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
Peyote, Shumla Caves Texas ~3700 BC

Aztec ‘Teonanacatl’ ~1400

Kykeon Eleusinian Mysteries ~1000 BC

Mayan mushroom stones ~1000 BC

1897

1900

“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

Arthur Heffter chemist
By taking Delysid [LSD] himself, the psychiatrist is able to gain an insight into the world of ideas and sensations of mental patients. Delysid can also be used to induce model psychoses of short duration in normal subjects, thus facilitating studies on the pathogenesis of mental disease.
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
CLASSICAL PSYCHEDELICS

- Psilocybin
- L-5-hydroxytryptamine (5-HT/Serotonin)
- 3,4,5-trimethoxyphenethylamine (Phenethylamine)
- Mescaline
- Lysergic acid diethylamide (LSD)
- N,N-dimethyltryptamine (DMT)
- Ergolide
- Tryptamines
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 Ross1,2,3,4,5,6, Anthony Bossis1,2,4, Jeffrey Guss1,2,4, Gabrielle Agin-Liebes10, Tara Malone1, Barry Cohen7, Sarah E Mennenga1, Alexander Belser9, Krystallia Kalliontz2, James Babb9, Zhe Su3, Patricia Corby2 and Brian L Schmidt2

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

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

![GRID-HAMD score over time](chart.png)
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
**Psilocybin versus Escitalopram for Depression**

**Phase 2, Double-Blind, Randomized, Controlled Trial**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment Details</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psilocybin</strong></td>
<td>(two 25-mg doses 3 wk apart) + placebo (microcrystalline cellulose)</td>
<td>30</td>
</tr>
<tr>
<td><strong>Escitalopram</strong></td>
<td>(10 mg daily [3 wk], then 20 mg [3 wk]) + placebo (psilocybin, 1-mg doses 3 wk apart)</td>
<td>29</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Change in QIDS-SR-16</th>
<th>59 Adults with moderate-to-severe major depressive disorder</th>
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<tbody>
<tr>
<td>Depressive symptom score at 6 wk</td>
<td>-8.0±1.0</td>
</tr>
<tr>
<td>Difference, -2.0 points (95% CI, -5.0 to 0.9)</td>
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</tbody>
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Overall incidence of adverse events was similar in the two groups.

No significant difference between psilocybin and escitalopram in QIDS-SR-16 score change from baseline.

R. Carhart-Harris et al. 10.1056/NEJMoa2032994
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

3 - 6 Weeks
- Weekly Visits (V1a, V1b, etc.)
- Screening Visit 1

Day 0
- Baseline session (Visit 2)
- Psilocybin session (Visit 3)

Day 1
- Day 1: Day after dosing (Visit 4)

Week 1
- Visit 5
- Week 2 (Visit 6 - Phone Visit)

Week 3
- Visit 7

Week 6
- Visit 8

Week 12
- Visit 10

Companion Visit 1
- Companion Visit 2
- Companion Visit 4
- Companion Visit 3

25 mg Psilocybin for 30 subjects

Accompanied by Companion
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!
Welcome to the Exploratory Therapeutics Laboratory

Our Vision
To explore the potential of psychedelic compounds and other rapidly-acting therapies to minimize human suffering and enhance lives.
ET Laboratory – Doctors + Boris Heifets, MD, PhD

Trisha Suppes, MD, PhD

Michael Ostacher, MD, MHP

Wendy Feng, MD

Laura Hack, MD, PhD
Staff and students

E. Grace Fischer
Study Coordinator

Sara Ellis
Study Coordinator

Jay Lyu
Doctoral Student

Edgardo Gamarra
Masters Student

Aileen Kucsera
Doctoral Student

Katherine Eisen, PhD

Melanie Lean, PsyD

Betsy Conlan, LCSW
Contact information for participant inquiries:

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• Sara Ellis at 650-223-1368

• Study Screening Line: (650) 849-0161

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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