The ghost in the machine?
examining change phenomena in psychedelic assisted psychotherapy

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Early History: Ceremonial

1932
1943–1960: Discovery of LSD, Sober Research

1960s: The Genie is Out of the Bottle

After a long winter, a cultural re-emergence of psychedelics and a spring of research is upon us…
What is being studied?

<table>
<thead>
<tr>
<th>Indication(s)</th>
<th>ketamine</th>
<th>MDMA</th>
<th>Psilocybin</th>
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</thead>
<tbody>
<tr>
<td>Treatment-resistant depression</td>
<td>• Treatment-resistant depression</td>
<td>• Treatment-resistant PTSD</td>
<td>• Depression at end of life</td>
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<tr>
<td>• Social anxiety in autistic adults</td>
<td>• Social anxiety in autistic adults</td>
<td>• Alcohol dependence</td>
<td></td>
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<tr>
<td>• Anxiety at end of life</td>
<td>• Anxiety at end of life</td>
<td>• Nicotine dependence</td>
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<tr>
<td>FDA/DEA Off-label/CS III Research only/CS I Research status</td>
<td>Research only/CS III</td>
<td>Research only/CS I</td>
<td>Research only/CS I</td>
</tr>
<tr>
<td>Many centers and private practitioners already provide ketamine infusions</td>
<td>Phase II trials wrapping up, phase III likely soon</td>
<td>Phase II</td>
<td></td>
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</tbody>
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MOA

| NMDA receptor antagonist | Releaser of 5-HT, prolactin, oxytocin | 5-HT2A receptor agonist |


Comparative Effect Sizes for Different Treatments

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<tr>
<th>Cohen's d</th>
<th>D = 0.11</th>
<th>D = 0.17</th>
<th>D = 0.47</th>
<th>D = 0.68</th>
<th>D = 1</th>
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Can Psychedelics Catalyze the Change Process in Therapy?

The psychedelic experience as archetype of the hero’s journey, a trip

When was the last time someone told you about their mystical transformative journey on Prozac?

Life event

Psychopathology/Distress

Psychedelic-Assisted Therapy

Story/Subjective

Spirit

Neurobiology

Change/Healing
Vitalism vs Mechanism

Mechanism – “the machine”
- A doctrine that holds natural processes (as of life) to be mechanically determined and capable of complete explanation by the laws of physics and chemistry
- The black box
- Deterministic limited by observational ability
- Historic explanatory model of western medicine

Vitalism – “the ghost in the machine”
- A doctrine that the processes of life are not entirely explicable by the laws of physics and chemistry and that life is in some part self determining
- Soul/Story/Journey
- Holistic/vague
- Historic explanatory model of psychedelic induced change

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But what is actually happening inside the brain?

If PTSD, Depression, and Addiction are Examples of Overly Rigid Brain States, Psychedelics May Be a Way to Loosen Them

Psilocybin
- Potent agonist at
  - 5-HT₆A
  - 5-HT₂C
  - 5-HT₂A
- Psychedelic effects blocked by ketanserin (selective 5-HT₂A antagonist)

Psilocybin Decreases Activity in Key Connectivity Hubs (proportionate to subjective effects)
- Thalamus
- Anterior cingulate
- Posterior cingulate


—A. Huxley, 1954
Psilocybin: Less Constrained, More Intercommunicative Brain Communication

Simplified visualization of the persistence homological scaffolds.

Placebo Psilocybin


Connectivity Hubs: Constrain, Route, Allow for Predictability


Does psilocybin loosen brain network rigidity found in depression?

Active in introspective, self-referential, complex mental imagery, metacognition, future predicting tasks
Important connectivity hub
Home of the ego?
“Overstable” in depression?

Under Psilocybin – both networks become underactive and noncompetitive
(DMN more deactivated than TPN – similar to experienced meditators)

Default mode network
Task-positive network


What Does MDMA Do?

Release of oxytocin
Increased prosocial behavior
Decreased fear

Release of prolactin
Interpersonal trust

Release of presynaptic 5-HT
Stimulation of postsynaptic 5-HT 
Receptors
Elevated mood
Prosocial behavior
Decreased fear


Rapid Reduction of Depression Lasting at Least 3 Months


Optimal Arousal Zone

Flooded, overwhelmed, treatment is intolerable

Optimal arousal zone?

Reluctant, emotional numbing, treatment is avoided

**MDMA Results in Decreased Activity in the Hippocampus and Right Amygdala**

CBF = cerebral blood flow.


**MDMA May Quiet the Fear Response of the Amygdala**


**Does MDMA Change the Emotional Distress Associated with Negative Memories?**


**Change from Baseline after First and Second MDMA Session and at 2 Months Post-treatment**

CAPS = Clinician-Administered PTSD Scale.


**Upcoming Findings on Psilocybin for Depression/Anxiety in Cancer**

Psilocybin, found in magic mushrooms, decreased anxiety and depression in patients diagnosed with life-threatening cancer. New research shows that patients who received a psilocybin dose that altered perception and produced mystical-type experiences reported significantly less anxiety and depression compared with patients who received a low dose of the drug. The positive effects lasted 6 months.

Caveats and Cautions

- Psychedelic medicines do not have any currently recognized therapeutic usages per the US Food and Drug Administration, and all available data derive from small studies.
- Multiple alternative treatments exist for both major depressive disorder and posttraumatic stress disorder that are far better studied, including the novel agent ketamine.
- Although adverse events associated with psilocybin and MDMA are generally mild (eg, transient increase in blood pressure, nausea, anxiety, headache), limited data are available compared to currently approved medications.
- It is unknown how many treatments patients would need to maintain long-term benefits or whether and/or how treatment with psychedelics might be combined with use of standard agents.

How is the psychedelic experience a hero’s journey?

What if the story/consciousness doesn’t matter?

And the clinical outcome is the same, regardless of subjective experience?

What if the subjective experience (“trip”) was just a “side effect” (epiphenomenon), and not the actual cause of the change?

How would this change our conversation around the re-imagination of psychedelics?

Does one need the subjective experience, the change of consciousness to experience healing?

What if the drug were administered under general anesthesia?

What if the healing was just “biological”, and had nothing to do with the subjective narrative?

Embracing non-duality and shadow

“And this too...” —Tara Brach, Buddhist teacher

- Psychedelic psychotherapy has the potential to bring non-dualistic (physiologic/mechanistic action AND narrative therapeutic journey/vitalism) to psychiatry.
- What are the shadow aspects of mechanistic, western thinking?
- What are the shadow aspects of vitalistic, psychedelic-informed thinking?
### Practical Take-Aways

1. Psychedelic drugs, such as psilocybin and MDMA, are far more than mere intoxicants and have a growing research base supporting their use in carefully controlled clinical settings as an adjunct to psychotherapy.

2. The importance of conscious experience in the change process of psychiatric treatment remains unanswered, but the answers to this question hold broad implications for our treatment models.

3. Functional network rigidity is a useful explanatory framework for helping patients understand the subjective experience of depression and anxiety and can become part of the education we provide to patients about their conditions.