# An Overview of the Evidence: Recent clinical trials with MDMA and Psilocybin

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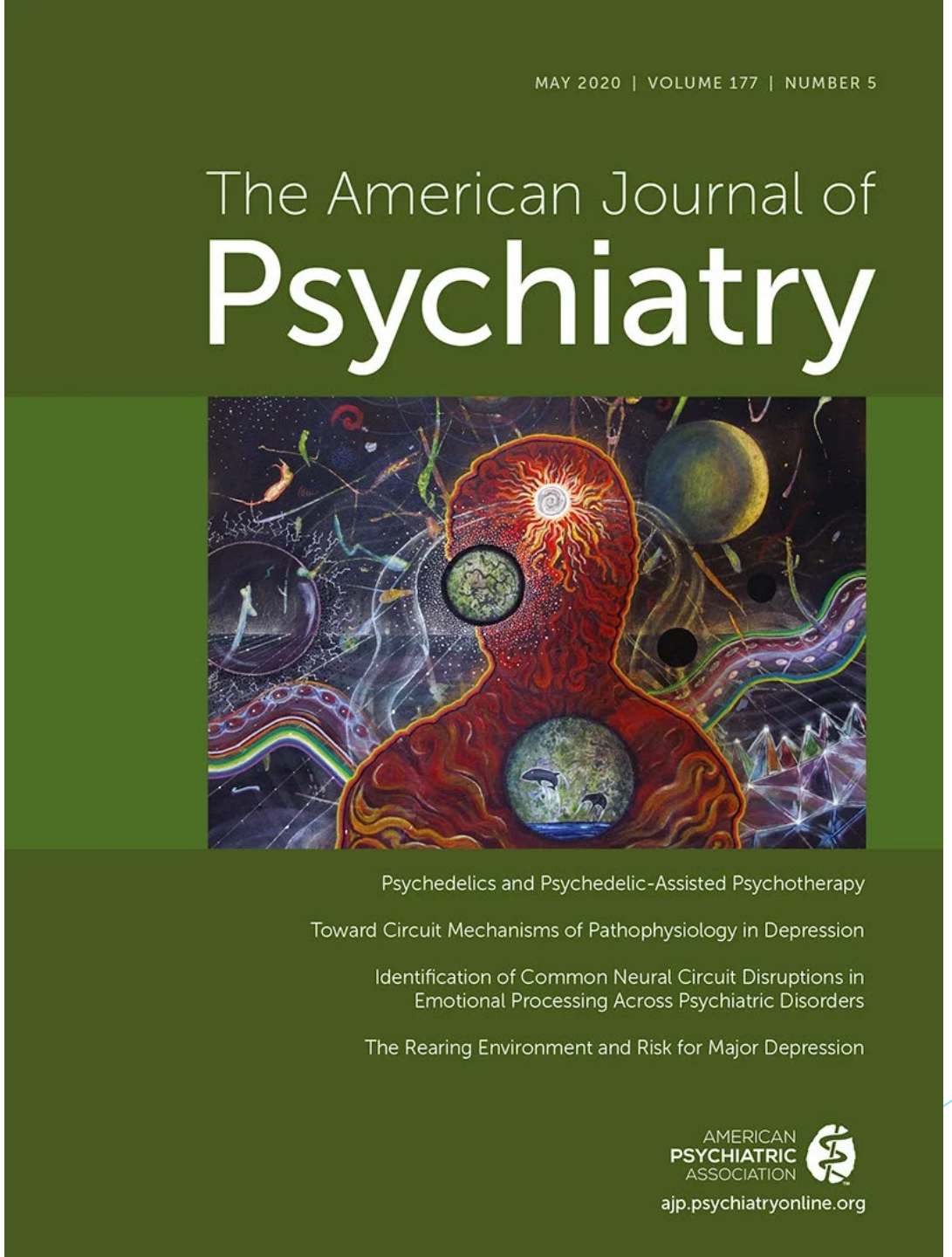
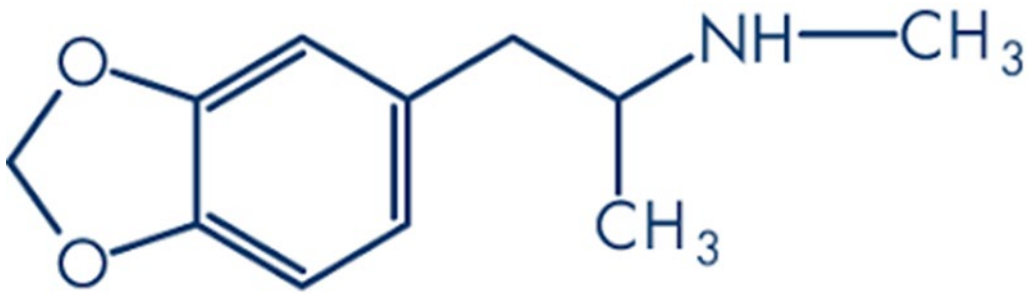
The Work Group on Biomarkers and Novel Treatments, A Division of The American Psychiatric Association Council of Research



# Efficacy of MDMA for the treatment of PTSD



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Published online 2019 May 7. doi: 10.1007/s00213-019-05249-5 PMID: 31065731

# MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials

Michael C. Mithoefer,[1] Allison A. Feduccia,[2] Lisa Jerome,[2] Anne Mithoefer,[3] Mark Wagner,[1] Zach Walsh,[4] Scott Hamilton,[5] Berra Yazar-Klosinski,[6] Amy Emerson,[2] and Rick Doblin[6]

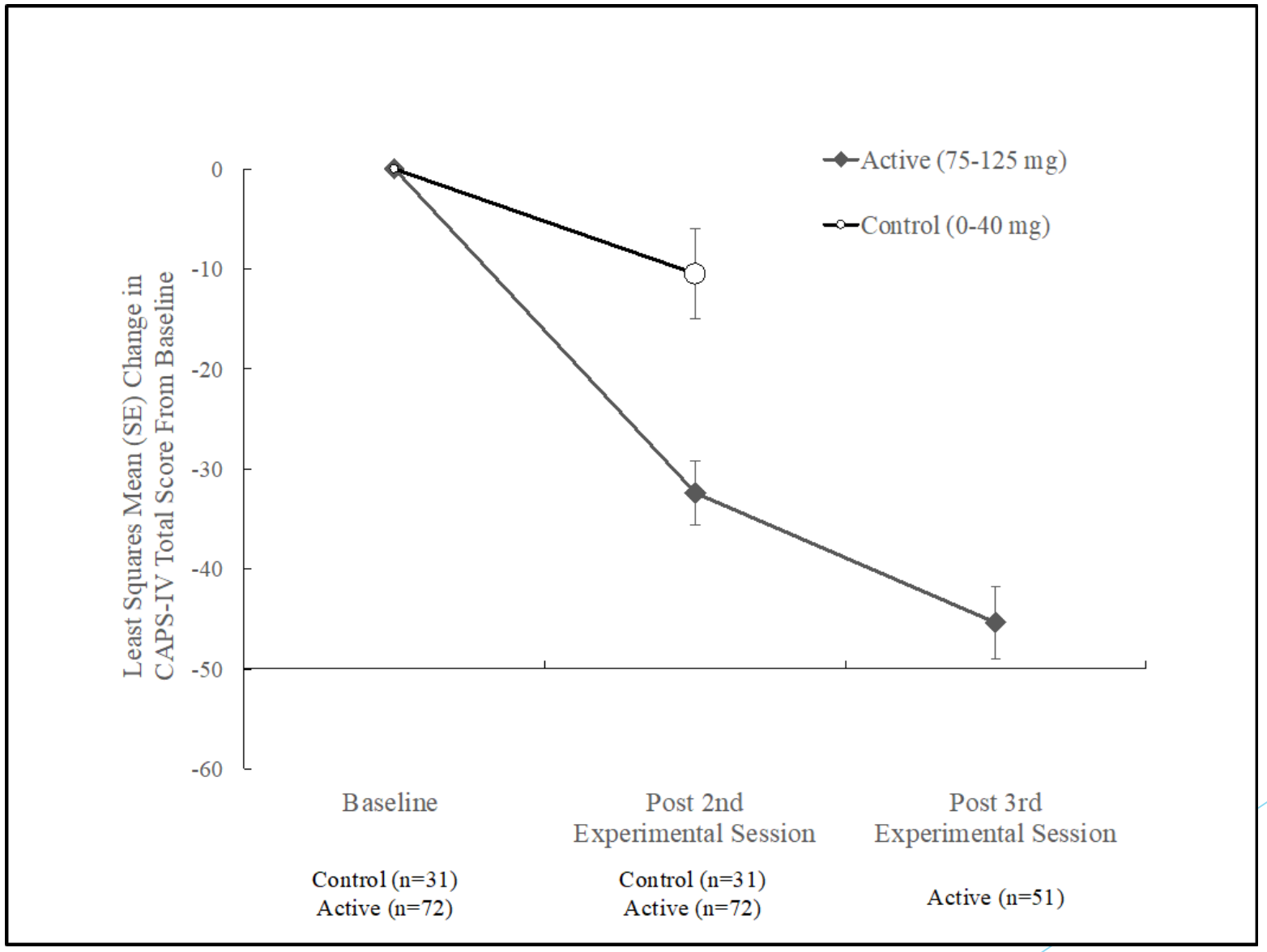
- Six completed Phase 2 Studies with MDMA Assisted Psychotherapy for PTSD from 2004 – 2017
- Intent to treat N= 105

- Three non-drug 90-min therapy sessions preceded the first MDMA exposure, and three to four followed each experimental session.

- Assessments with CAPS-IV were administered at baseline and at follow-up visits occurring 1 to 2 months after the second and third experimental drug sessions and at additional time points in some studies.

- Participants received an active doses of MDMA 75–125 mg (n=72) or placebo/control doses 0–40 mg MDMA (n=31) coupled with manualized psychotherapy sessions in two or three 8-h sessions spaced a month apart.

# CAPS-IV total score least squared mean estimates at endpoints




($P < 0.001$)

- The dropout rate was 7.6% (8/105), with six participants terminating early, but having completed at least one experimental session and follow-up assessment.

- This falls below an average reported dropout rate of 29% for clinical trials that have investigated trauma focused therapy and / or medication management (0–79%) (Lee et al. 2016).


- Lee, D. J., Schnitzlein, C. W., Wolf, J. P., Vythilingam, M., Rasmusson, A. M., & Hoge, C. W. (2016). Psychotherapy Versus Pharmacotherapy for Posttraumatic Stress Disorder: Systemic Review and Meta-Analyses to Determine First-Line Treatments. *Depression & Anxiety (1091-4269)*, *33*(9), 792–806. https://doi-org.ezproxy.med.nyu.edu/10.1002/da.22511

nature medicine



Article | Open Access | Published: 10 May 2021

# MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

Jennifer M. Mitchell, Michael Bogenschutz, [...]Rick Doblin

*Nature Medicine* (2021) | Cite this article



## Abstract

Post-traumatic stress disorder (PTSD) presents a major public health problem for which currently available treatments are modestly effective. We report the findings of a randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial (NCT03537014) to test the efficacy and safety of 3,4-methylenedioxymethamphetamine

# MDMA-Assisted Psychotherapy Found Superior to Placebo in Phase 3 Trial

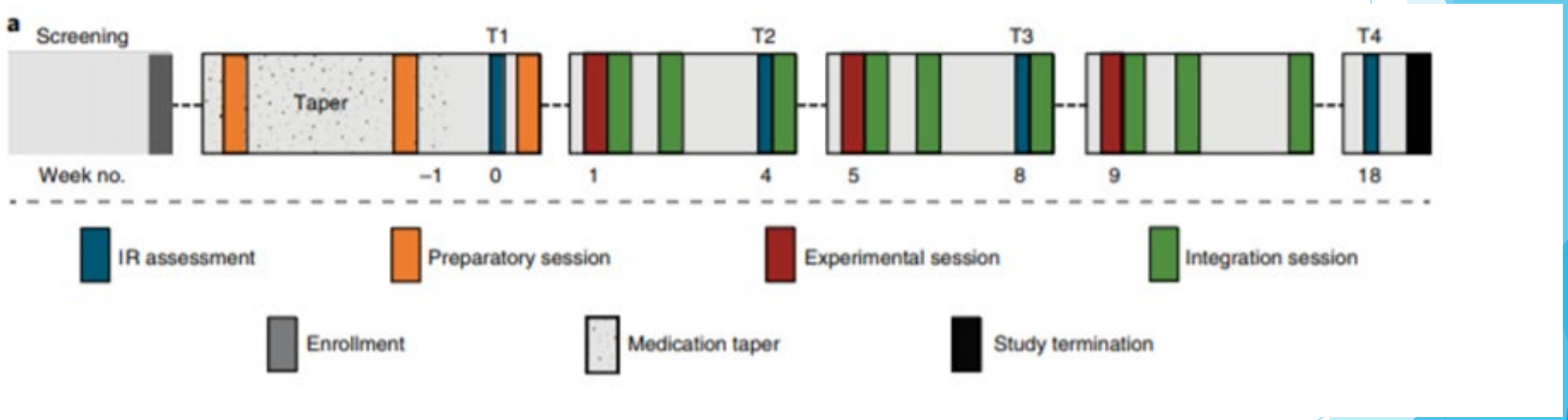
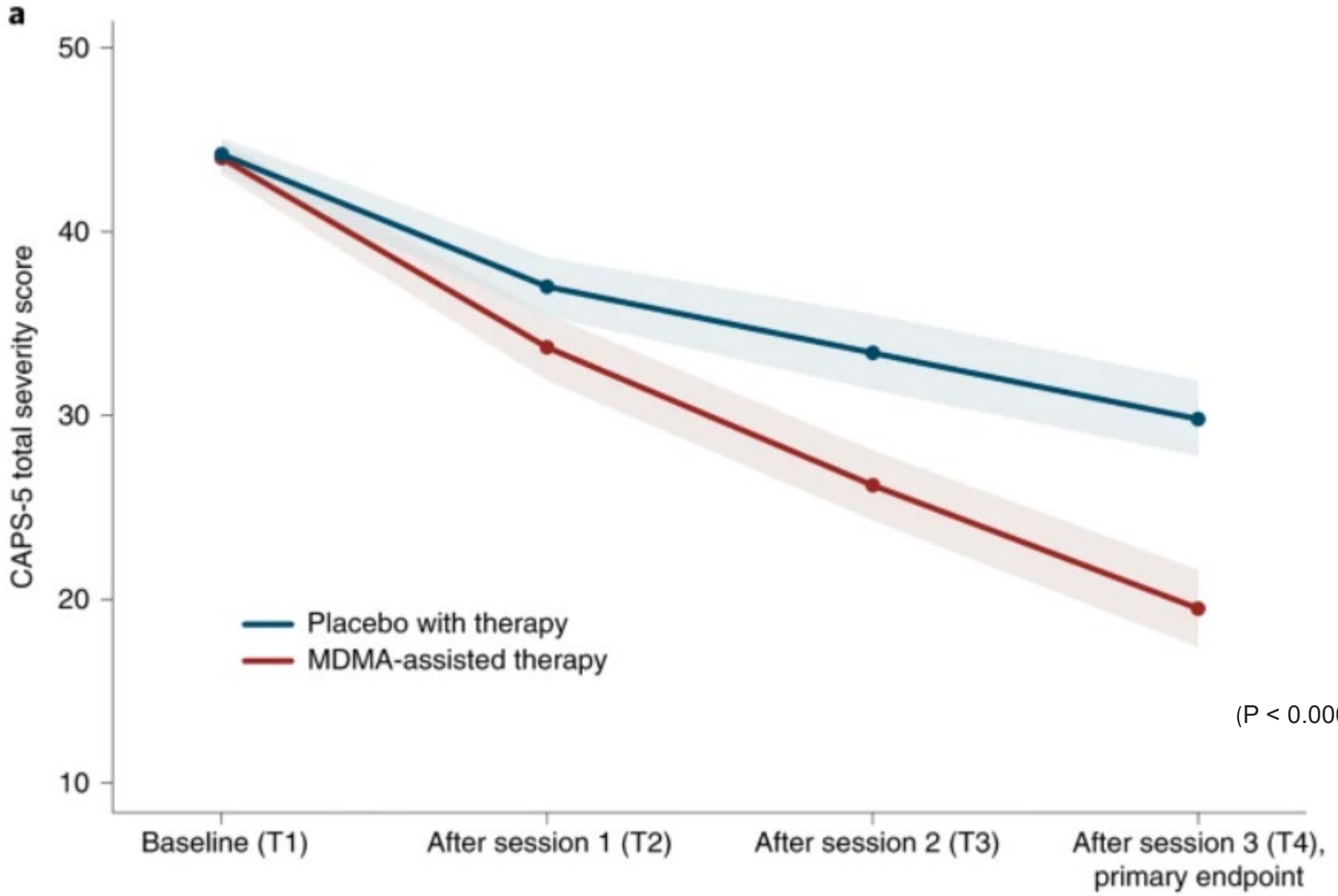
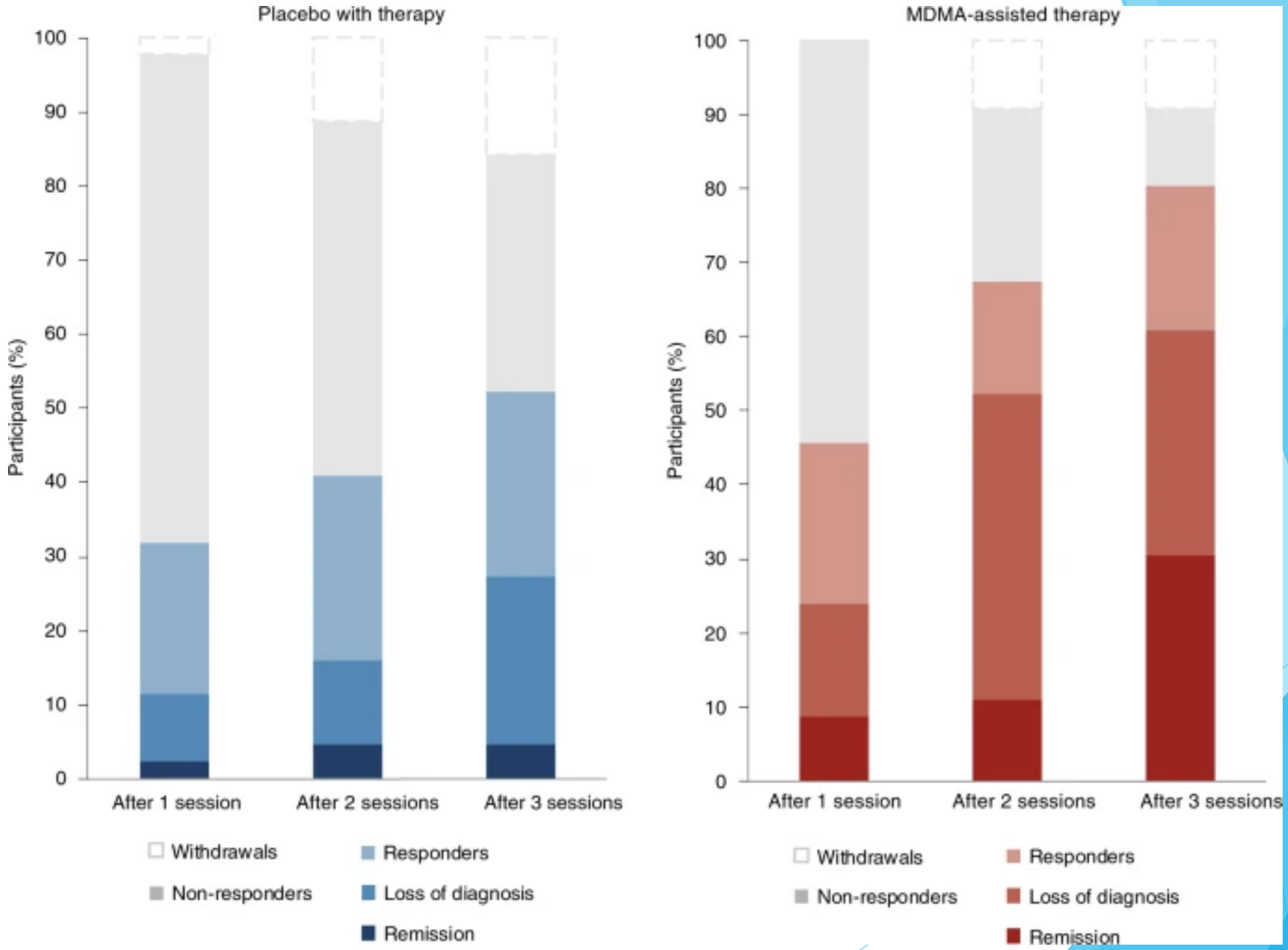


**Fig. 2: Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group.**




(P < 0.0001)

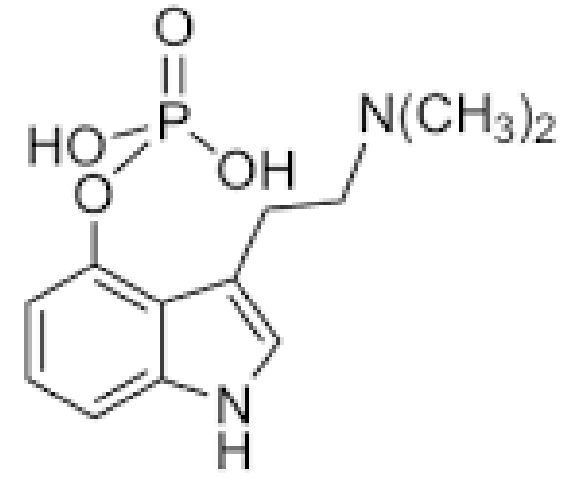

Placebo with therapy
MDMA-assisted therapy
Participants (%)
100
90
80
70
60
50
40
30
20
10
0
After 1 session
After 2 sessions
After 3 sessions
Withdrawals
Non-responders
Responders
Loss of diagnosis
Remission

- MDMA did not induce adverse events of abuse potential, suicidality or QTc prolongation.

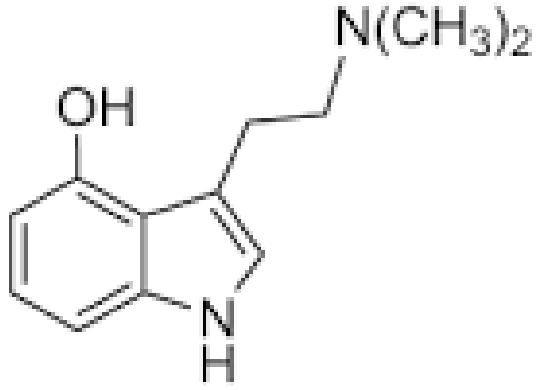
- The study team managed to train 80 new therapists in the process of MDMA-assisted psychotherapy using a manual, which suggests that the treatment is scalable.

- A second phase 3 trial of MDMA-assisted psychotherapy involving 100 additional patients is under way in Europe and the United States.

# Psilocybin




Psilocybin (**1**)




Psilocin (**2**)

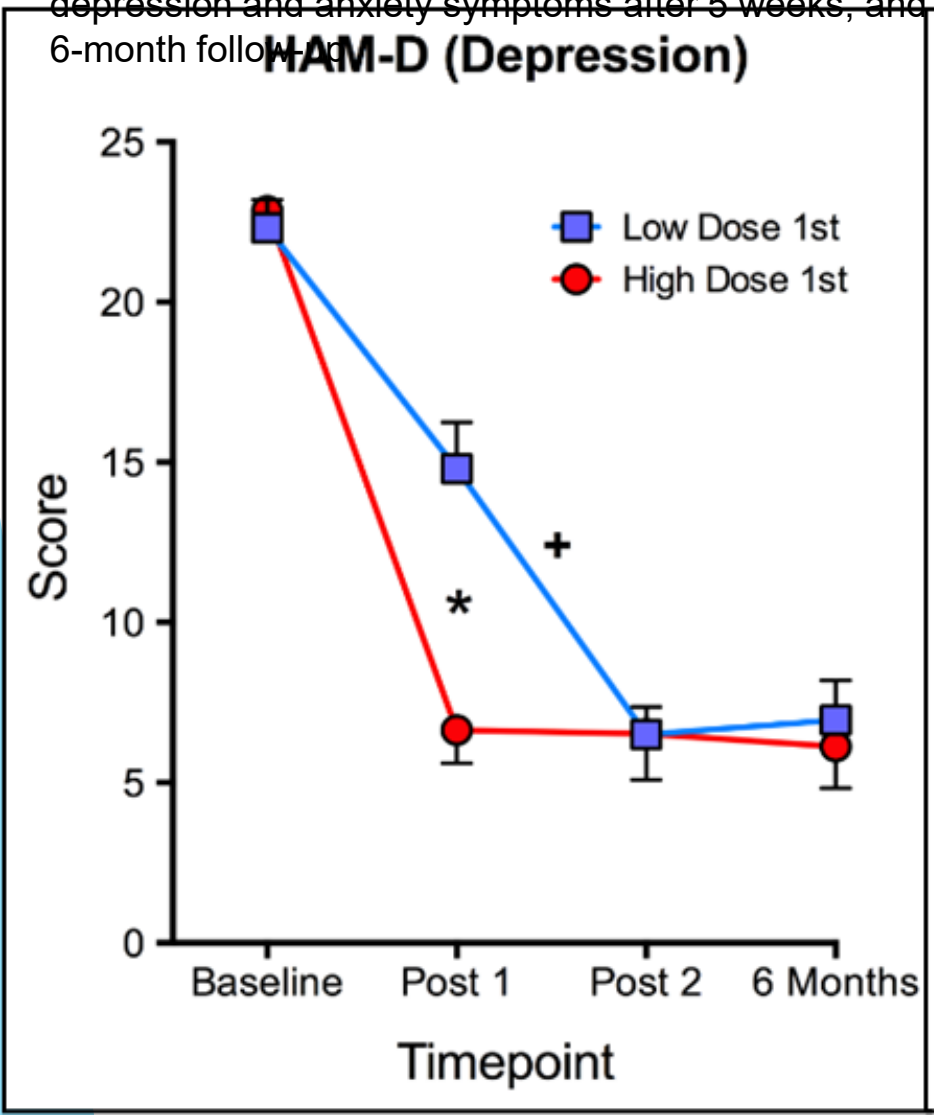
# The efficacy of Psilocybin for Anxiety and/or Depression related to diagnosis of a life-threatening illness.

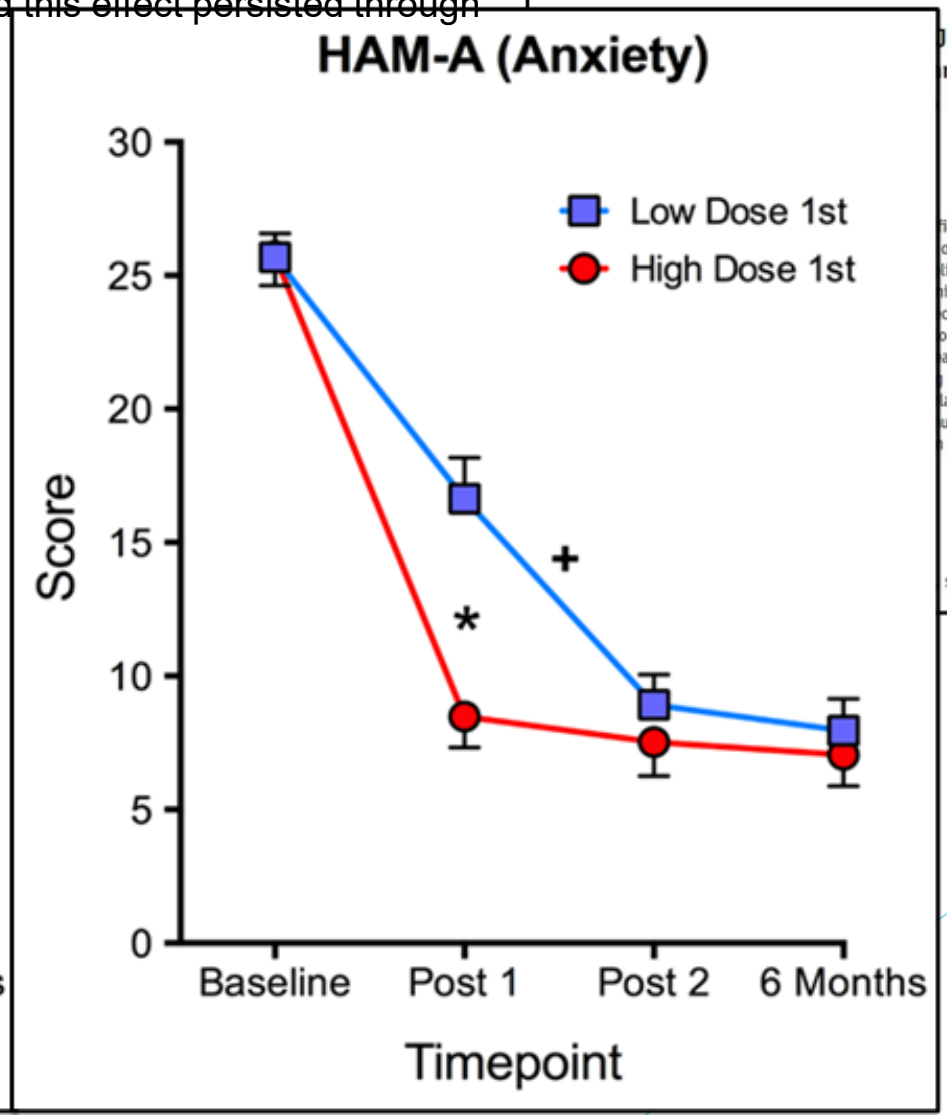
Griffiths et al. 2016

A double-blind randomized crossover study

High dose  psilocybin (active drug) vs. low dose psilocybin (control)

High-dose but not low-dose psilocybin produced large and significant decreases in depression and anxiety symptoms after 5 weeks, and this effect persisted through 6-month follow-up.




Original Paper

**Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial**

Psychopharm

Journal of Psychopharmacology
1–17
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DOI: 10.1177/0269881116675513
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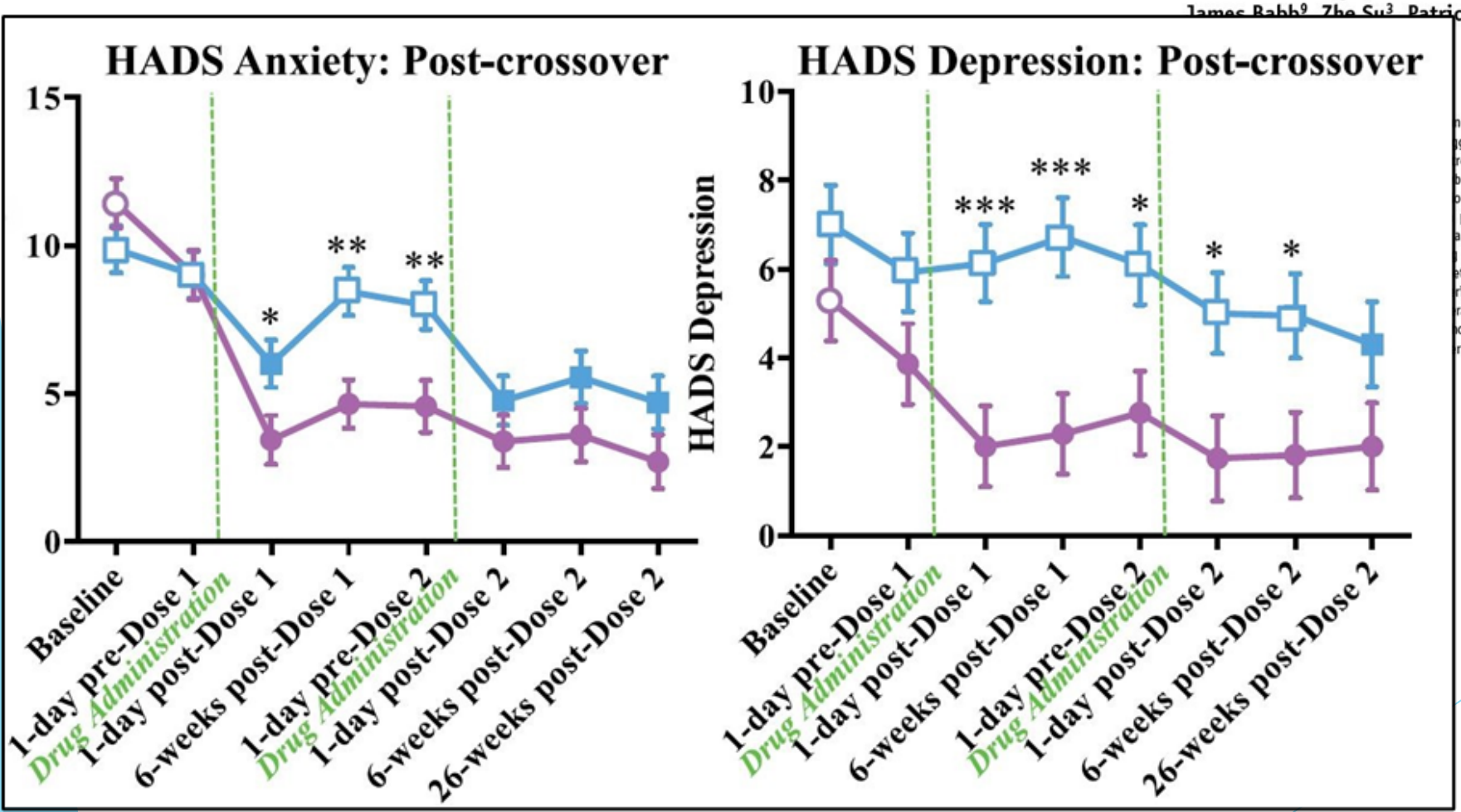
Johnson[1], Michael A Carducci[3],
rds[1], Brian D Richards[1],
Klinedinst[1]

ficant symptoms of depression and anxiety. Previous studies suggest that psilocybin may decrease
of psilocybin were studied in 51 cancer patients with life-threatening diagnoses and symptoms of
lind, cross-over trial investigated the effects of a very low (placebo-like) dose (1 or 3 mg/70 kg)
inistered in counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up.
ctancy effects. Participants, staff, and community observers rated participant moods, attitudes,
ocybin produced large decreases in clinician- and self-rated measures of depressed mood and
aning, and optimism, and decreases in death anxiety. At 6-month follow-up, these changes were
to show clinically significant decreases in depressed mood and anxiety. Participants attributed
lationships, and spirituality to the high-dose experience, with >80% endorsing moderately or
unity observer ratings showed corresponding changes. Mystical-type psilocybin experience on
therapeutic outcomes.

symptom remission, mystical experience

Ross et al. 2016
N=29
Double Blind placebo controlled randomized crossover study
Niacin (control) vs. Single high dose psilocybin (active drug)

There were significant reductions in all the **primary measures (HADS total, HADS-A, HADS-D, BDI, STAI state, STAI trait)** in the psilocybin group compared with the control group immediately after the experimental session, and these reductions were maintained until crossover of the control group at week 7.




Original Paper

Psychopharm

Journal of Psychopharmacology
2016, Vol. 30(12) 1165–1180

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DOI: 10.1177/0269881116675512
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# 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]

nd depression are common in patients with cancer, and are associated with poor psychiatric and medical
gests a role for psilocybin to treat cancer-related anxiety and depression.
rolled, crossover trial, 29 patients with cancer-related anxiety and depression were randomly assigned and
bin (0.3 mg/kg) or niacin, both in conjunction with psychotherapy. The primary outcomes were anxiety
or to the crossover at 7 weeks.
produced immediate, substantial, and sustained improvements in anxiety and depression and led to
and hopelessness, improved spiritual wellbeing, and increased quality of life. At the 6.5-month follow-
anxiolytic and anti-depressant effects (approximately 60–80% of participants continued with clinically
ety), sustained benefits in existential distress and quality of life, as well as improved attitudes towards
rience mediated the therapeutic effect of psilocybin on anxiety and depression.
rapy, single moderate-dose psilocybin produced rapid, robust and enduring anxiolytic and anti-depressant
ological distress.
r: NCT00957359

# Efficacy of Psilocybin for the Treatment of Substance use Disorders

Bogenschutz et al.
N=10
Open Label psilocybin for alcohol dependence.
Abstinence not biologically verified / self report.
Abstinence significantly increased after the first psilocybin session at 4 weeks and was largely sustained through 36 weeks.

*Original Paper*

# Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study

**Michael P Bogenschutz[1], Alyssa A Forcehimes[1], Jessica A Pommy[1], Claire E Wilcox[1], PCR Barbosa[2] and Rick J Strassman[1]**

Psychopharm

*Journal of Psychopharmacology*
2015, Vol. 29(3) 289–299

DOI: 10.1177/0269881114565144
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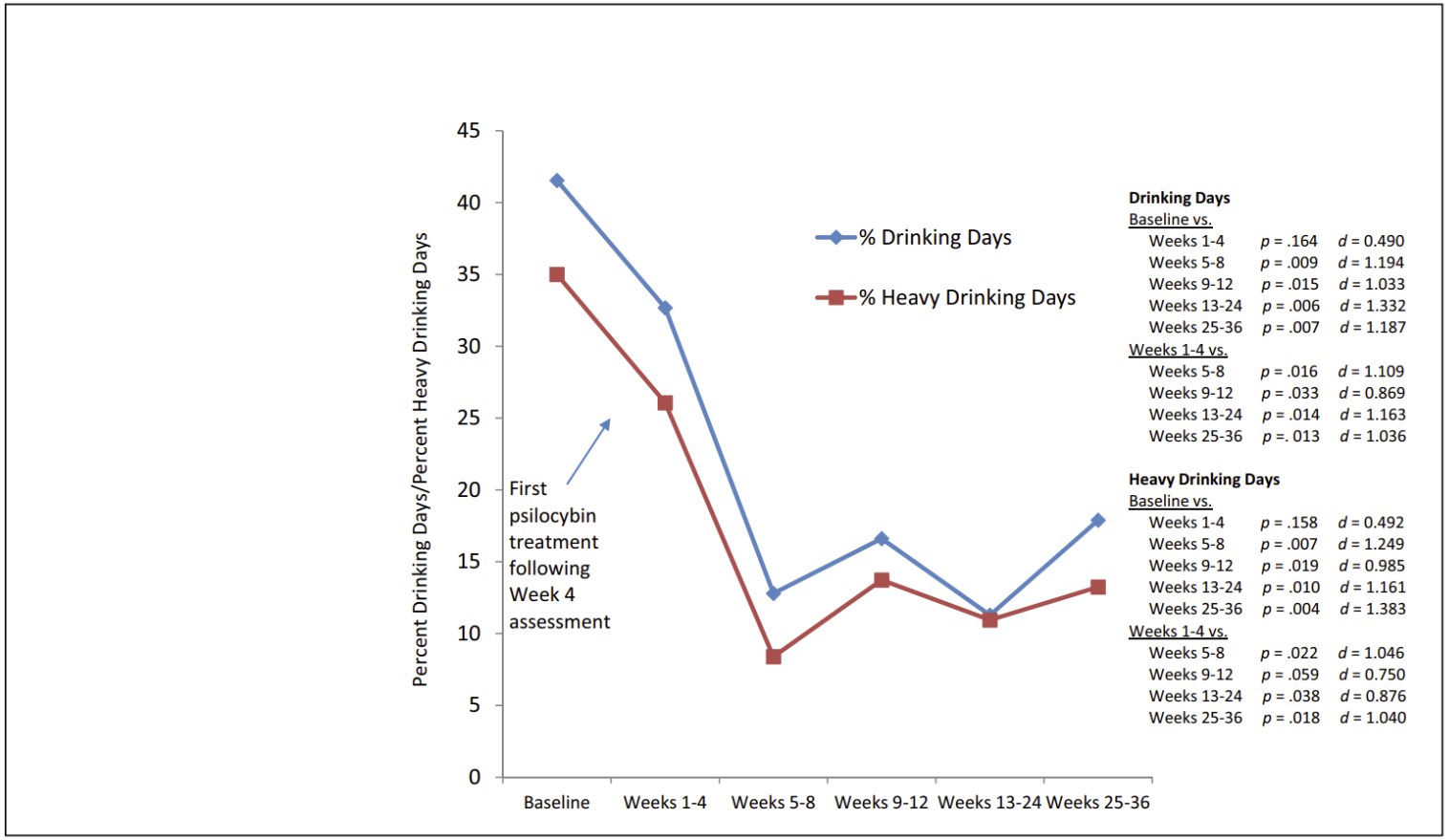



**Figure 3.** Drinking outcomes and effect sizes.
Means shown are for all available data ($n$ = 10 at baseline, $n$ = 9 at all other time points). $p$-values are from paired $t$-tests (df = 8). Cohen's $d$ is shown for the contrast between baseline or weeks 1–4 and each follow-up time point.

agonist) hallucinogens have clinically relevant effects in alcohol and drug addiction. Although ybin in various populations, there have been no studies on the efficacy of psilocybin for alcohol concept study to quantify acute effects of psilocybin in alcohol-dependent participants and to volunteers with DSM-IV alcohol dependence received orally administered psilocybin in one or Enhancement Therapy and therapy sessions devoted to preparation for and debriefing from the bin were qualitatively similar to those described in other populations. Abstinence did not increase participants had not yet received psilocybin), but increased significantly following psilocybin ned at follow-up to 36 weeks. The intensity of effects in the first psilocybin session (at week 4) -8 ($r$ = 0.76 to $r$ = 0.89) and also predicted decreases in craving and increases in abstinence self- tment-related adverse events. These preliminary findings provide a strong rationale for controlled mechanisms.

Johnson et al.
N=15
Open Label
At the 6-month follow-up, 12 of the 15 participants (80%) were laboratory-verified as abstinent; 10 participants (67%) remained abstinent at 12 months, and nine (75%) at 2.5 years.




Published in final edited form as:

*Am J Drug Alcohol Abuse*. 2017 January ; 43(1): 55–60. doi:10.3109/00952990.2016.1170135.


## Long-term Follow-up of Psilocybin-facilitated Smoking Cessation

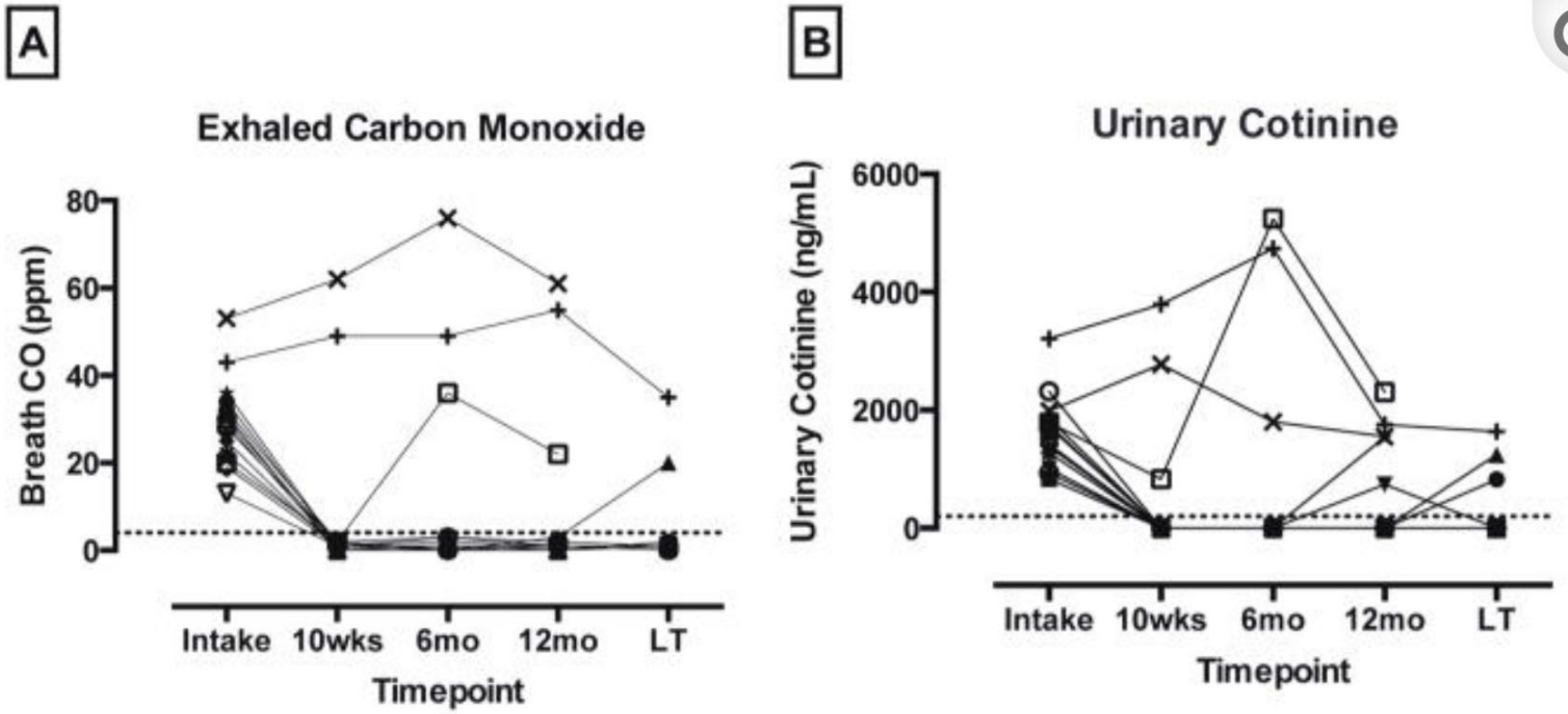

**Matthew W. Johnson, PhD**[1], **Albert Garcia-Romeu, PhD**[1], and **Roland R. Griffiths, PhD**[1,2]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD


found that two to three moderate to high
agonist psilocybin, in combination with
on, resulted in substantially higher 6-
ved with other medications or CBT alone.

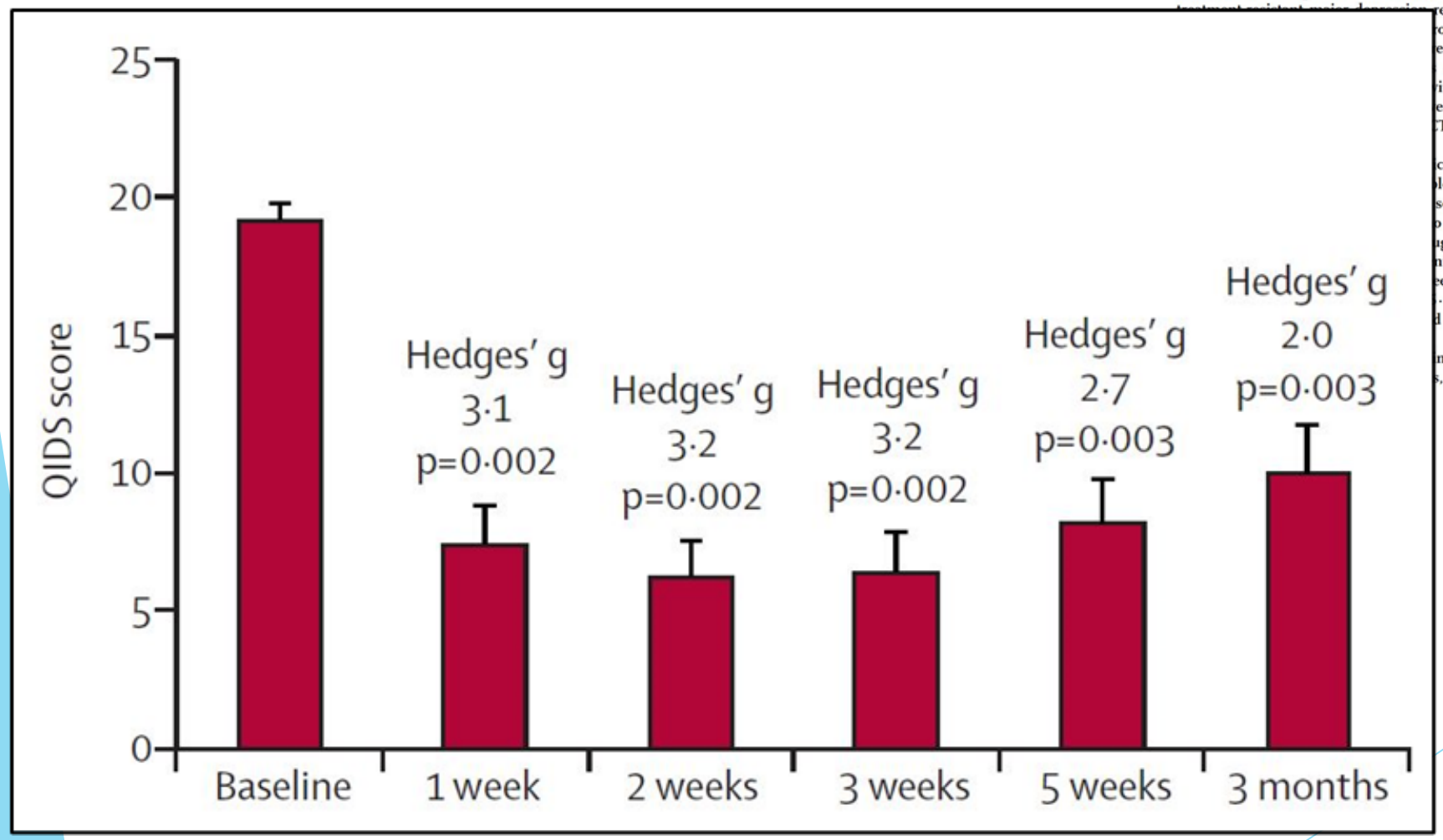
n-facilitated smoking cessation program at



# Efficacy of Psilocybin for Depression and Treatment Resistant Depression (TRD)

# Carhart-Harris et al. 2016

The mean change in QIDS score was −11.8 (SD=4.9; p=0.002) at 1 week and −9.2 (SD=6.0; p=0.003) at 3 months.




## 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, [illegible] received two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in a [illegible]ol group. Psychological support was provided before, during, and after each [illegible]e for feasibility was patient-reported intensity of psilocybin's effects. Patients [illegible] during the dosing sessions and subsequent clinic and remote follow-up. [illegible]ith standard assessments from 1 week to 3 months after treatment, with the [illegible]e Symptoms (QIDS) serving as the primary efficacy outcome. This trial is [illegible]TN14426797.

[illegible]c effects typically became detectable 30–60 min after dosing, peaked 2–3 h [illegible]le levels at least 6 h after dosing. Mean self-rated intensity (on a 0–1 scale) [illegible]session and 0·75 (SD 0·27) for the high-dose session. Psilocybin was well [illegible]o serious or unexpected adverse events occurred. The adverse reactions we [illegible]ıg onset (all patients), transient confusion or thought disorder (nine patients), [illegible]nts), and transient headache (four patients). Relative to baseline, depressive [illegible]eek (mean QIDS difference –11·8, 95% CI –9·15 to –14·35, p=0·002, Hedges' [illegible]·69 to –12·71, p=0·003, Hedges' g=2) after high-dose treatment. Marked and [illegible]l anhedonia were also noted.

[illegible]minary support for the safety and efficacy of psilocybin for treatment-resistant [illegible]s, with more rigorous designs, to better examine the therapeutic potential of

*Lancet Psychiatry* 2016; 3: 619–27

Published Online May 17, 2016 http://dx.doi.org/10.1016/S2215-0366(16)30065-7

See Comment page 592

*Contributed equally

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ORIGINAL ARTICLE

# Trial of Psilocybin versus Escitalopram for Depression

Robin Carhart-Harris, Ph.D., Bruna Giribaldi, B.Sc., Rosalind Watts, D.Clin.Psy., Michelle Baker-Jones, B.A., Ashleigh Murphy-Beiner, M.Sc., Roberta Murphy, M.D., Jonny Martell, M.D., Allan Blemings, M.Sc., David Erritzoe, M.D., and David J. Nutt, M.D.



April 15, 2021
N Engl J Med 2021; 384:1402-1411
DOI: 10.1056/NEJMoa2032994
Chinese Translation 中文翻译



## Abstract

**BACKGROUND** Psilocybin may have antidepressant properties, but direct comparisons between psilocybin and established treatments for depression are lacking.

**METHODS** In a phase 2, double-blind, randomized, controlled trial involving patients with long-standing, moderate-to-severe major depressive disorder, we compared psilocybin with escitalopram, a selective serotonin-reuptake inhibitor, over a 6-week period. Patients were assigned in a 1:1 ratio to receive two separate doses of 25 mg of psilocybin 3 weeks apart plus 6 weeks of daily placebo (psilocybin group) or two separate doses of 1 mg of psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram (escitalopram group); all the patients received psychological support. The primary outcome was the change from baseline in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16; scores range from 0 to 27, with higher scores indicating greater depression) at week 6. There were 16 secondary outcomes, including QIDS-SR-16 response (defined as a reduction in score of >50%) and QIDS-SR-16 remission (defined as a score of ≤5) at week 6.

Related Articles

EDITORIAL APR 15, 2021

Back to the Future — The Therapeutic Potential of Psychedelic Drugs

J.A. Lieberman

The NEW ENGLAND JOURNAL of MEDICINE

# Psilocybin versus Escitalopram for Depression

PHASE 2, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

**59**

**Adults with moderate-to-severe major depressive disorder**

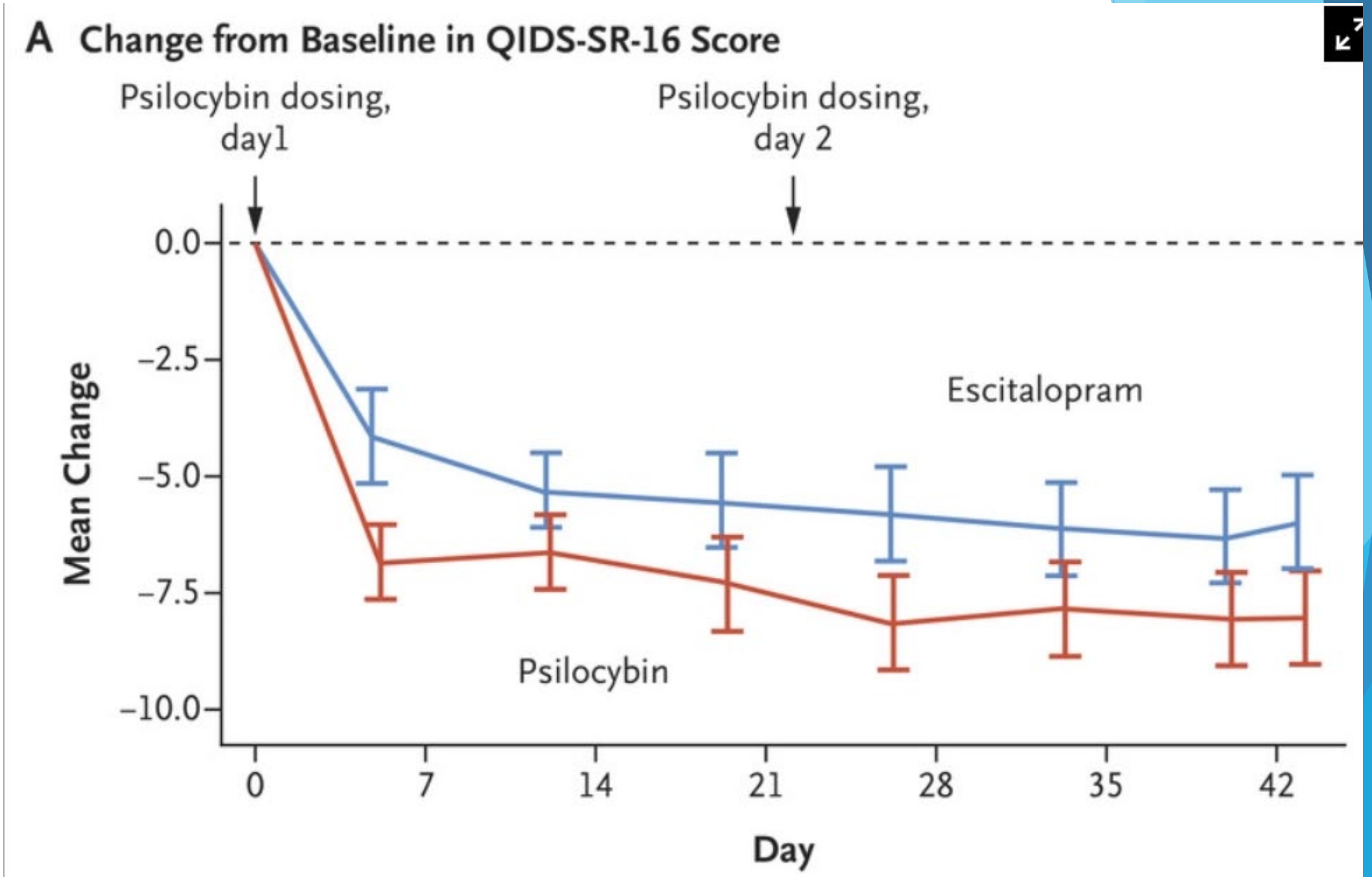
| | Psilocybin | Escitalopram |
|---|---|---|
| | (two 25-mg doses 3 wk apart) + placebo (microcrystalline cellulose) | (10 mg daily [3 wk], then 20 mg [3 wk]) + placebo (psilocybin, 1-mg doses 3 wk apart) |
| | N=30 | N=29 |
| Change in QIDS-SR-16 depressive symptom score at 6 wk (range, 0–27; higher score = greater depression) | −8.0±1.0 | −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/NEJMoa2032994


A Change from Baseline in QIDS-SR-16 Score
Psilocybin dosing, day1
Psilocybin dosing, day 2
0.0
−2.5
−5.0
−7.5
−10.0
Mean Change
Escitalopram
Psilocybin
0
7
14
21
28
35
42
Day

- Based on **change in depression scores on the QIDS** at week 6, **this trial did not show a significant difference** in antidepressant effects between psilocybin and escitalopram

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

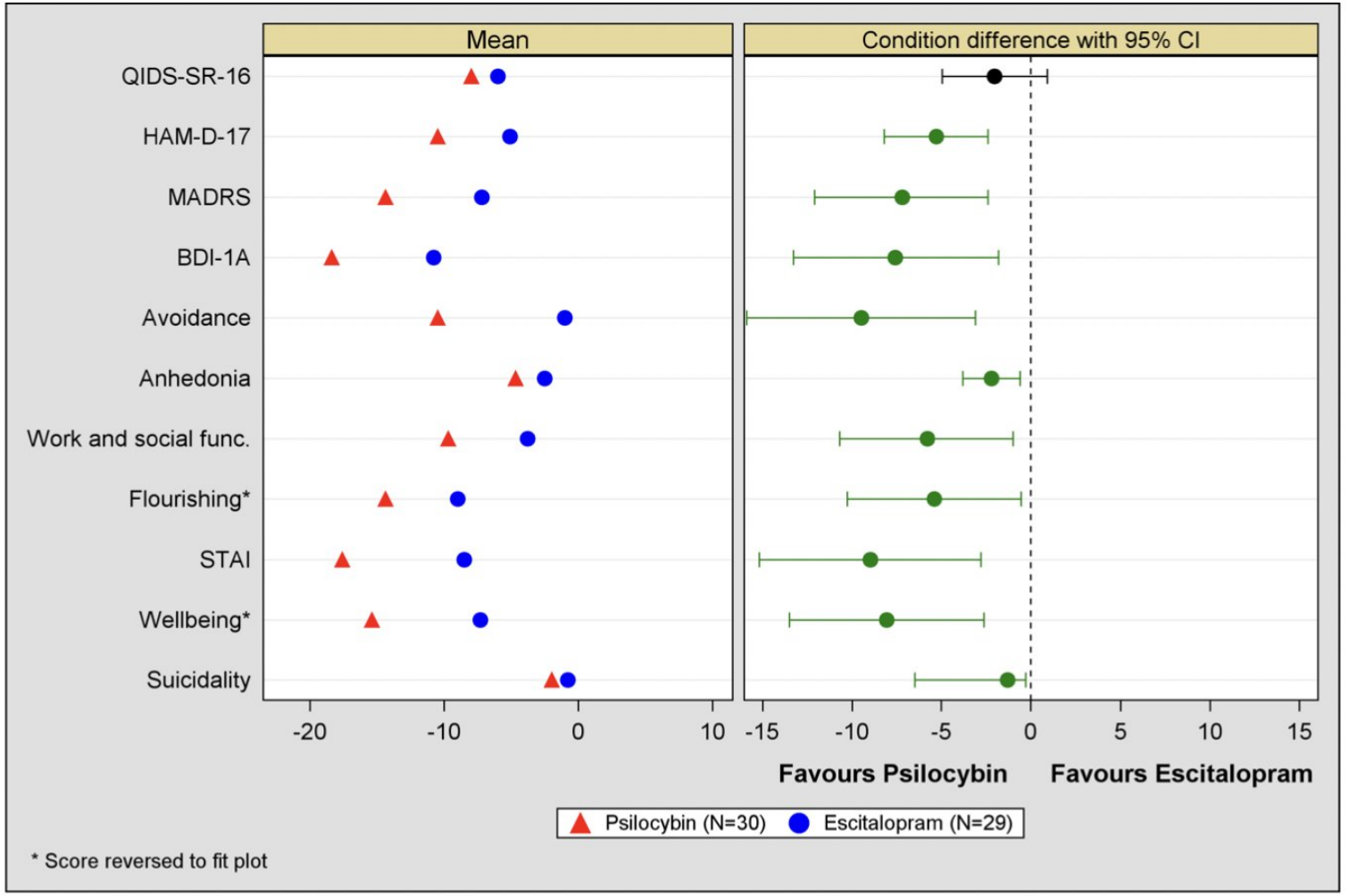
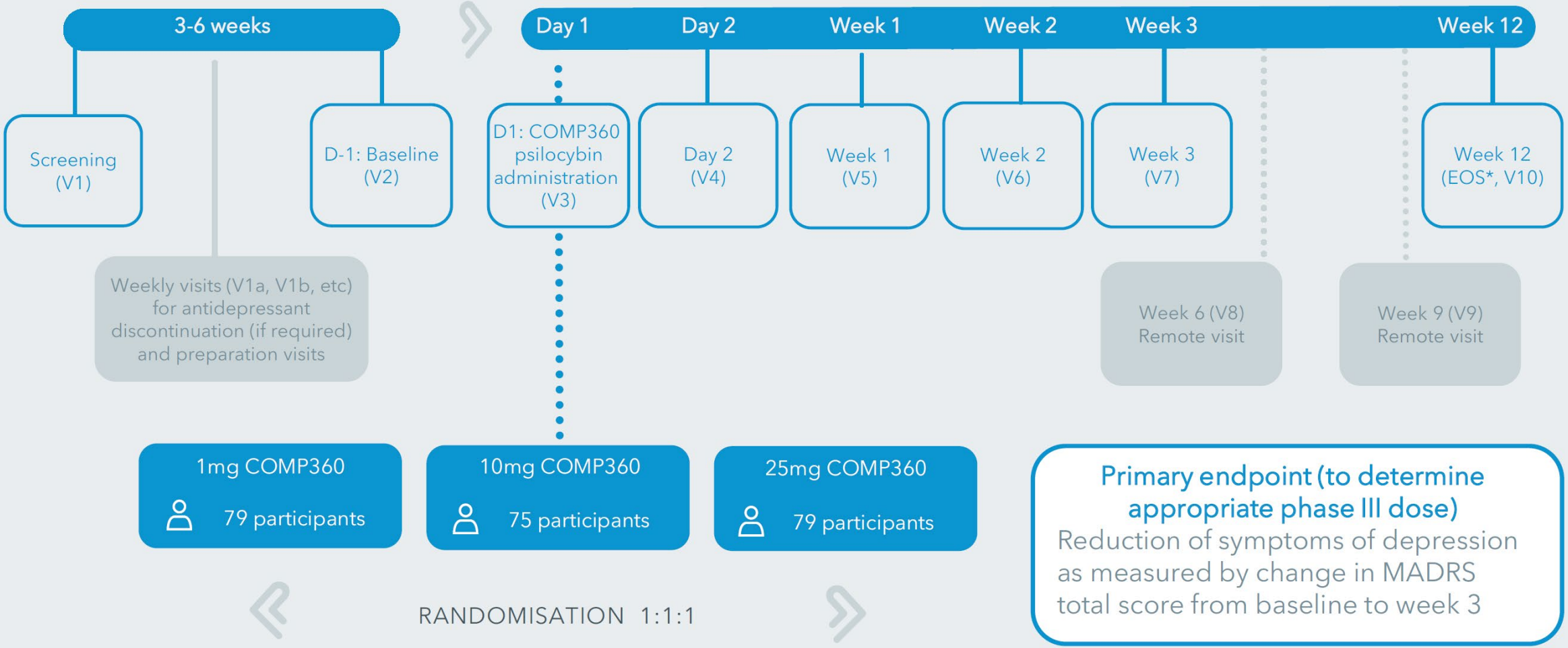



**Figure S4. All (mean change) efficacy outcomes compared between conditions at week 6 (primary endpoint).** Escitalopram in blue, psilocybin in red. Green confidence intervals (CIs) indicate no crossing of zero (i.e., > 95% confidence in difference), black CIs indicate crossing of zero and hence no 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.

# COMP360 psilocybin for TRD

Randomized controlled double-blind Phase IIb study.

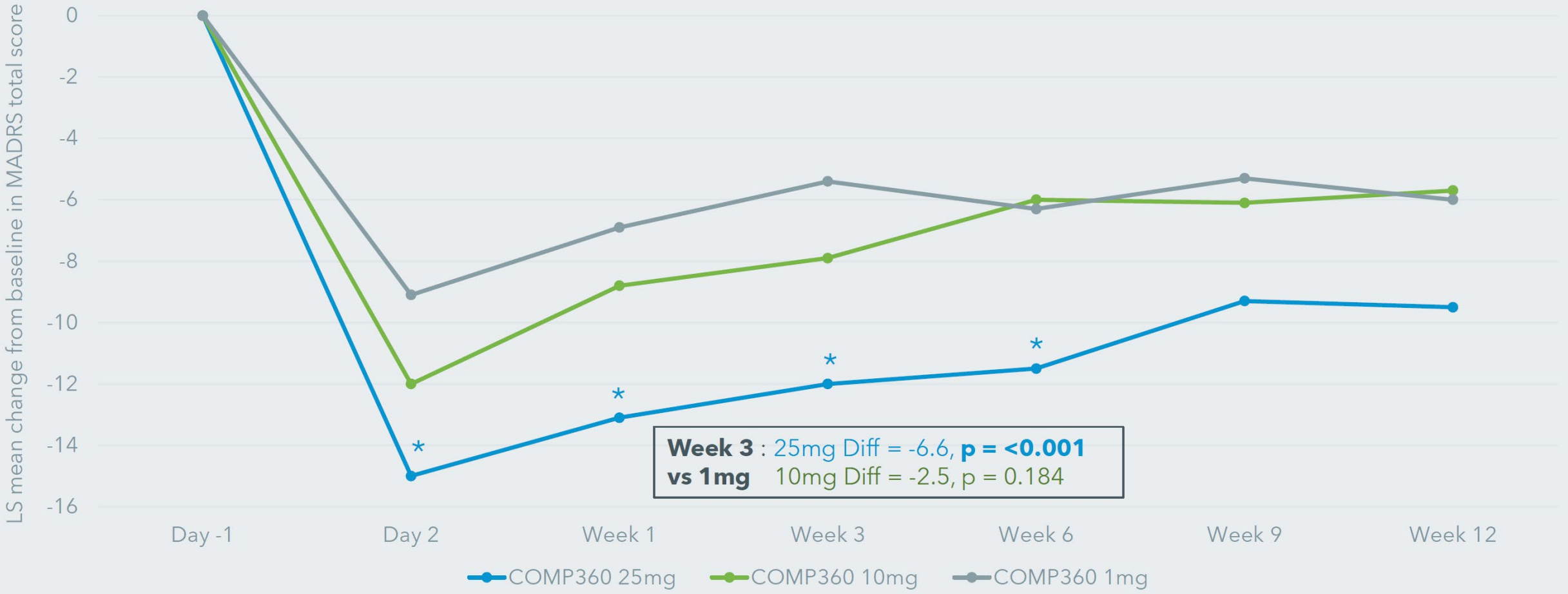
# COMP 001 study design and endpoints




**Note:** MADRS = Montgomery-Åsberg Depression Rating Scale; EOS = end of study; TRD = treatment-resistant depression; D = day; V = visit

# 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

# Treatment emergent serious adverse events (TESAEs) ordered by 25mg arm

| MedDRA preferred term | COMP360 25mg | COMP360 10mg | COMP360 1mg | Overall |
|---|---|---|---|---|
| | N=79 | N=75 | N=79 | N=233 |
| | Number of patients per category (%) | | | |
| **Patients with a TESAE** | **5 (6.3)** | **6 (8.0)** | **1 (1.3)** | **12 (5.2)** |
| | Any TESAE | | | |
| Suicidal behaviour | 3 (3.8) | 0 | 0 | 3 (1.3) |
| Intentional self-injury[1] | 2 (2.5) | 2 (2.7) | 1 (1.3) | 5 (2.1) |
| Suicidal ideation | 2 (2.5) | 2 (2.7) | 0 | 4 (1.7) |
| Drug withdrawal syndrome[2] | 1 (1.3) | 0 | 0 | 1 (0.4) |
| Adjustment disorder with anxiety | 1 (1.3) | 0 | 0 | 1 (0.4) |
| Adjustment disorder with mixed anxiety and depressed mood | 1 (1.3) | 0 | 0 | 1 (0.4) |
| Depression | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Hospitalisation | 0 | 1 (1.3) | 0 | 1 (0.4) |

19 TESAEs were reported in total, experienced by 12 patients

*(note: two patients had the same TESAE twice)*

All suicidal behaviours were experienced at least one month after COMP360 administration

**Note:** MedDRA = Medical Dictionary for Regulatory Activities; TESAE = treatment emergent serious adverse event; N = number of participants in the population

1= These were cases of non-suicidal self-injury (including) superficial cutting, scratching and punching which, although not meeting criteria for a TESAE, were classed as TESAEs in this study due to the protocol specifying that any behaviours on the Columbia-Suicide Severity Rating Scale, completed by participants at every study visit, be reported as a TESAE

2 = Codeine withdrawal

# COMP360 psilocybin therapy and SSRIs in TRD

An open-label study included 19 patients from clinical sites in Ireland and the United States.

- The primary endpoint was the change in baseline MADRS total score at 3 weeks in patients receiving 25mg COMP360 psilocybin therapy given in augmentation with their existing SSRI antidepressant regimen.

- The baseline MADRS score of patients entering the study was 31.7, representing moderate to severe depression.

- MADRS scores were assessed by blinded independent raters at baseline, on the day following COMP360 psilocybin therapy, and at weeks 1, 2 and 3.

- There was a rapid response from day 2 to week 3 after COMP360 therapy, which is also consistent with the phase IIb results.

- 8 of the 19 patients (42.1%) were responders at week 3 (compared with 36.7% at week 3 in the phase IIb trial) and all 8 were also remitters.

- The mean reduction from baseline observed in MADRS total score was 14.9 at week 3 (compared with a 12.0 mean reduction in MADRS in the phase IIb trial).

- 25mg COMP360 psilocybin therapy was generally well-tolerated when it was administered simultaneously with the patient's SSRI treatment.

- There were no treatment-emergent adverse events (TEAEs) (no suicidal ideation, suicidal behavior or intentional self-injury).

# Limitations

- Issues of blinding for participants and therapists due to robust and rapid onset of perceptual / behavioral changes produced by psilocybin and MDMA.
- Homogenous group of participants, who are predominately Caucasian and educated.
- Relatively small sample size due to limited funding (NIH just recently started funding psilocybin research).
- Several of the phase II trials were crossover in design.
- Limited information on the psychotherapeutic interventions used in the majority these trials.

# Conclusion

- The evidence base suggests that MDMA and psilocybin, when administered in **proper controlled settings** and with **adequate psychological support** with **trained practitioners**, may exert relatively durable, **clinically-significant therapeutic effects** for at least a subset of individuals with PTSD, MDD, substance-use disorders, and anxiety and/or depression related to diagnosis of a life-threatening illness.

# Thank You