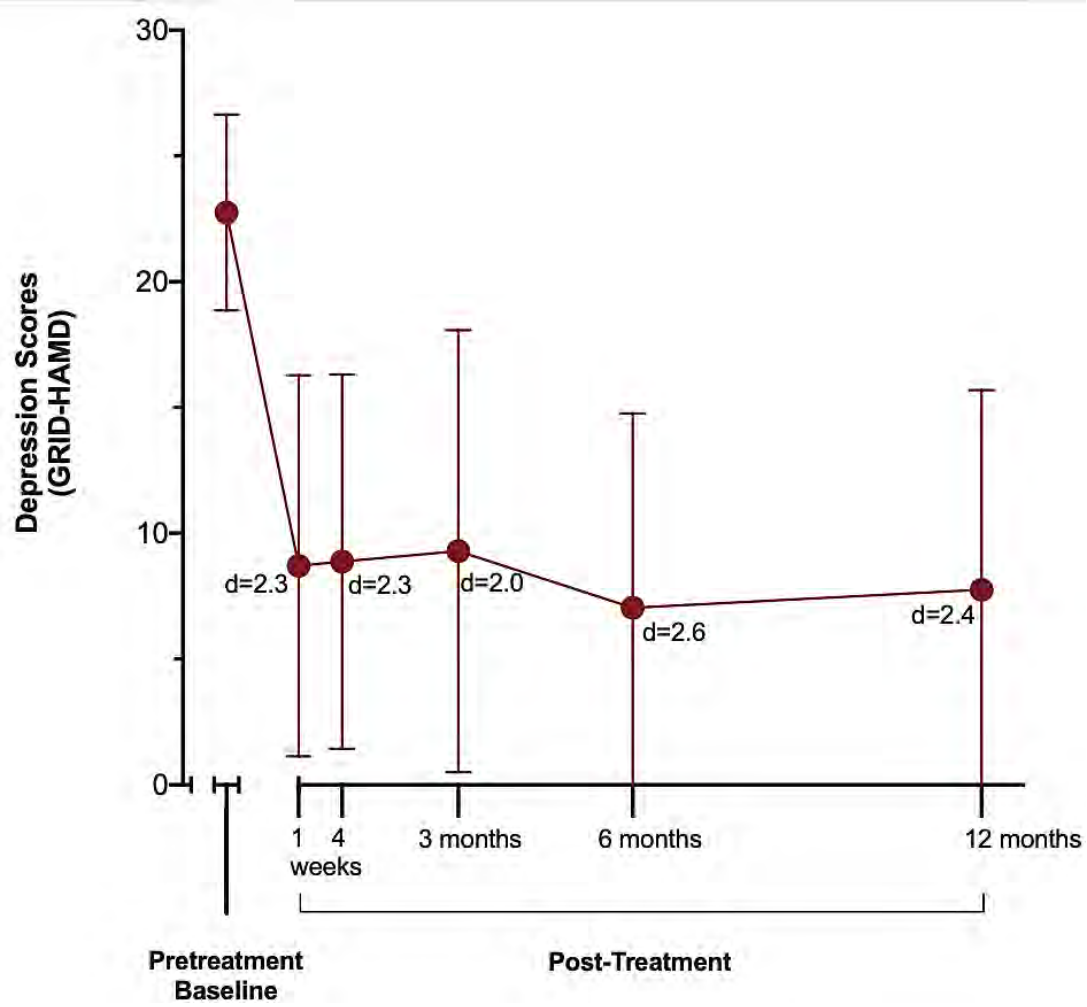
Effects of Psilocybin-Assisted Therapy on MDD

- 27 participants with MDD randomized to immediate treatment (n = 15) or delayed treatment (8-week waiting list control condition; n = 12)
- 2 psilocybin sessions (**session 1:** 20 mg/70 kg; **session 2:** 30 mg/70 kg) in the context of supportive psychotherapy (approximately 11 hours); sessions 1 to 2 weeks apart
- Immediate treatment group had more improvement than delayed treatment group from week 1 through week 8
- 67% response rate at week 1 and 71% at week 4
- Well tolerated with no unexpected or serious side effects



- Davis AK, et al. JAMA Psychiatry. 2021;78:481-489. Erratum in: JAMA Psychiatry. 2021 Feb 10.

Prospective 12-Month Follow-Up

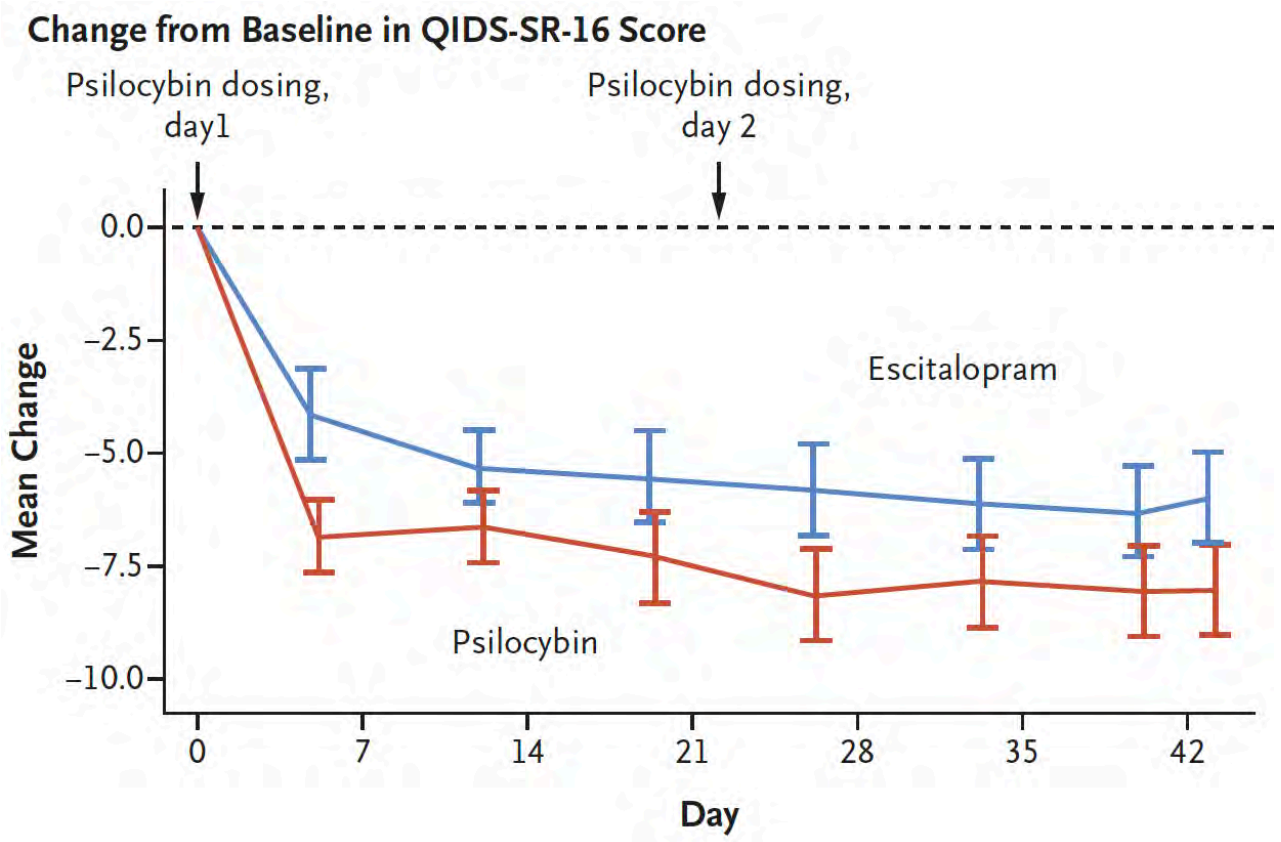


- Treatment response and remission were 75% and 58%, respectively, at 12 months
- No serious adverse events judged to be related to psilocybin in the long-term follow-up period
- No participants reported psilocybin use outside of the context of the study
- Ratings of personal meaning, spiritual experience, and mystical experience after sessions predicted increased well-being at 12 months but did not predict improvement in depression

- Gukasyan N, et al. J Psychopharmacol. 2022;36:151-158.

Psilocybin vs Escitalopram for MDD (N = 59)

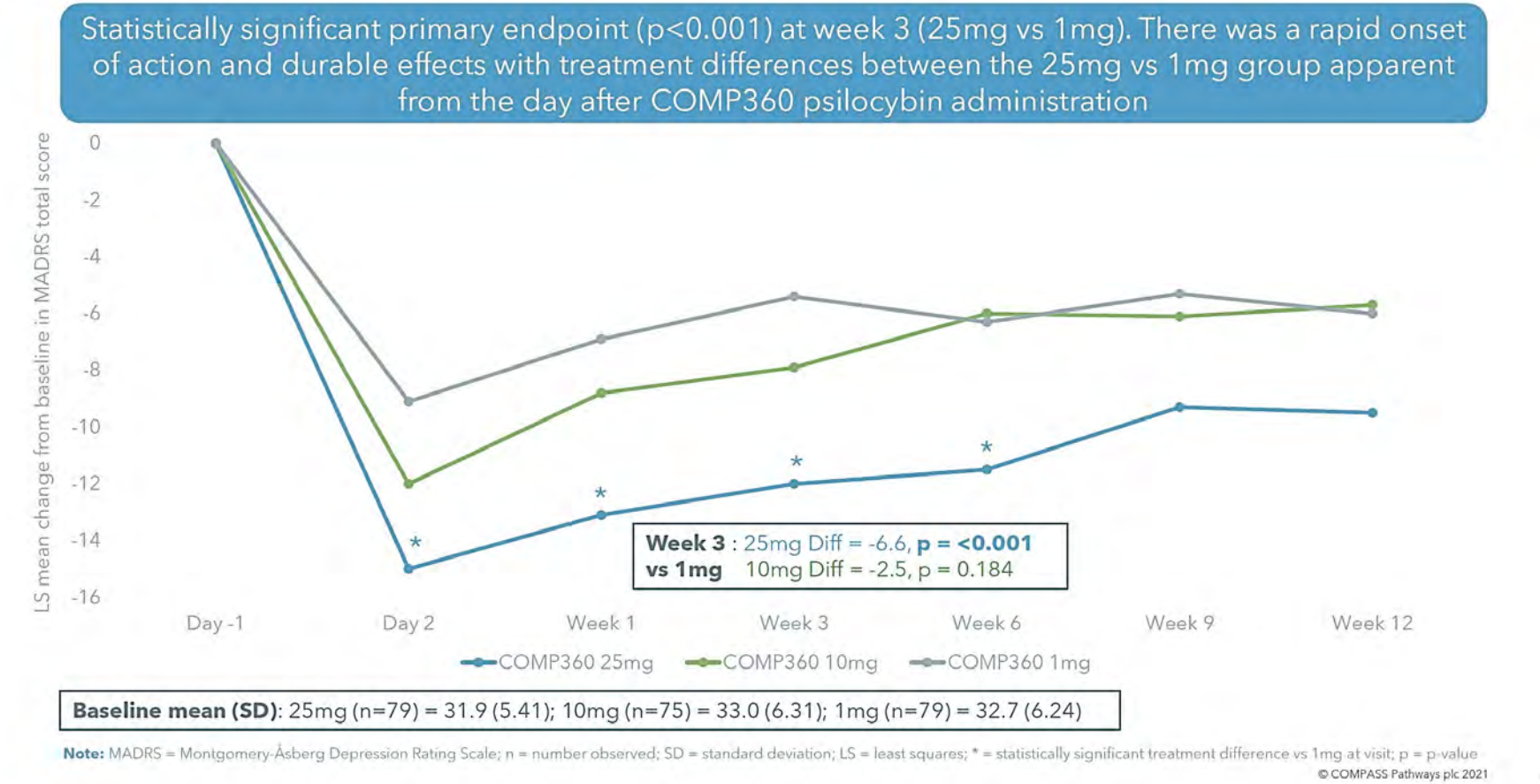
- Double-blind, randomized, controlled trial involving 59 patients with MDD
- 6-week study
- Patients were assigned to receive 2 separate doses of 25 mg of psilocybin 3 weeks apart plus 6 weeks of daily placebo (psilocybin group, N = 30) or 2 separate doses of 1 mg of psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram (escitalopram group, N = 29)
- All patients received psychological support
- No significant differences in change in QIDS-16 scores or adverse events
- Not a treatment resistant population



- QIDS, Quick Inventory of Depressive Symptomatology.
  Carhart-Harris R, et al. N Engl J Med. 2021;384:1402-1411.

Randomized, International, Multicenter, Double Blind, Phase 2 Dose-Finding Study

- **Primary Endpoint: Change in MADRS From Baseline (N = 233)**



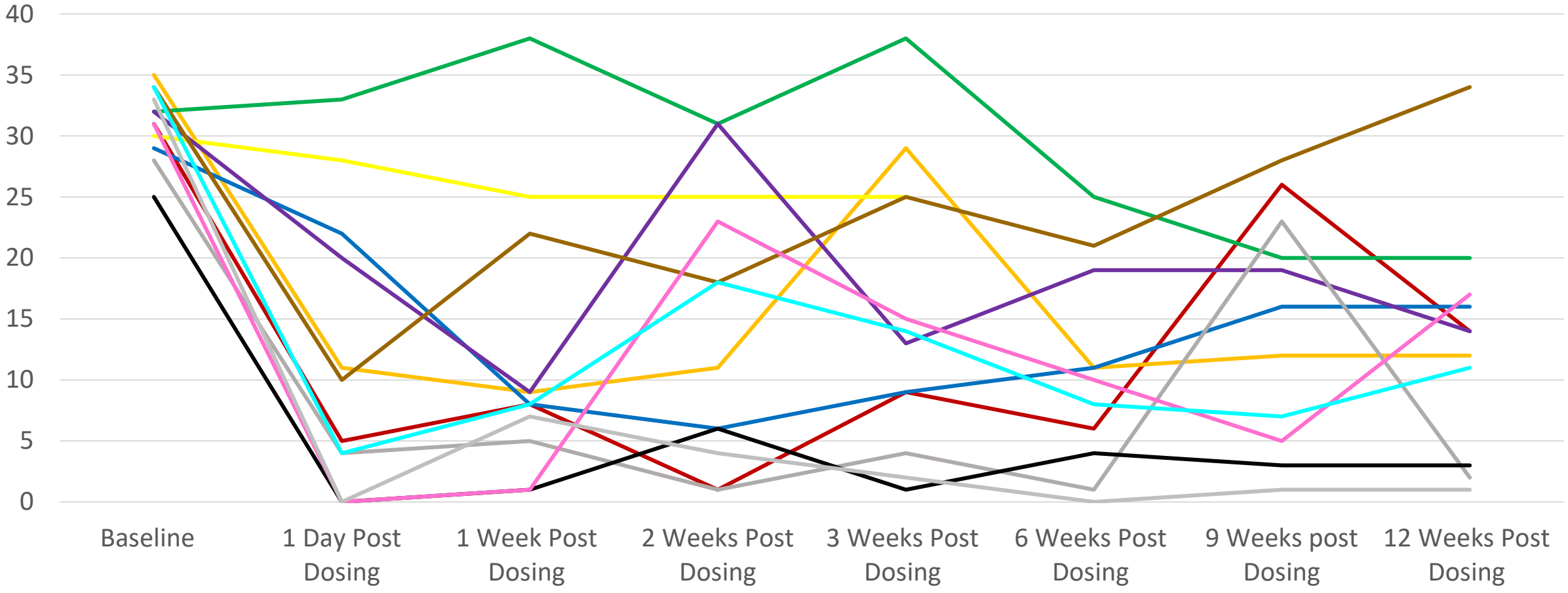
- Have successfully discontinued all serotonergic medications at least 2 weeks prior to dosing
  - Failure to respond to an adequate dose and duration of 2, 3, or 4 pharmacological treatments for the current episode HAM-D ≥ 18 at screening and baseline
  - Single or recurrent episode of depression; if single then > 3 months, < 2 years
  - Randomized to receive 1 mg, 10 mg or 25 mg along with psychological support

- HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.
- Goodwin GM, et al. APA Annual Meeting 2022; Abstract Number: 5301, Poster Session 6.

Investigator Initiated Trial in Severe Treatment Resistant Depression (>4 treatment failures)

- 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
- 75% remission rate 1 week post dose, also 75% response rate
- 25% remission rate 12 weeks post dose, 58% response rate at 12 weeks (compare to STAR-D response in less ill population)
- Lower likelihood of response with comorbid PTSD or absence/low grade psychedelic experience

COMP360 in 12 MDD patients with at least 5 treatment failures in current episode (MADRS)



Presented at SOBP May 2022, New Orleans. Aaronson, S et. al.

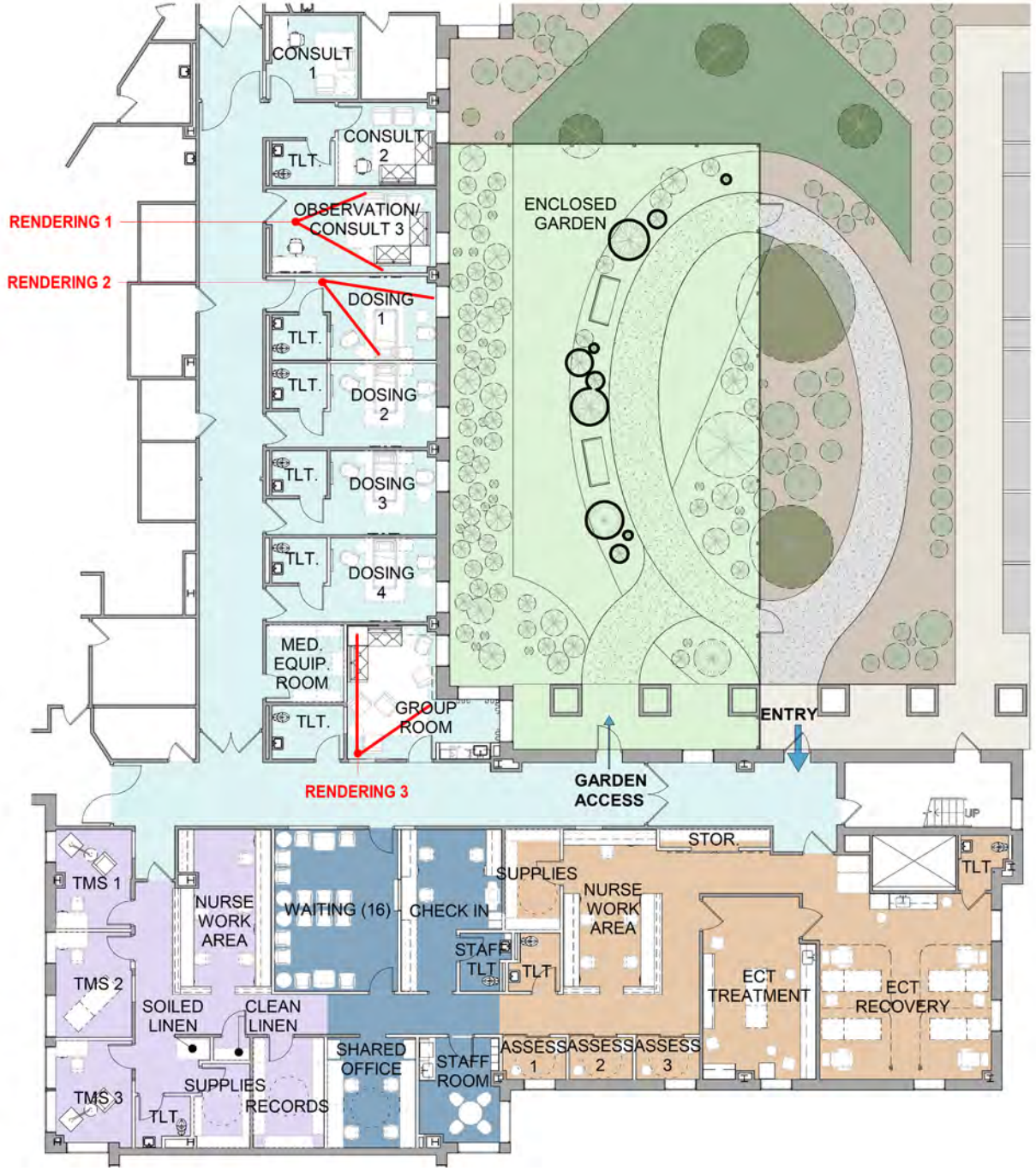
Other Research Findings

- Generally can see enduring effects after only one or two doses of psychedelic
- Clearly need an adequate protocol for administration paying close attention to “set and setting” as this seems to lead to improved experience for the study subject as well as better outcomes
- Little evidence for unexpected adverse events
- Good evidence for meaningful change in patients suffering with depression and anxiety in terminal cancer as well as an improved sense of wellness in normal volunteers

What Does Psychedelic Assisted Psychotherapy Look Like

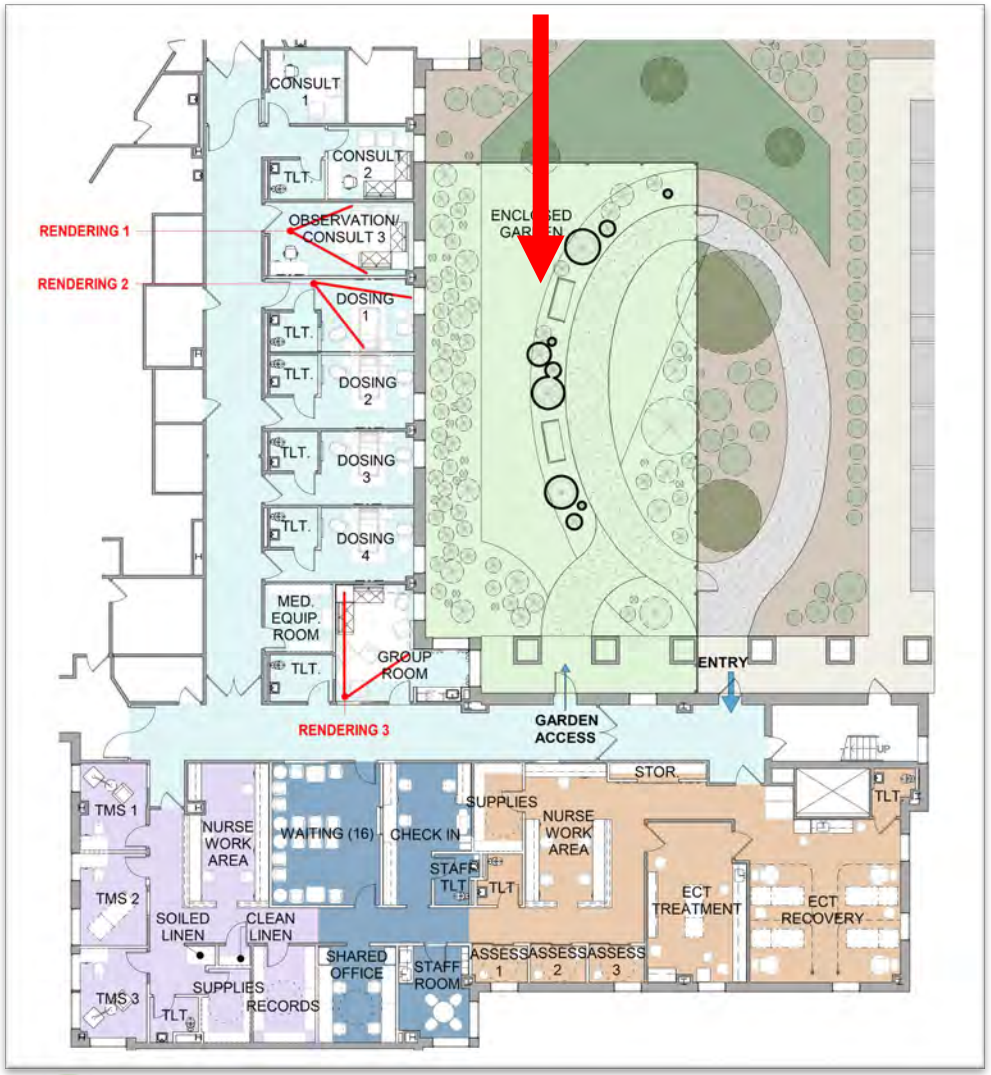
- Careful screening of potential subjects
- Three sessions with the therapist prior to dosing
- Dosing session—assume 9 hours from arrival to departure, two experienced therapists available for the entire session
- Check in with psychiatrist after dosing
- Integration session #1 one day after dosing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

FLOORPLAN



Sheppard Pratt

Courtyard



Sheppard Pratt

Dosing Room

Qualities of a Good Study Subject

- Realistic expectations including acceptance of study parameters (study may be an randomized trial)
- Ability to connect fairly quickly with the study psychiatrist and therapist
- Capacity for trust (careful with PTSD survivors of early trauma)
- Willingness to:
  - Accept the experience
  - Trust, let go, be open
  - Move toward rather than away from challenging experiences

Exclusion Criteria

- Primary psychotic disorder or bipolar illness
- Imminent risk for self harm (chronic suicidal ideation may be a target)
- Concurrent substance abuse (except when we get to substance use studies)
- Uncontrolled medical illness
- Inability to tolerate study procedures

Challenges to the Research Paradigm

- Lots of interested parties with problematic agendas
- Unrealistic expectations for FDA approval
- The downside of high visibility—lots of patients want to try it, lots of docs want to be able to participate
- Massive job to undo many decades of misinformation about psychedelics
- What are the best outcome measures—the change from the psychedelic experience is not well captured in scales we rely on

What Does Improvement Look Like in Psychedelic Therapy

- Study subject comments:
  - One year after dosing, participant reports some return of depressive symptoms—”but I still don’t hate my parents”
  - 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 is Captured and What is Not by MADRS

Captured

Mood change

Self criticism (pessimism)

Sense of connection
(hedonia item)

- Not Captured
  - Improved cognitive flexibility
  - Creative thinking
  - Sense of well being
  - Change in observing ego
  - Perspective on self and life events
  - Acceptance
  - Engagement
  - Control over mood state
  - Sense of “stuckness” in past

Current Activities at Sheppard Pratt

- Completed participation in phase 2 trial
- Completion of state of the art dosing facility
- Enrolling in randomized trial for anorexia
- Phase 3 pivotal/registration trial to begin Fall 2022
- Enrolling in several investigator initiated open label studies in:
  - Severe treatment resistant depression (5 or more treatment failures in current episode) COMPLETED
  - Bipolar type 2 depression. Enrollment complete
  - Depression with suicidal ideation (scores of 3 or 4 on CSSR-S). First 6 participants dosed

Lessons Learned

- Don’t yet have our arms around truly capturing the effect on participants. Change in perspective and level of function may be more critical than changes in vegetative symptoms
- Preparation of participants is critical. The more someone accepts that they have to work for change the more likely a better outcome is
- Participant selection is key, notice how many folks are screened to get subjects. (1000 volunteers screen to find 59 subjects in Carhart-Harris study).
- Prepare for potential regression given the ego dissolution seen

Psychedelic Research in the Time of Covid

- Sheppard Pratt research was shut down for about 10 months
- Trying to figure out what sessions can be done remotely and what needs to be done in person
- Current iteration is around how many and which of the meetings with the therapist can be remote.
- Day before and day after dosing must be in person. First meeting must be in person.
- Other sessions subject to negotiation and comfort level between therapist and participant

Take Aways

- Psychedelics coupled with psychotherapy may offer a unique intervention for patients we have been unable to treat with conventional pharmaco or psycho therapies
- Their utility appears to cut across multiple diagnostic categories
- We may need to invent a novel research paradigm to adequately grasp the changes in consciousness and mindset that these drugs can provoke
- This is a very exciting time to be a clinical researcher in difficult to treat psychiatric conditions

Audience Response Question 2

The biggest problem for the development of psychedelics:

a. The mental health field is not prepared for the paradigm shift
b. Too many factions (not for profit, for profit, insurers, regulatory bodies) have different agendas
c. Getting beyond the old stigmas against psychedelics
d. All of the above
e. Other