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60's Revenge: Psychedelics in Treatment Resistant Conditions

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Learning Objective

Review the clinical data for the use of psychedelics in the management of treatment resistant conditions.

Agenda

- Context of new research
  - LSD, Psilocybin, MDMA, Ayahusca
- Prior issues and use
- Areas of Investigation
  - Treatment resistant depression
  - PTSD
- Cautionary Notes

Context of New Research

- Limits of current treatments for many common psychiatric disorders and reduced drug discovery by pharmaceutical houses
- Anxiety, alcoholism, depression, and PTSD
- Wave of interest by new generation of researchers and in entrepreneurial circles

Context of New Research

- A variety of agents have been studied often requiring complex approval processes due to restrictions
- Among these are LSD, MDMA, ayahusca and psilocybin
- Most studied for clinical purposes
  - Psilocybin – Mood and anxiety disorders
  - MDMA – PTSD
- Imaging studies

MDMA: 3,4-methylenedioxy-methamphetamine; street name: Ecstasy/Molly

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

LSD Neuroimaging

Neural correlates of the LSD experience revealed by multimodal neuroimaging

Robin L. Carhart-Harris[a,1], Suresh Muthukumaraswamy[b,c,d], Leor Roseman[a,e,2], Mendel Kaelen[a,2], Wouter Droog[b], Kevin Murphy[b], Enzo Tagliazucchi[f,g], Eduardo E. Schenberg[a,h,i], Timothy Nest[j], Csaba Orban[a,e], Robert Leech[e], Luke T. Williams[a], Tim M. Williams[k], Mark Bolstridge[a], Ben Sessa[a,l], John McGonigle[a], Martin I. Sereno[m], David Nichols[n], Peter J. Hellyer[e], Peter Hobden[b], John Evans[b], Krish D. Singh[b], Richard G. Wise[b], H. Valerie Curran[o], Amanda Feilding[p], and David J. Nutt[a]

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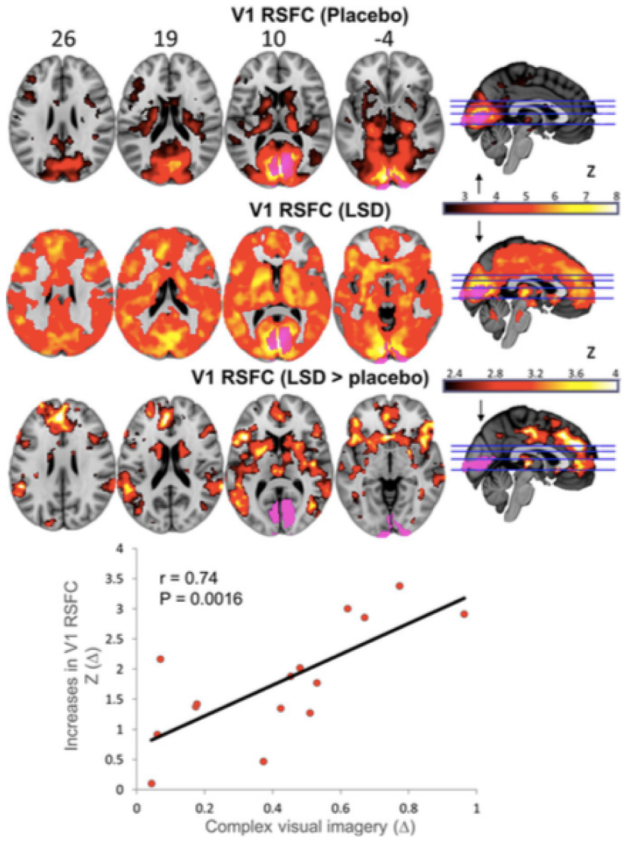
Carhart-Harris RL, et al. *Proc Natl Acad Sci U S A.* 2016;113(17):4853-4858.

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

Carhart-Harris RL, et al. *Proc Natl Acad Sci U S A*. 2016;113(17):4853-4858.

Psilocybin

- Clinical studies
- Mood and anxiety studies in end of life care
- Treatment resistant depression

Psilocybin

Original Paper

Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial

Stephen Ross[1,2,3,4,5,6], Anthony Bossis[1,2,4], Jeffrey Guss[1,2,4], Gabrielle Agin-Liebes[10], Tara Malone[1], Barry Cohen[7], Sarah E Mennenga[1], Alexander Belser[8], Krystallia Kalliontzi[2], James Babb[9], Zhe Su[3], Patricia Corby[2] and Brian L Schmidt[2]

Psychopharm

Journal of Psychopharmacology
1–16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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 niacin, 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 demoralization 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: NCT00957359

DOI: 10.1177/0269881116675512

Psilocybin in 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

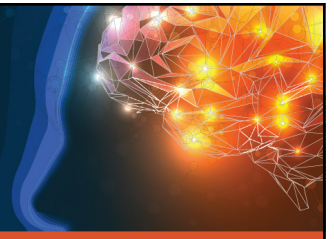
Ross S, et al. *J Psychopharmacol*. 2016;30(12):1165-1180.

Psilocybin in End of Life Care

- 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 $p < .05$ 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

Ross S, et al. *J Psychopharmacol.* 2016;30(12):1165-1180.

Psilocybin Treatment Resistant Depression Proof of Concept Trial



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

Robin L Carhart-Harris, Mark Bolstridge, James Rucker, Camilla M J Day*, David Erritzoe, Mendel Kaelen, Michael Bloomfield, James A Rickard, Ben Forbes, Amanda Feilding, David Taylor, Steve Pilling, Valerie H Curran, David J Nutt*

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 Symptoms (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=3·1) 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.

Lancet Psychiatry 2016; 3: 619–27

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See Comment page 592

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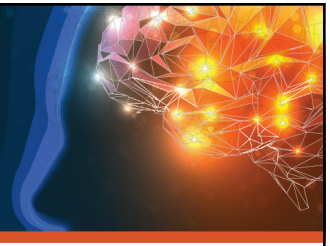
Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

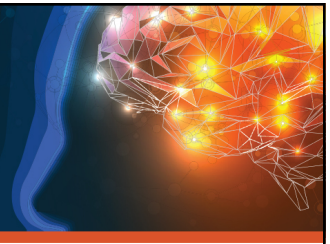
Psilocybin Treatment Resistant Depression Proof of Concept Trial



- 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

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

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* = .002, Hedges' g = 3.1) and 3 mon (–9·2, 95% CI –5.69 to –12·71, *p* = .003, Hedges' g = 2) after high-dose treatment
- Marked and sustained improvements in anxiety and anhedonia were also noted

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Psilocybin Treatment Resistant Depression Proof of Concept Trial

	QIDS						BDI			STAI-T			SHAPS			HAM-D		MADRS		GAF	
	Base-line	1 week	2 weeks	3 weeks	5 weeks	3 months	Base-line	1 week	3 months	Base-line	1 week	3 months	Base-line	1 week	3 months	Base-line	1 week	Base-line	1 week	Base-line	1 week
Mean (SD)	19·2 (2·0)	7·4 (4·9)	6·3 (4·6)	6·4 (5·1)	8·2 (5·4)	10·0 (6·0)	33·7 (7·1)	8·7 (8·4)	15·2 (11·0)	70·1 (5·8)	40·6 (14·2)	54·8 (14·5)	7·5 (3·7)	1·4 (2·7)	2·8 (3·7)	21·4 (4·5)	7·4 (6·9)	31·0 (5·0)	9·7 (9·8)	50·3 (9·2)	77·7 (13·0)
Difference versus baseline (95% CI)	..	−11·8 (−9·15 to −14·35)	−12·9 (−10·64 to −15·16)	−12·8 (−9·9 to −15·6)	−11·0 (−7·7 to −14·2)	−9·2 (−5·69 to −12·71)	..	−25·0 (−20·1 to −29·9)	−18·5 (−11·8 to −25·2)	..	−29·5 (−22·03 to −36·97)	−15·3 (−7·77 to −22·83)	..	−6·1 (−4·46 to −7·74)	−4·7 (−3·29 to −6·11)	..	−14·0 (−9·6 to −18·4)	..	−23·3 (−17·1 to −29·5)	..	27·3 (18·0 to 36·6)
Z	..	−3·1	−3·1	−3·06	−2·9	−3·0	..	−3·1	−3·1	..	−3·1	−2·9	..	−3·1	−3·1	..	−3·0	..	−3·1	..	3
Hedges' g*	..	3·1	3·2	3·2	2·7	2·0	..	3·2	2·0	..	2·7	1·4	..	1·9	1·3	..	2·4	..	2·7	..	2·4
p value*	..	0·002	0·002	0·002	0·003	0·003	..	0·002	0·002	..	0·002	0·004	..	0·002	0·002	..	0·003	..	0·002	..	0·003

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=Snaith-Hamilton Pleasure Scale. HAM-D=Hamilton Depression Rating scale. MADRS=Montgomery-Åsberg Depression Rating Scale. GAF=Global Assessment of Functioning. *Compared with baseline.

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

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Psilocybin for Treatment Resistant Depression: Neuroimaging

SCIENTIFIC REPORTS

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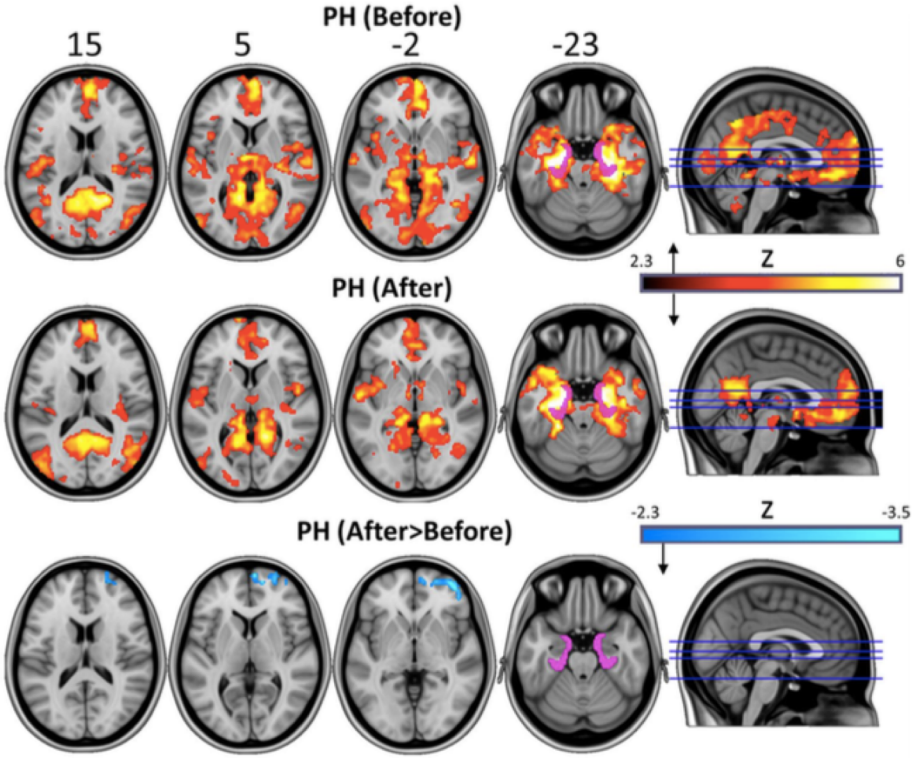
Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms

Robin L Carhart-Harris[1], Leor Roseman[1,2], Mark Bolstridge[1], Lysia Demetriou[5,6], J Nienke Pannekoek[1,7], Matthew B Wall[1,4,5], Mark Tanner[5], Mendel Kaelen[1], John McGonigle[5], Kevin Murphy[3], Robert Leech[2], H Valerie Curran[4] & David J Nutt[1]

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 47% 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 'psychedelics' yet were related to clinical outcomes. A 'reset' therapeutic mechanism is proposed.

Carhart-Harris RL, et al. *Sci Rep*. 2017;7(1):13187.

Psilocybin for Treatment Resistant Depression: Neuroimaging



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

RSFC – Resting-state functional connectivity

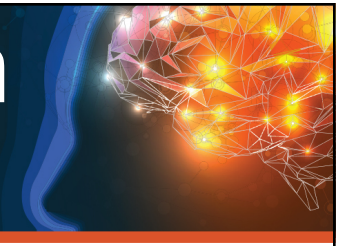
Carhart-Harris RL, et al. *Sci Rep*. 2017;7(1):13187.

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)

Carhart-Harris RL, et al. *Sci Rep*. 2017;7(1):13187.

MDMA-Assisted Psychotherapy in Phase 2 Trial for PTSD



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 C 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.

Lancet Psychiatry 2018

Published Online
May 1, 2018
http://dx.doi.org/10.1016/S2215-0366(18)30135-4

Mithoefer MD, et al. *Lancet Psychiatry.* 2018;5(6):486-497.

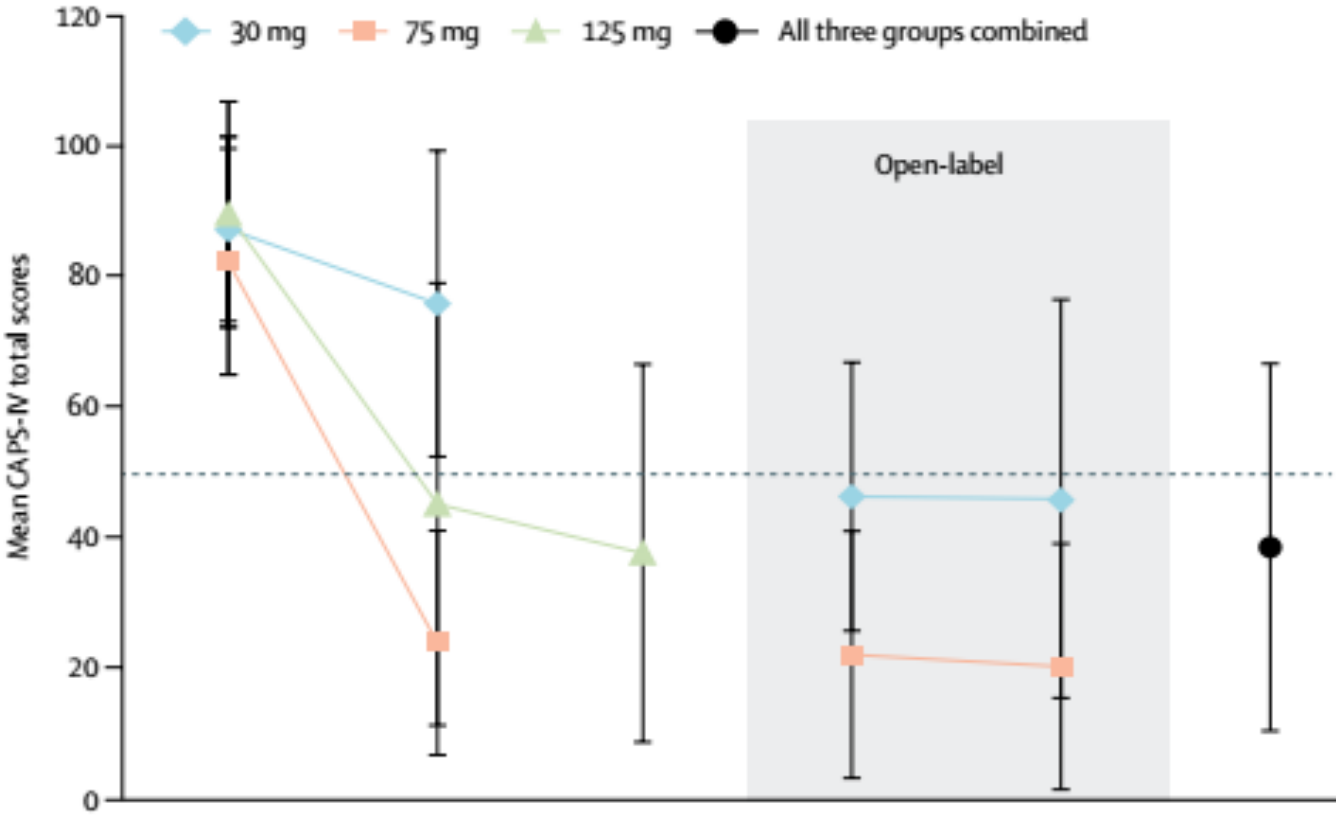
MDMA-Assisted Psychotherapy in Veterans and First Responders with Chronic PTSD

- 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*

Mithoefer MD, et al. *Lancet Psychiatry.* 2018;5(6):486-497.

MDMA Phase 2 Trial for PTSD
Mean CAPS-IV Total Scores



- 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*

Mithoefer MD, et al. *Lancet Psychiatry.* 2018;5(6):486-497.

Cautionary Notes

- The history of psychedelics and their legal status as highly restricted compounds of course make this a more complex issue
- While 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, or even more disturbingly their use in unethical and dangerous research designs surreptitiously funded by national security authorities, makes the status of these compounds more complex and suspect

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Cautionary Notes

- Despite extensive evidence of the safety of these compounds in well-selected individuals under careful supervision, as in these studies, their prior history and the general history of expansion of indications for clinical agents, including their clinically questionable use after approval for specific indications, is an important cautionary tale.
- Beyond the clinical utility of these agents in individuals who are facing critical existential issues in end-of-life settings, it is likely that studies will expand into other important clinical populations such as those with treatment-resistant depression, where an initial proof of concept study showed similar responses to those reported in these studies

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Cautionary Notes

- 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.
- Many participants rated their psilocybin experience as among the most profound and meaningful of their lives. The benefit of these experiences on mood and anxiety seemingly continued to affect them months later, despite single administration of psilocybin and their serious medical conditions.

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

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.

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

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.

1Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

Call to Action

- While very preliminary clinical 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

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.