Psychedelic and Related Compounds 2021: State of the Field

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Disclosures

- **Consultant:** Compass Pathways; Mental Health Data Services, Inc. (MHDS); Pear Therapeutics

- **Stockholder (directly purchased or options):** Mental Health Data Services, Inc. (MHDS); Quartet Health, Inc., Pear Therapeutics, Karuna Therapeutics
Agenda

- Context of new research
  - Psilocybin, MDMA,
- Prior issues and use
- Areas of Investigation
  - Treatment resistant depression
  - PTSD
  - Major Depression
- Current state of the Field
Context of New Research

- Limits of current treatments for many common psychiatric disorders and reduced drug discovery by pharmaceutical houses
- Anxiety, alcoholism, Mood disorders, and PTSD
- Wave of interest by new generation of researchers and in entrepreneurial circles
A variety of agents have been studied often requiring complex approval processes due to restrictions.

Among these are LSD, MDMA, ayahuasca and psilocybin.

Most studied for clinical purposes:
- Psilocybin – Mood and anxiety disorders, End of life anxiety
- MDMA – PTSD

Imaging and psychological states.
Prior Issues and Use

- Complex past history
- Use of many agents by tribes in different cultures
- Often used as part of established religious rituals
- Widespread nonclinical use
LSD and Psilocybin

- Both powerful 5HT2A agonists
- Evidence of change in cerebral blood flow and functional connectivity
Neural correlates of the LSD experience revealed by multimodal neuroimaging


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Edited by Marcus E. Raichle, Washington University in St. Louis, St. Louis, MO, and approved March 1, 2016 (received for review September 17, 2015)

LSD Neuroimaging

- Significant between condition differences (orange = increases) in RSFC between the V1 seed region (purple) and the rest of the brain (n = 15)

RSFC – Resting-state functional connectivity
Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution

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http://dx.doi.org/10.1016/j.cub.2016.02.010

LSD Neuroimaging

Psilocybin

- Clinical studies
- Mood and anxiety studies in end of life care
- Treatment resistant depression
- Major Depression
Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Roland R Griffiths1,2, Matthew W Johnson1, Michael A Carducci3, Annie Umbricht2, William A Richards1, Brian D Richards1, Mary P Cosimano1 and Margaret A Klinedinst1

Abstract
Cancer patients often develop chronic, clinically significant symptoms of depression and anxiety. Previous studies suggest that psilocybin may decrease depression and anxiety in cancer patients. The effects of psilocybin were studied in 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. This randomized, double-blind, crossover trial investigated the effects of a very low (placebo-like) dose (1 or 3 mg/70 kg) vs. a high dose (22 or 30 mg/70 kg) of psilocybin administered in a counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up. Instructions to participants and staff minimized expectancy effects. Participants, staff, and community observers rated participant moods, attitudes, and behaviors throughout the study. High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety. At 6-month follow-up, these changes were sustained, with about 83% of participants continuing to show clinically significant decreases in depressed mood and anxiety. Participants attributed improvements in attitudes about life/self, mood, relationships, and spirituality to the high-dose experience, with 80% endorsing moderately or greater increased well-being/life satisfaction. Community observer ratings showed corresponding changes. Mystical-type psilocybin experience on session day mediated the effect of psilocybin dose on therapeutic outcomes.

Psilocybin

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, Anthony Bossis1,2,4, Jeffrey Guss1,2,4, Gabrielle Agin-Lahesm1, Tara Malone1, Barry Cohen7, Sarah E Mennenga6, Alexander Belser6, Krystalia Kalliontz6, James Babb7, Zhe Su7, Patricia Corby2 and Brian L Schmidt2

Abstract

Background: Clinically significant anxiety and depression are common in patients with cancer, and are associated with poor psychiatric and medical outcomes. Historical and recent research suggests a role for psilocybin to treat cancer-related anxiety and depression.

Methods: In this double-blind, placebo-controlled, crossover trial, 29 patients with cancer-related anxiety and depression were randomly assigned and received treatment with single-dose psilocybin (0.3 mg/kg) or placebo, both in conjunction with psychotherapy. The primary outcomes were anxiety and depression assessed between groups prior to the crossover at 7 weeks.

Results: Prior to the crossover, psilocybin produced immediate, substantial, and sustained improvements in anxiety and depression and led to decreases in cancer-related distress and hopelessness. Improved spiritual wellbeing, and increased quality of life. At the 6.5-month follow-up, psilocybin was associated with enduring anxiolytic and anti-depressant effects (approximately 60–80% of participants continued with clinically significant reductions in depression or anxiety), sustained benefits in existential distress and quality of life, as well as improved attitudes towards death. The psilocybin-induced mystical experience mediated the therapeutic effect of psilocybin on anxiety and depression.

Conclusions: In conjunction with psychotherapy, single moderate-dose psilocybin produced rapid, robust and enduring anxiolytic and anti-depressant effects in patients with cancer-related psychological distress.

Trial Registration: ClinicalTrials.gov Identifier: NCT0097359

DOI: 10.1177/0269881116675512

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Psilocybin Ross End of Life Care

- Ross et al. studied 29 cancer patients using a 2 session, double-blind, crossover (7 weeks after administration of dose 1) design employing psilocybin first then niacin second, or niacin first and psilocybin second.

- Both groups had extensive orientation to the trial and psychotherapy with supportive, psychodynamic, and existential elements.

Psilocybin produced immediate and ongoing anxiolytic and antidepressant response

- 83% in the psilocybin-first group (vs. 14% in the niacin-first group) meeting criteria for antidepressant response seven weeks after dose 1.

- Pre-crossover results were significant post initial drug administration, although Beck Depression Index between groups was significant at the p < 0.05 level, 1 day prior to initial drug administration but not at baseline.

- At follow-up at 6.5 months (after both groups received psilocybin), antidepressant or anxiolytic response rates were in the 60–80% range depending upon measure.

- Subjects’ mystical or spiritual experiences highly correlated with clinical response and mediated four out of six primary outcome measures.

Psilocybin Griffiths End of Life Care

- 51 cancer patients using a 2 session, double-blind, crossover (5 weeks after administration of dose 1) design employing high-dose psilocybin 1st, then very low-dose (PBO-like) psilocybin second, or very low-dose (PBO-like) psilocybin first and high-dose psilocybin second
- Use of low-dose psilocybin as its own control, instructional language to subjects that aimed to minimize the PBO response, and extensive supportive meetings with study personnel (but not formalized psychotherapy) were distinctive element of the study design

Psilocybin Griffiths End of Life Care

- High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety.
  5 weeks after session 1, 92% in the high-dose psilocybin-first group (vs. 32% in the low dose-first group) showed clinically significant response and 60% vs 16% symptom remission.
- At 6 mon follow-up (after both groups received high-dose psilocybin), changes were sustained, with ~80% continuing to show clinically significant decreases in depressed mood and anxiety. Subjects’ mystical or spiritual experiences were highly correlated with clinical response and mediated seven of the primary outcome measures.

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


Summary

Background Psilocybin is a serotonin receptor agonist that occurs naturally in some mushroom species. Recent studies have assessed the therapeutic potential of psilocybin for various conditions, including end-of-life anxiety, obsessive-compulsive disorder, and smoking and alcohol dependence, with promising preliminary results. Here, we aimed to investigate the feasibility, safety, and efficacy of psilocybin in patients with unipolar treatment-resistant depression.

Methods In this open-label feasibility trial, 12 patients (six men, six women) with moderate-to-severe, unipolar, treatment-resistant major depression received two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in a supportive setting. There was no control group. Psychological support was provided before, during, and after each session. The primary outcome measure for feasibility was patient-reported intensity of psilocybin’s effects. Patients were monitored for adverse reactions during the dosing sessions and subsequent clinic and remote follow-up. Depressive symptoms were assessed with standard assessments from 1 week to 3 months after treatment, with the 16-item Quick Inventory of Depressive Symptomatology (QIDS) serving as the primary efficacy outcome. This trial is registered with ISRCTN, number ISRCTN14426797.

Findings Psilocybin’s acute psychedelic effects typically became detectable 30–60 min after dosing, peaked 2–3 h after dosing, and subsided to negligible levels at least 6 h after dosing. Mean self-rated intensity (on a 0–1 scale) was 0.51 (SD 0.36) for the low-dose session and 0.75 (SD 0.27) for the high-dose session. Psilocybin was well tolerated by all of the patients, and no serious or unexpected adverse events occurred. The adverse reactions we noted were transient anxiety during drug onset (all patients), transient confusion or thought disorder (nine patients), mild and transient nausea (four patients), and transient headache (four patients). Relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference −11.8, 95% CI −9.15 to −14.35, p = 0.002, Hedges’ g=2) and 3 months (−9.2, 95% CI −5.69 to −12.71, p = 0.003, Hedges’ g=2) after high-dose treatment. Marked and sustained improvements in anxiety and anhedonia were also noted.

Interpretation This study provides preliminary support for the safety and efficacy of psilocybin for treatment-resistant depression and motivates further trials, with more rigorous designs, to better examine the therapeutic potential of this approach.

Psilocybin Treatment Resistant Depression
Proof of Concept Trial

- The inclusion criteria were major depression of a moderate to severe degree (17+ on the 21-item Hamilton Depression Rating scale [HAM-D]), and no improvement despite two adequate courses of antidepressant treatment of different pharmacological classes lasting at least 6 weeks within the current depressive episode.

- Subjects received two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in a supportive setting.

Psilocybin Treatment Resistant Depression
Proof of Concept Trial

- The adverse reactions we noted were transient anxiety during drug onset (all patients), transient confusion or thought disorder (9 patients), mild and transient nausea (4 patients), and transient headache (4 patients).
- Relative to baseline, depressive symptoms were markedly reduced 1 wk (mean QIDS difference $-11.8$, 95% CI $-9.15$ to $-14.35$, $p = 0.002$, Hedges’ $g = 3.1$) and 3 mon ($-9.2$, 95% CI $-5.69$ to $-12.71$, $p = 0.003$, Hedges’ $g = 2$) after high-dose treatment.
- Marked and sustained improvements in anxiety and anhedonia were also noted.

## Psilocybin Treatment Resistant Depression Proof of Concept Trial


### Table 3: Clinical ratings at baseline and follow-up

<table>
<thead>
<tr>
<th>QIDS</th>
<th>BDI</th>
<th>STAI-T</th>
<th>SHAPS</th>
<th>HAM-D</th>
<th>MADRS</th>
<th>GAF</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>1 week</td>
<td>2 weeks</td>
<td>3 weeks</td>
<td>5 weeks</td>
<td>3 months</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>19.2 (4.9)</td>
<td>7.4 (4.6)</td>
<td>6.3 (5.1)</td>
<td>6.4 (5.3)</td>
<td>8.2 (5.4)</td>
<td>10.0 (6.0)</td>
</tr>
<tr>
<td>Difference versus baseline</td>
<td>-11.8 (-9.1 to -14.5)</td>
<td>-12.9 (-10.4 to -15.6)</td>
<td>-12.8 (-10.1 to -15.6)</td>
<td>-12.0 (-9.6 to -14.6)</td>
<td>-9.2 (-6.8 to -12.8)</td>
<td>-25.0 (-20.1 to -29.9)</td>
</tr>
<tr>
<td>Hedges’ g*</td>
<td>3.1</td>
<td>3.2</td>
<td>3.2</td>
<td>2.7</td>
<td>2.0</td>
<td>3.2</td>
</tr>
<tr>
<td>p value*</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.003</td>
<td>0.003</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Follow-up refers to the period starting after the second (high-dose) administration of psilocybin. Clinician-administered ratings (HAM-D, MADRS, and GAF) were completed only at baseline and 1 week after the high-dose session. QIDS=Quick Inventory of Depressive Symptoms. BDI=Beck Depression Inventory. STAI-T=State-Trait Anxiety Inventory. SHAPS=Snell-Hamilton Pleasure Scale. HAM-D=Hamilton Depression Rating scale. MADRS=Montgomery-Åsberg Depression Rating Scale. GAF=Global Assessment of Functioning. *Compared with baseline.
Psilocybin with psychological support is showing promise as a treatment model in psychiatry but its therapeutic mechanisms are poorly understood. Here, cerebral blood flow (CBF) and blood oxygen-level dependent (BOLD) resting-state functional connectivity (RSFC) were measured with functional magnetic resonance imaging (fMRI) before and after treatment with psilocybin (serotonin agonist) for treatment-resistant depression (TRD). Quality pre and post treatment fMRI data were collected from 16 of 19 patients. Decreased depressive symptoms were observed in all 19 patients at 1-week post-treatment and 4746 met criteria for response at 5 weeks. Whole-brain analyses revealed post-treatment decreases in CBF in the temporal cortex, including the amygdala. Decreased amygdala CBF correlated with reduced depressive symptoms. Focusing on a priori selected circuitry for RSFC analyses, increased RSFC was observed within the default-mode network (DMN) post-treatment. Increased ventromedial prefrontal cortex-bilateral inferior lateral parietal cortex RSFC was predictive of treatment response at 5 weeks, as was decreased parahippocampal-prefrontal cortex RSFC. These data fill an important knowledge gap regarding the post-treatment brain effects of psilocybin, and are the first in depressed patients. The post-treatment brain changes are different to previously observed acute effects of psilocybin and other "psychoactive" agents and represent a "reset" therapeutic mechanism is proposed.
Psilocybin for Treatment Resistant Depression: Neuroimaging

- Decreased PH-PFC RSFC predicts better long-term prognosis

RSFC – Resting-state functional connectivity
Psilocybin for Treatment Resistant Depression: Neuroimaging

- Quality pre and post treatment fMRI data were collected from 16 of 19 patients in open label trial one day after 25 mg dose.
- Decreased depressive symptoms were observed in all 19 patients at 1-week post-treatment and 47% met criteria for response at 5 weeks.
- Decreased parahippocampal-prefrontal cortex RSFC was predictive of treatment response at 5 weeks.
- Results revealed that patients scoring highest on ‘peak’ or ‘mystical’ experience had the greatest decreases in PH RSFC in limbic (e.g. bilateral amygdala) and DMN-related cortical regions (e.g. the PCC).

Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer

Gabielle I Agin-Liebes¹,², Tara Malone²,³, Matthew M Yalch¹, Sarah E Mennenga², K Linnae Ponté⁴, Jeffrey Guss²,³,⁵, Anthony P Bossis²,³,⁵, Jim Grigsby⁶,⁷, Stacy Fischer⁶,⁷ and Stephen Ross²,³,⁵

Follow up to Ross et al (2016) which showed large scale reductions (60—80%) in anxiety and depression at 6.5 months post trial for cancer patients.

Of 16 patients still alive, 15 participated follow up at 3.2 and 4.5 years.

Long Term Follow up Psilocybin in Existential Anxiety and Depression

Figure 1. Primary outcome variables: cancer-related anxiety and depression (post-crossover).

Means (± standard error (SE)) for primary outcome measures for both dose-sequence groups combined are shown at the following time points: Baseline (N=16), 6.5 months (parent study endpoint N=16), mean 3.2 years (first follow up N=16), and mean 4.5 years (second follow up N=14). Closed points represent significant within-subject differences relative to scores at baseline. Longitudinal within-subject effect sizes, represented as Cohen’s d, are shown above time points. HADS: Hospital Anxiety and Depression Scales; STAI: State-Trait Anxiety Inventory.
Long Term Follow up Psilocybin in Existential Anxiety and Depression

**Figure 2.** Percentage of participants with antidepressant or anxiolytic response rates and antidepressant symptom remission at final follow-up. Data are percentages of participants (in both dose sequence groups combined) fulfilling criteria for antidepressant or anxiolytic response or antidepressant symptom remission (Hospital Anxiety and Depression Scale-Depression (HADS-D), Beck Depression Inventory (BDI)) at the 4.5-year point (second long-term follow-up; N=14). Clinical response was defined as 50% or greater decrease in each measure relative to baseline; symptom remission was defined as 50% or greater decrease in the measure relative to baseline and a score of ≤7 on HADS-D or ≤12 on BDI.
Long Term Follow up Psilocybin in Existential Anxiety and Depression

**Figure 4.** Persisting effects attributed to psilocybin administration. Percentage of volunteers who endorsed persisting effects attributable to psilocybin administration on the Persisting Effects Questionnaire at the 4.5-year point (second long-term follow-up: N=14): percentage who endorsed “among the top five” or “the single most” personally meaningful experiences; “among the top five” or “the single most” spiritually significant experiences; “moderate,” “strong” or “extreme” positive behavioral change; and “increased moderately” or “increased very much” well-being or life satisfaction.
96% rated the experience among the 5 most meaningful in their lives
Challenging Experiences with Psilocybin

Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences

Theresa M Carbonaro¹, Matthew P Bradstreet¹, Frederick S Barrett¹, Katherine A MacLean¹, Robert Jesse¹,², Matthew W Johnson¹ and Roland R Griffiths¹,³

Carbonaro TM, J Psychopharmacology 2016 30 (12) 1268-78

Tufts Medical Center
Challenging Experiences with Psilocybin

- 2000 participants 78% male
- Average 30 years old
- On-line survey of their “single most psychologically difficult or challenging experience after taking psilocybin mushrooms. Of these
  - 39% rated the experience as among the top five (including single most) most challenging experiences of their lifetime,
  - 11% reported putting themselves or others at risk of physical harm,
  - 2.6% reported behaving in a physically aggressive or violent manner
  - 2.7% reported getting medical help
  - 1 year or later, 7.6% reported that they sought treatment
Challenging Experiences with Psilocybin

- Linked to
- High Dose
- Prior Mental State
- Set and Setting
Psilocybin vs. Escitalopram for MDD

**Psilocybin versus Escitalopram for Depression**

**PHASE 2, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL**

<table>
<thead>
<tr>
<th>Group</th>
<th>Intervention</th>
<th>Duration</th>
<th>Placebo</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psilocybin</td>
<td>(two 25-mg doses 3 wk apart) + placebo (microcrystalline cellulose)</td>
<td>N=30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>(10 mg daily [3 wk], then 20 mg [3 wk]) + placebo (psilocybin, 1-mg doses 3 wk apart)</td>
<td>N=29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Change in QIDS-SR-16 depressive symptom score at 6 wk**

- **Psilocybin:** -8.0±1.0
- **Escitalopram:** -6.0±1.0

**Difference, -2.0 points (95% CI, -5.0 to 0.9)**

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/NEJMo2032994

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Psilocybin vs. Escitalopram for MDD Primary Outcomes

A. Change from Baseline in QIDS-SR-16 Score

B. Change from Baseline in WEMWBS Score

R. Carhart-Harris et al
N Engl J Med 2021; 384:1402-1411
Psilocybin vs. Escitalopram for MDD
Secondary Outcomes

Section S6. Supplemental Figure S4: Mean change for primary & secondary efficacy outcomes with confidence intervals

Figure S4. All (mean change) efficacy outcomes compared between conditions at week 6 (primary endpoint). Escitalopram in blue, psilocybin in red. Green confidence intervals (CIs) indicate no crossing of zero (i.e., > 95% confidence in difference), black CIs indicate crossing of zero and hence no between condition statistical difference. CIs are not corrected for multiple comparisons. Left panel is mean, right panel is mean difference and 95% CI. QIDS-SR-16 = primary outcome. All others are secondary outcomes.

R. Carhart-Harris et al
N Engl J Med 2021; 384:1402-1411
Psilocybin vs. Escitalopram for MDD Secondary Outcomes

Figure S7. EBI scores range 0-100, where 100 = “the most imaginable”. See 14 for the original validation paper on the EBI. Left panel is mean and 95% CI, middle panel is mean diff of session 1 and 2 + 95% CI, right panel also mean and 95% CI.

R. Carhart-Harris et al
N Engl J Med 2021; 384:1402-1411
Psilocybin vs. Escitalopram for MDD
Secondary Outcomes

- Emotional breakthrough, Mystical Experience Questionnaire and Challenging Experience Questionnaire scores combined, significantly predicted subsequent changes in well-being ($r=0.45, p=0.0005, n=75$), with each scale contributing significant predictive value.

R. Carhart-Harris et al
N Engl J Med 2021; 384:1402-1411
Psilocybin vs. Escitalopram for MDD
Secondary Outcomes

- Emotional breakthrough and Mystical Experience Questionnaire scores predicted increases in well-being and Challenging Experience Questionnaire scores predicted less increase.
- For example: “I experienced a resolution of a personal conflict/trauma.”
- Or: “I was able to get a sense of closure on an emotional problem.”

R. Carhart-Harris et al
N Engl J Med 2021; 384:1402-1411
Participant disposition and demographics

Randomised (n=233)

Allocation

COMP360 25mg (n=79)
- Completed (n=74)
- Discontinued (n=5)
  - Withdrawal by participant (n=2)
  - Adverse event (n=2)
  - Lost to follow-up (n=1)

COMP360 10mg (n=75)
- Completed (n=66)
- Discontinued (n=9)
  - Withdrawal by participant (n=6)
  - Adverse event (n=2)
  - Lack of efficacy (n=1)

COMP360 1mg (n=79)
- Completed (n=69)
- Discontinued (n=10)
  - Withdrawal by participant (n=6)
  - Lost to follow-up (n=2)
  - Lack of efficacy (n=1)
  - Physician decision (n=1)

Follow-up

131 (56%) patients were from Europe, 102 (44%) from North America

219 (94%) patients had no prior psilocybin experience

Participant demographics (age, gender, race, BMI, baseline depression symptom severity) were well balanced across the three groups

Note: BMI = body mass index; n = number of participants; follow-up = post-COMP360 administration to week 12

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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.

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

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Key secondary endpoint - MADRS responders

25mg group demonstrated rapid response, with treatment differences from day 2 to week 3 compared with the 1mg group.

Responser: ≥50% decrease in MADRS total score from baseline

<table>
<thead>
<tr>
<th>Week</th>
<th>COMP360 25mg</th>
<th>COMP360 10mg</th>
<th>COMP360 1mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>42</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Week 1</td>
<td>35</td>
<td>17</td>
<td>12</td>
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<td>Week 3</td>
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<td>Week 6</td>
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<td>11</td>
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<td>Week 9</td>
<td>20</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Week 12</td>
<td>26</td>
<td>12</td>
<td>13</td>
</tr>
</tbody>
</table>

Note: MADRS = Montgomery-Asberg Depression Rating Scale; number of responders stated in bar.
Participants who started new treatment for depression were assumed to be non-responders, hence decreasing numbers reflecting antidepressant use over time.
Key secondary endpoint - MADRS remitters

25mg group demonstrated rapid remission, with treatment differences from day 2 to week 3 compared with the 1mg group.

Note: MADRS = Montgomery-Åsberg Depression Rating Scale; number of remitters stated in bar
Participants who started new treatment for depression were assumed to be non-remitters, hence decreasing numbers reflecting antidepressant use over time.
MADRS sustained responders at week 12

Higher proportion of sustained responders found in the 25mg vs 1mg arm

Sustained responder*—patients meeting the MADRS response criteria at week 3 and at week 12, and at least at one visit out of week 6 and week 9, and who did not start any new treatments for depression

Note: MADRS = Montgomery-Åsberg Depression Rating Scale; number of sustained responders stated in bar
Statistical significance cannot be claimed on secondary endpoints due to hierarchical testing being broken for the 10mg vs 1mg dose on the primary endpoint
Participants who started new treatment for depression were assumed to be non-responders, hence decreasing numbers reflecting antidepressant use over time
*The protocol-defined sustained response up to week 12 was 20.3% of patients in the 25mg group vs 10.1% in the 1mg group

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MDMA
3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial

Michael Mithoefer, Ann T Mithoefer, Allison A Feduccia, Lisa Jerome, Mark Wagner, Joy Wymer, Julie Holland, Scott Hamilton, Berra Yazar-Klosinski, Amy Emerson, Rick Doblin

Summary
Background Post-traumatic stress disorder (PTSD) is prevalent in military personnel and first responders, many of whom do not respond to currently available treatments. This study aimed to assess the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treating chronic PTSD in this population.
MDMA-Assisted Psychotherapy in Veterans and First Responders with Chronic PTSD

- RCT of service personnel ≥18 year old with chronic PTSD duration of ≥6 months who had a CAPS-IV total score of ≥50
- Randomized to MDMA + psychotherapy 30 mg (active control, n = 7), 75 mg (n = 7), or 125 mg (m = 12) administered orally in 2 x 8 hr sessions with psychotherapy

CAPS-IV = Clinician Administered PTSD Scale for DSM-IV
Active doses (75 mg and 125 mg) of MDMA with adjunctive psychotherapy in a controlled setting were effective and well tolerated in reducing PTSD symptoms in veterans and first responders.

CAPS-IV = Clinician Administered PTSD Scale for DSM-IV
Meta-analysis Prolonged Exposure vs. MDMA

Treating posttraumatic stress disorder with MDMA-assisted psychotherapy: A preliminary meta-analysis and comparison to prolonged exposure therapy

Timothy Amoroso¹ and Michael Workman²

Tufts Medical Center

Amoroso T and Workman M J Psychopharmacology 2016 30 (7) 595-600
## Table 1. Summary of effect sizes by treatment type.

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges' $g$ primary outcome</th>
<th>Hedges' $g$ secondary outcome</th>
<th>Dropout rate % (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>1.08</td>
<td>0.77</td>
<td>27.0 (10.8)</td>
</tr>
<tr>
<td>MDMA-AP</td>
<td>1.17</td>
<td>0.87</td>
<td>12.7 (5.6)</td>
</tr>
</tbody>
</table>

*The primary outcome measures focus exclusively on PTSD symptomology and included CAPS, MPSS-SR, PCL, PSS-I, PDS, and the SI-PTSD. Both MDMA-AP studies used the CAPS for a primary outcome measure.

*Secondary outcome measures accounted for other factors (e.g., quality of life, depression, anxiety, etc.) and included CES-D, GHQ-28, BDI, HADS, IES-R, QOLI, SAS-SR, PDS, and the STAI. Mithoefer et al. (2011) used the IES-R as a secondary outcome measure, while Oehen et al. (2013) used the PDS.

PE: prolonged exposure therapy; MDMA-AP: MDMA-assisted psychotherapy.
MDMA for PTSD Phase 3

Mitchell et al 2021 Nature Medicine
After psychiatric medication washout, participants (n = 90) were randomized 1:1 to receive manualized therapy with MDMA or with placebo, combined with three preparatory and nine integrative therapy sessions. PTSD symptoms, measured with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5, the primary endpoint), and functional impairment, measured with the Sheehan Disability Scale (SDS, the secondary endpoint) were assessed at baseline and at 2 months after the last experimental session.
MDMA was found to induce significant and robust attenuation in CAPS-5 score compared with placebo (P < 0.0001, d = 0.91) and to significantly decrease the SDS total score (P = 0.0116, d = 0.43). The mean change in CAPS-5 scores in participants completing treatment was −24.4 (s.d. 11.6) in the MDMA group and −13.9 (s.d. 11.5) in the placebo group.
MDMA for PTSD Phase 3

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Mitchell et al 2021 Nature Medicine
MDMA for PTSD Phase 3

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MDMA for PTSD Phase 3

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MDMA for PTSD Phase 3

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Psilocybin in end of life care: Implications for further research

Paul Summergrad
The history of psychedelics and their legal status as highly restricted compounds of course make this a more complex issue. The use of psilocybin and related compounds in spiritual ceremonies has a very long history in many traditional and non-Western cultures. The more recent history of widespread non-clinical use makes the status of these compounds more complex and suspect. Changing legalization and regulatory environment. While there is evidence of the safety of these compounds in well-selected individuals under careful supervision other use has seen more adverse experience.
These compounds have important value in understanding the neural networks that support a well-delineated sense of self and other, and potentially in antidepressant or anxiolytic mechanisms of action.

However, neuroimaging studies with psilocybin and other psychedelics agents are in their early stages and have small subject size.

Many participants rated their psilocybin experience as among the most profound and meaningful of their lives. How to understand the role of these experience and their neural correlates is an important area of ongoing research.

Tufts Medical Center
Current State of the Field and Cautionary Notes

- It is unclear at present to what degree this benefit is due to the power of these experiences, ongoing changes in neural mechanisms, or other causes.
- The experiences of salience, meaningfulness, and healing that accompanied these powerful spiritual experiences and that were found to be mediators of clinical response in both of these care fully performed studies are also important to understand in their own right and are worthy of further study and contemplation.

Current State of the Field and Cautionary Notes

- Given the strength of these findings, more extensive studies to replicate these outcomes are called for, as are studies in more diverse clinical populations.
- It is difficult to blind these agents adequately, consideration should be given to including research groups that have had less prior involvement in this area to minimize placebo responsiveness.
- The complex history and legal status of psilocybin and related agents suggests additional thought be given as to how to deal with the unique legal, ethical, and regulatory issues surrounding clinical use of these agents.
While preliminary data support the use of psychedelics for the management of treatment resistant conditions, clinicians should proceed with caution, recognizing that more extensive studies are warranted.

More recent double-blind studies for well defined clinical conditions show less clear-cut outcomes.
Discussion