An overview of psilocybin-assisted therapy for psychiatric conditions

Sandeep Nayak, MD
Postdoctoral Fellow
Johns Hopkins Center for Psychedelic and Consciousness Research
OVERVIEW

1. Brief background on psychedelics
2. Clinical studies
3. Mechanisms
1. Brief background on psychedelics

- What are psychedelics?
- What effects do they have?
- Study procedures
What are psychedelics?

• “Classic psychedelic”
  – Psilocybin
  – LSD
  – Mescaline (peyote)
  – DMT (ayahuasca, yopo)
All psychedelics mimic serotonin
What effects do psychedelics have?

- Visual
- Meaning enhancing
- Broadening of emotional range
- Altered sense of self
- Memory
- Mystical-type experiences
What effects do psychedelics have?

“A psychedelic drug is one which has small likelihood of causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, produces thought, mood, and perceptual changes otherwise rarely experienced except perhaps in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory and acute psychoses.”

- Dr. Lester Grinspoon
What effects do psychedelics have?

“I was now a Not-self, simultaneously perceiving and being the Not-self of the things around me. To this new-born Not-self, the behavior, the appearance, the very thought of the self it had momentarily ceased to be... seemed... enormously irrelevant.”
Multiple models of use

• Traditional Sacramental
• Recreational
• Psychotomimetic
• Psycholytic
• Chemotherapeutic
• Psychedelic
Context dependency

• “The responses described in clinical experiments on Whites are so different from the responses described by Indian Peyotists... as to fall into completely different categories. They do not seem to be talking about the same thing” (Slotkin, 1956)

Context dependency

- In this era, white participants who took peyote in a research setting had experiences characterized by suspiciousness, feelings of meaninglessness and distress, “hallucinations largely idiosyncratic in content”, and a general lack of therapeutic benefits.

Context dependency

• In contrast, American Indian peyotists generally took the cactus in a ceremonial setting, with a presumption of a meaningful, beneficial experience and had therapeutic benefits and “welcome feelings of contact with a new, more meaningful... reality prefigured in doctrinal knowledge” (Wallace, 1959)

Multiple models of use

• Strong context dependency of effects
  • Patient expectations
  • Preceding psychotherapy
  • Setting
  • Support
Osmond Saskatchewan alcohol trials

• Initial rationale:
  • Psychotomimetic
  • Mimic Delirium Tremens
  • “hit rock bottom”
Meta-Analysis of controlled trials of LSD for Alcoholism:
Across studies, LSD doubled the odds a patient would be alcohol free
Krebs T S, Johansen P J Psychopharmacol 2012;26:994-1002

<table>
<thead>
<tr>
<th>First follow-up</th>
<th>Follow-up (months)</th>
<th>LSD (n/N)</th>
<th>Control (n/N)</th>
<th>Odds Ratio (95% CI)</th>
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</thead>
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<tr>
<td>Smart et al., 1966</td>
<td>6</td>
<td>3/10</td>
<td>7/20</td>
<td>1.41 (0.36-5.60)</td>
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<td>Hollister et al., 1969</td>
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<td>18/36</td>
<td>11/36</td>
<td>2.27 (0.87-5.94)</td>
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<td>Ludwig et al., 1969</td>
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<td>94/132</td>
<td>25/44</td>
<td>1.88 (0.93-3.81)</td>
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<td>Bowen et al., 1970</td>
<td>12</td>
<td>9/22</td>
<td>7/22</td>
<td>1.48 (0.43-5.10)</td>
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<tr>
<td>Pahnke et al., 1970</td>
<td>6</td>
<td>34/73</td>
<td>13/44</td>
<td>2.08 (0.94-4.60)</td>
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<tr>
<td>Tomsovic &amp; Edwards, 1970</td>
<td>3</td>
<td>30/52</td>
<td>17/45</td>
<td>2.25 (0.99-5.10)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>325</strong></td>
<td><strong>211</strong></td>
<td><strong>1.96 (1.36-2.84)</strong></td>
</tr>
</tbody>
</table>

**Figure 2.** Improvement on alcohol misuse at the first available follow-up after LSD versus control treatments.

*aContinuous outcome data.*
Study Procedures

• Patient selection
• Strong interpersonal support/psychotherapy
• Meetings:
  — Preparation
  — Dosing
  — Integration
Prep and Drug Sessions

• Prep sessions

• Drug session:
  – The 7-hr drug sessions are conducted in a living-room-like environment
  – Two monitors are present throughout the session
Follow-up (integration)

• Meetings with both facilitators in days and weeks following dosing sessions

• Review of experiences on session day and interim events
  - Goal is to help the participant understand and incorporate insights from the experience into their daily lives
2. Clinical studies

- Major depression
- Substance use disorders
Critiques

• Hype: Enthusiastic patients and researchers
  • Selection bias
  • Allegiance effects
• De facto unblinded
  • Nocebo effects
• Includes psychotherapy (?)
Depression studies

- Johns Hopkins open-label waitlist control (Davis et al., 2021)
- Imperial college psilocybin vs escitalopram (Carhart-Harris et al., 2021)
- Compass Phase 2 TRD trial
12-mo f/u
A Change from Baseline in QIDS-SR-16 Score

Psilocybin dosing, day 1
Psilocybin dosing, day 2

Mean Change

0.0

-2.5

-5.0

-7.5

-10.0

0 7 14 21 28 35 42

Day

Escitalopram
Psilocybin

Imperial College
London
A QIDS SR−16 posterior distribution of group difference
Skeptical Prior

B HAMD−17 posterior distribution of group difference
Skeptical Prior

C MADRS posterior distribution of group difference
Skeptical Prior

D BDI−1A posterior distribution of group difference
Skeptical Prior

Dotted line indicates Minimally Clinically Important Difference (MCID)
Bar indicates median and 95% CI
Primary endpoint - change from baseline in MADRS total score

Statistically significant primary endpoint (p<0.001) at week 3 (25mg vs 1mg). There was a rapid onset of action and durable effects with treatment differences between the 25mg vs 1mg group apparent from the day after COMP360 psilocybin administration.

Week 3: 25mg Diff = -6.6, p = <0.001 vs 1mg
10mg Diff = -2.5, p = 0.184

Baseline mean (SD): 25mg (n=79) = 31.9 (5.41); 10mg (n=75) = 33.0 (6.31); 1mg (n=79) = 32.7 (6.24)

Note: MADRS = Montgomery-Åsberg Depression Rating Scale; n = number observed; SD = standard deviation; LS = least squares; * = statistically significant treatment difference vs 1mg at visit; p = p-value
Modern Trials for SUDs

- Completed
  - Alcohol
  - Tobacco
- Ongoing/planned
  - Alcohol
  - Tobacco
  - Comorbidity with mood disorders
  - Cocaine
  - Methamphetamine
  - Opioid
Psilocybin for DSM-IV Alcohol Dependence

• Open-label pilot study (N =10) of 1-2 doses psilocybin + MET for alcohol dependence

• Significantly decreased drinking up to 36 weeks later

Bogenschutz et al. J Psychopharmacol. 2015; 29(3): 289-299
Psilocybin for DSM-IV Alcohol Dependence

• Open-label pilot study ($N = 10$) of 1-2 doses psilocybin + MET for alcohol dependence

• Significantly decreased drinking up to 36 weeks later

Fiore et al., 1994
Meta-analysis:
13 nicotine patch trials

Paszek et al., 2017
Meta-analysis:
5 bupropion trials

Baker et al., 2016
Varenicline vs. NRT
• 12 weeks of bupropion + NRT + counseling followed by:
  • No further treatment
  • NRT for 1 year
  • Comprehensive CBT intervention including mood, weight management, social support + smoking focus for 1 year
Smoking cessation pilot
Johnson et al., 2014

Pilot Study of the 5-HT$_{2A}$R Agonist Psilocybin in the Treatment of Tobacco Addiction

Matthew W. Johnson, PhD$^1$, Albert Garcia-Romeu, PhD$^1$, Mary P. Cosimano, MSW$^1$, and Roland R. Griffiths, PhD$^{1,2}$
Smoking cessation pilot

**Table 1.** Demographic and smoking characteristics, N=15.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>10 M, 5 F</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 (10.5)</td>
<td>26-65</td>
</tr>
<tr>
<td>Education b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>4 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Bachelor's degree</td>
<td>7 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Graduate degree</td>
<td>4 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Cigarette dependence (FTCD) c</td>
<td>5.3 (1.3)</td>
<td>3-8</td>
</tr>
<tr>
<td>Years smoking</td>
<td>31 (9.9)</td>
<td>10-49</td>
</tr>
<tr>
<td>Previous quit attempts</td>
<td>6 (3.6)</td>
<td>2-12</td>
</tr>
<tr>
<td>Cigarettes/day at intake</td>
<td>19 (2.9)</td>
<td>15-25</td>
</tr>
<tr>
<td>Breath CO at intake</td>
<td>30 (9.9)</td>
<td>13-53</td>
</tr>
<tr>
<td>Urine cotinine at intake</td>
<td>1676 (594)</td>
<td>841-3212</td>
</tr>
</tbody>
</table>

- About 1 pack a day
- Mean duration 31 years
- Mean 6 quit attempts
Open-label pilot study design

• Uncontrolled
• 15-week intervention
• CBT for smoking cessation x4 weeks
• Up to 3 psilocybin doses (20-30mg/70kg)
• Typical preparation, dosing, integration procedures
7-day Point Prevalence Abstinence (N = 15)
Qualitative reports

It felt like I’d died as a smoker and was resurrected as a non-smoker. Because it’s my perception of myself, and that’s how I felt. So I jumped up and I said ‘I’m not a smoker anymore, it’s all done’.

I was in love with everything. In love with the couch, in love with the whole room, the people in it ... Love is a pretty big distraction from addiction and ... my attention kept going back to it, that great feeling of love and acceptance.

I think if you didn’t have that [the rapport] I'm not sure if it would work. I don’t know. And then the trust with the people, the folks in this clearly – when you know that people want you to do well...want this to work for you...and then you don’t want to let them down. Because there’s so much invested.

Noorani et al., 2018
Ongoing comparative effectiveness trial

Active Treatment (weeks 1-13)
Ongoing comparative effectiveness trial

Active Treatment (weeks 1-13)

Weeks 1-2  |  Weeks 3-4
Orientation | Randomization
CBT + MRI pre | CBT + prep.

4 weeks CBT
Ongoing comparative effectiveness trial

Active Treatment (weeks 1-13)

- Weeks 1-2: Orientation
- CBT + MRI pre

- Weeks 3-4: Randomization
- CBT + prep.

Randomize
Ongoing comparative effectiveness trial

Active Treatment (weeks 1-13)

Weeks 1-2  Weeks 3-4
Orientation  Randomization
CBT + MRI pre  CBT + prep.

Week 5
Psiloc. Integration
Target Quit Support Abstinence
MRI post
Patch Dose taper

Psilocybin vs Nicotine patch
Ongoing comparative effectiveness trial

Active Treatment (weeks 1-13)

Weeks 1-2  Weeks 3-4  Orientation  Randomization  CBT + MRI pre  CBT + prep.

Week 5
- **Psilo.**
- Integration
- Target Quit
- Support Abstinence
- MRI post
- MRI MRI post
- Patch
- Dose taper

Follow-up Period

3mo 6mo 12mo  
followup followup followup

MRI Long-term

Long-term follow-up
- About 1 pack a day
- Mean duration 26 years
- Mean 7 quit attempts
Ongoing/Future trials

• MDD-AUD comorbidity (Hopkins)
• Alcohol (NYU)
• Cocaine (University of Alabama at Birmingham)
• Methamphetamine (Portland VA)
• Tobacco
• Opioid (Hopkins)
3. Mechanisms

- Subjective effects are therapeutic
- Enhanced (context-dependent) plasticity
- Neuroimaging findings
5HT-2A receptor

• 5HT-2A receptor widely expressed throughout cortex
• Primarily layer V pyramidal neurons
• Most, if not all psychedelic effects blocked by 2A antagonist ketanserin
Psychological mechanisms of action

- Mystical experience
  - Unity, deeply felt positive mood, transcendence of space/time, ineffability, sense of reverence
  - Dose-dependent
  - Correlated with enduring improvements in quality of life, meaningfulness of the experience, various clinical outcomes
Mystical Experience on Session Days Predicts Later Therapeutic Outcomes

- Smoking Craving Change Score: $r = -0.65, p = 0.009$
- Depression Change Score: $r = -0.41, p = 0.048$
- Anxiety Change Score: $r = -0.59, p < 0.001$
The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects
David B. Yaden and Roland R. Griffiths*

The Subjective Effects of Psychedelics May Not Be Necessary for Their Enduring Therapeutic Effects
David E. Olson*
Common factors of psychotherapy

- Common factors of psychotherapy (Frank, 1993):
  - emotionally charged, confiding relationship with an expert
  - healing setting
  - rationale, conceptual scheme, or myth
  - Therapeutic ritual
Mechanisms

• Psychotherapy
  • Psychological insight\(^1\)
  • Increased mindfulness/acceptance\(^2-4\)
  • Mystical/Peak experiences
  • Self-mastery/emotional skills
  • Interpersonally intimate, trusting environment

\(^1\) Davis et al. (2021). *J. Psychopharmacol*, 35(4), 437-446.
\(^2\) Madsen et al. (2020). *Eur Neuropsychopharm* 2020; 5
\(^3\) Soler et al. (2016) *Psychopharmacology (Berl)* 2016; 233: 823–829
\(^4\) Wolff et al. (2020). *Front Psychiatry* 2020; 11: 5
Mechanisms

• Psychotherapy
  • Psychological insight
  • Increased mindfulness/acceptance
  • Mystical/Peak experiences
  • Self-mastery/emotional skills
  • Interpersonally intimate, trusting environment

• Enhanced context-dependent plasticity?

References:
2 Madsen et al. (2020). *Eur Neuropsychopharm, 2020; 5*
3 Soler et al. (2016) *Psychopharmacology (Berl) 2016; 233: 823–829*
4 Wolff et al. (2020). *Front Psychiatry 2020; 11: 5*
Enhanced structural and functional plasticity

• Psilocybin induces rapid and persistent growth in dendritic spines and synapse formation in vitro\textsuperscript{1} and in vivo\textsuperscript{2} in rodents


MDMA but not cocaine reopens Social Reward Learning Critical Period

This is context dependent
Psilocybin and LSD also reopen Social Reward Learning Critical Period
This effect lasts for weeks
Neuroimaging theories

• REBUS/Entropic brain (Carhart-Harris & Friston, 2019)
• Altered thalamic gating (Vollenweider & Preller, 2020)
“To make biological survival possible, Mind at Large has to be funnelled through the reducing valve of the brain and nervous system. What comes out at the other end is a measly trickle of the kind of consciousness which will help us to stay alive on the surface of this particular planet.”
Why Interrupting the Default Mode Network with Psychedelics is Good for Mental Health

pamela  •  January 14, 2020

How To Tame the "Default Mode" of Your Wild Mind

Liberate yourself from repetitive, unhelpful thought patterns in 5 steps

The Default Mode Network: The Hidden Key to a Calmer, Happier, Content You
The Default-Mode Network Example

- DMN assoc w/ self-processing
- Psychedelics reduce DMN activity
- Psychedelics cause "ego dissolution"
The Default-Mode Network Example

- DMN assoc w/ self-processing
- Psychedelics reduce DMN activity
- Psychedelics cause “ego dissolution”

- dMn IS tHE egO
- dmn reDUctIOn IS The meChanIsM OF pSYcHEDELIc ego dIsSOLUTION
The Default-Mode Network Example

- However:
  - DMN decoherence rarely the strongest effect
  - Doesn’t always correlate well with relevant subjective measures
  - Seen with other drugs
Thank you!

CPCR team members:
- Roland Griffiths, Ph.D.
- Matthew Johnson, Ph.D.
- Fred Barrett, Ph.D.
- Albert Garcia-Romeu, Ph.D.
- Alan Davis, Ph.D.
- Mary Cosimano, M.S.W.
- William Richards, Ph.D.
- Natalie Gukasyan M.D.
- Manoj Doss, Ph.D.
- David Yaden, Ph.D.
- Ceyda Sayali, Ph.D.
- Nate Sepeda
- Anna Stearn
- Sam Hilbert
- Jess Lombardi
- Ian Geithner
Probability of weaker psilocybin effect with concurrent antidepressant

(n = 595)

Probability of weaker effect with 95% Confidence Intervals
Residential Psychedelic (LSD) Therapy for the Narcotic Addict

A Controlled Study

Charles Savage, MD, O. Lee McCabe, PhD, Baltimore

Fig 1.—Percent of patients maintaining total abstinence at 3-, 6-, 9-, and 12-month follow-up.