PSYCHEDELIC PSYCHIATRY

Substance Use Disorders: A Comprehensive Review and Update 2021

Franklin King IV, MD

Director, Training and Education,

Center for Neuroscience of Psychedelics

Massachusetts General Hospital

Disclosures

"Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose."

What are psychedelics?

- Psychedelic, 1956 = “mind-manifesting”
- Change in consciousness, often with profound, transformative experience of spiritual or mystical importance, and/or personal meaning
- “Ego dissolution” – decreased boundary between self and world; increased connectedness
- Increased sensory experiences: synesthesia, visual imagery and/or hallucinations

What are psychedelics?

- Tryptamines
  - (LSD, psilocybin, DMT/ayahuasca)
- Phenethylamines
  - (mescaline, MDMA)

- Ibogaine

- Ketamine

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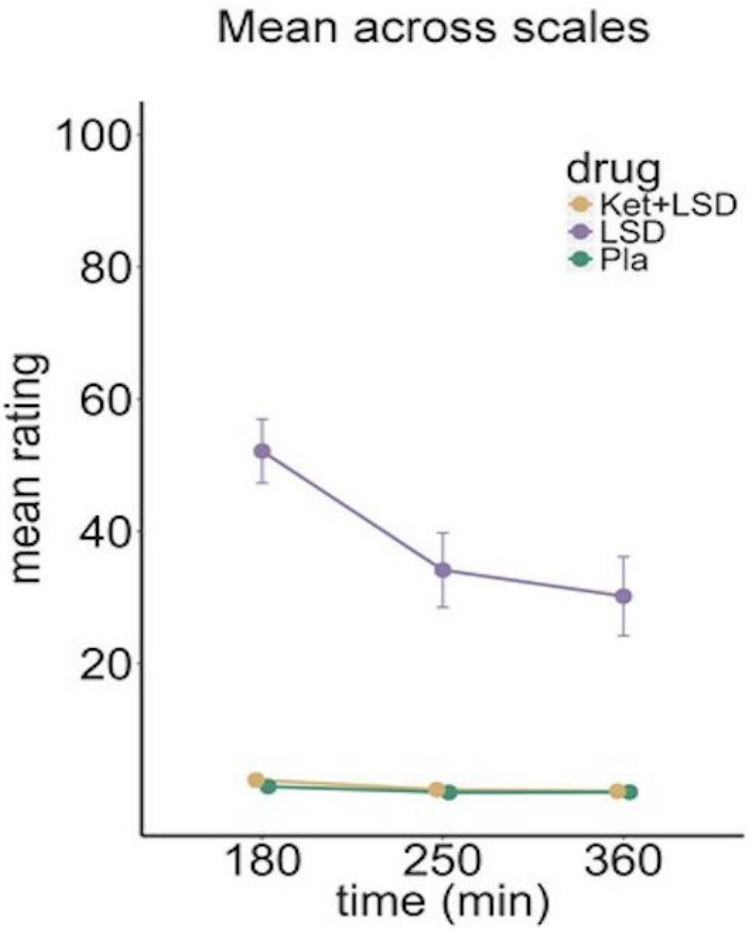
I. PHARMACOLOGY, SAFETY AND TOXICITY

Pharmacology

- Acute effects: 6-12 hours (LSD), 4-6 hours (psilocybin, ayahuasca)
- Primary psychedelic effect via 5HT-2A agonism
  - Blocked by ketanserin
- Partial agonist at 5HT-1A
- Increased cortical glutamate



Preller, *Elife* 2018

Pharmacology

- Tachyphylaxis occurs after 3-4 days of administration
- Cross tolerance between compounds
- Correlates with downregulation of 5-HT2A receptors in animal models
- Implications for microdosing

Nichols *Pharmacol Rev* 2016

Safety & physiologic effects

- Negative effects (dose dependent):
  - Headache, nausea, fatigue most common (<50%)
- Sympathetic changes:
  - ↑BP, ↑HR (mild), ↑temperature (rare)
  - Mydriasis, increased reflexes
- Well tolerated in medically ill subjects (terminal cancer, geriatric patients)
- Toxicity: no LD50 established for humans, likely in grams or kilograms
- No evidence for mutagenic effects or neurotoxicity

Passie *CNS Neuroscience and Therapeutics* 2008

Safety & physiologic effects

Safety, tolerability, pharmacokinetics, and pharmacodynamics of low dose lysergic acid diethylamide (LSD) in healthy older volunteers

Neiloufar Family[1] · Emeline L. Maillet[1] · Luke T. J. Williams[1] · Erwin Krediet[1] · Robin L. Carhart-Harris[2] · Tim M. Williams[3] · Charles D. Nichols[4] · Daniel J. Goble[5] · Shlomi Raz[1]

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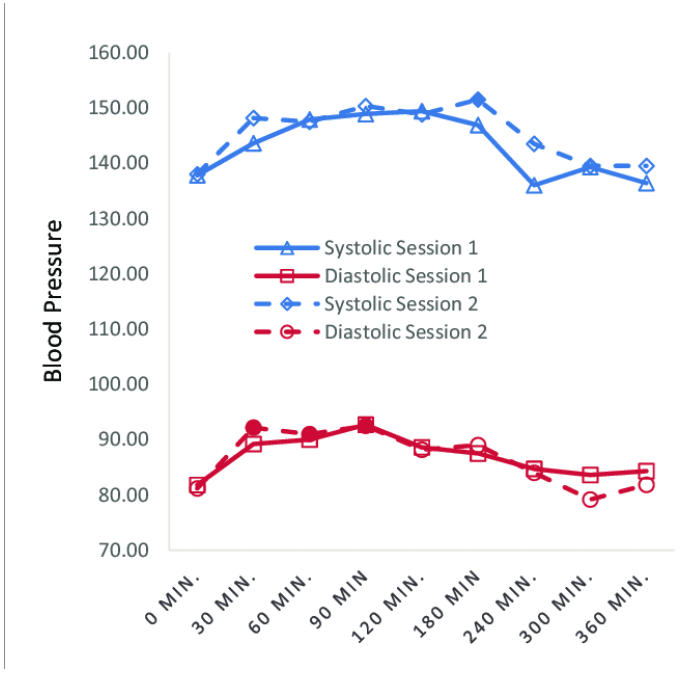

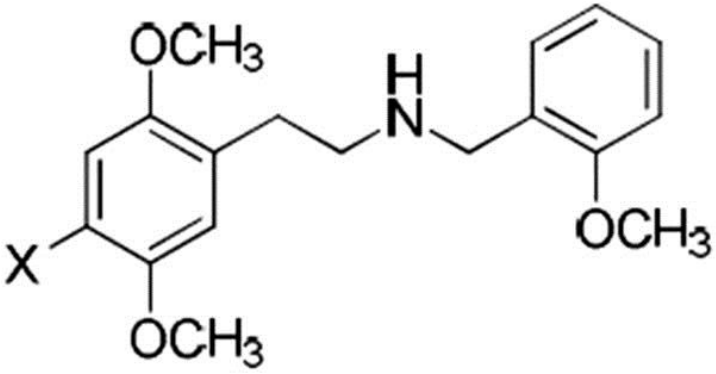

25H-NBOMe, X = H
25C-NBOMe, X = Cl
25B-NBOMe, X = Br
25I -NBOMe, X = I

Psychological safety: the bad trip

- Anxiety, fear/panic, dysphoria, and/or paranoia
- Variety of modalities:
  - Sensory: frightening illusions
  - Somatic: hyperawareness of body processes
  - Personal: distressing thoughts about oneself
  - Metaphysical: fearful thoughts about the world, society, evil forces
- In clinical settings, primary intervention is interpersonal support (pharm rescue usually not needed)

Johnson 2008, Studerus 2011

Psychological safety: post-acute effects and screening

- Prolonged psychosis?: 1/1200 subjects experienced psychosis > 48h
  - Subject's twin had schizophrenia
- No cases of prolonged psychosis in modern studies
  - Screening: personal or family history of bipolar or schizophrenia contraindicated
  - HPPD has not been reported following any clinical studies
- Catastrophic behaviors (eg suicide) rare, but have occurred in non-controlled settings
  - Preparation, controlled settings, psychological support

Cohen 1960, Krebs 2013, Studerus 2011

II. THERAPEUTIC USE: GENERAL PRINCIPLES

Psychological effects

- Effects often long lasting: increased well being, enhanced appreciation, increased openness
- Majority of subjects in controlled settings report experience as enriching or meaningful, even if the session was marked by dysphoria
- 14-month follow-up of non-clinical study: among 5 most personally meaningful (58%) and spiritually significant (67%) experiences in their lives

Griffiths 2018 *J Psychopharmacol.*

Psycholytic or psychedelic therapy?

- Psycholytic therapy: emphasis on therapy itself, used lower doses
- Psychedelic therapy: higher doses to facilitate a transcendent experience, therapist's role is more supportive during session
  - Therapy focused on extensive preparation before and integration sessions afterward
- Many studies using psychedelics used neither and tied patients to beds, blindfolded

Psychedelic therapy?

Administration of Lysergide and Ephedrine

On the day drugs were given patients went to the psychiatric ward of a general hospital (Toronto Western Hospital) in a fasting and drug-free state, except patients receiving phenytoin, who were maintained as usual on this drug or given a 250-mg dose intramuscularly, as an anticonvulsant precaution, shortly after admission to the ward. The patient was placed in a single room, attached to the bed by a light but strong (Posey) belt for security. Either 800 μg of lysergide or 60 mg of ephedrine sulfate was administered, double blind according to a prearranged schedule. A particularly large dose of lysergide was used in order to be certain that important effects were not missed by using minimal doses.

Smart et al, Quart. J. Stud. Alcohol, 1966

Psychedelic assisted psychotherapy

- All recent studies have utilized psychological support during the treatment session
- Mostly based on models developed in 1960s (Stan Grof)
- Therapist is available at all times, but patients encouraged to have an internal experience and explore this
- Set and setting
- Quiet room, calming décor, instrumental music, eye shades, non-directive therapy

Psychedelic assisted psychotherapy

Microdosing

- Use of very small doses (≤0.05 typical dose) with minimal acute drug effects
- Schedule varies, usually taken only a few days each week
- LSD, psilocybin most commonly used
- Observational study: increased mood, attention, well being, creativity on dosing days but no residual effects

III. ANXIETY AND DEPRESSION

Psilocybin-assisted psychotherapy for treatment resistant depression

- Open label
- 20 participants with treatment-resistant depression
- 2 oral doses of psilocybin, 7 days apart (10mg, 25mg) (open label)
- Preparatory sessions, psychological support during psilocybin, integration session post treatment
- Followed at weeks 1-5, 3 months and 5 months
- Depression scores significantly reduced at all time points

Carhart Harris, *Psychopharmacol* 2018

Psilocybin-assisted psychotherapy for treatment resistant depression

Table 2

Individual patient clinical ratings: clinical outcomes at various time points. The clinician administered ratings were completed at baseline and 1 week post-dosing only

	BDI				STAI					S
	Baseline	**1 week**	**3 months**	**6 months**	**Baseline**	**1 week**	**3 months**	**6 months**	**Baseline**	**1**
Mean (SD)	34.5 (7.3)	11.8 (11.1)	19.2 (13.9)	19.5 (13.9)	68.6 (6.1)	44.8 (15.7)	56.5 (13.3)	53.8 (13.3)	6.6 (4.1)	1.
Difference vs baseline (SD)		− 22.7 (10.6)	− 15.3 (13.7)	− 14.9 (12.0)		− 23.8 (15.2)	− 12.2 (12.7)	− 14.8 (14)		− (4
Cohen's *d*		2.5	1.4	1.4		2.2	1.2	1.5		1.
p value		$p < 0.001$	$p < 0.001$	$p < 0.001$		$p < 0.001$	$p < 0.001$	$p < 0.001$		*p*

Carhart Harris, *Psychopharmacol* 2018

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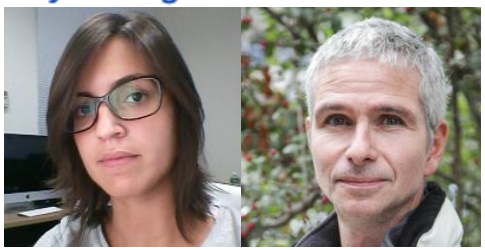
Carhart Harris, *Psychopharmacol* 2018

Psychological Medicine



Original Article

Cite this article: Palhano-Fontes F *et al* (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological Medicine* **49**, 655–663. https://doi.org/10.1017/S0033291718001356

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Revised: 16 April 2018
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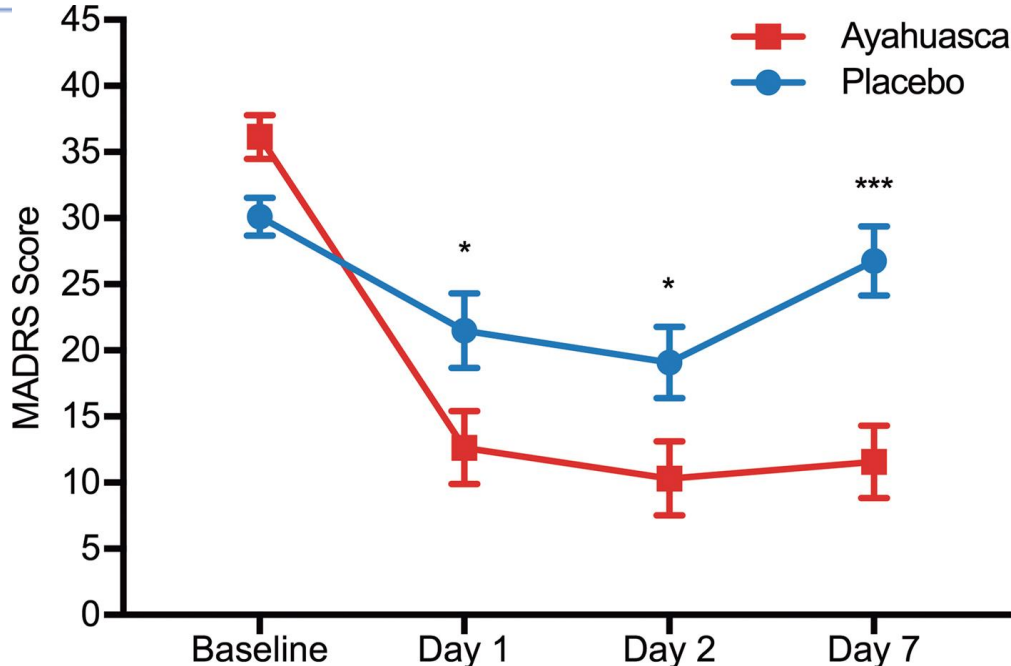
Key words:

Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial

Fernanda Palhano-Fontes[1,2], Dayanna Barreto[2,3], Heloisa Onias[1,2], Katia C. Andrade[1,2], Morgana M. Novaes[1,2], Jessica A. Pessoa[1,2], Sergio A. Mota-Rolim[1,2], Flávia L. Osório[4,5], Rafael Sanches[4,5], Rafael G. dos Santos[4,5], Luís Fernando Tófoli[6], Gabriela de Oliveira Silveira[7], Mauricio Yonamine[7], Jordi Riba[8], Francisco R. Santos[9], Antonio A. Silva-Junior[9], João C. Alchieri[10], Nicole L. Galvão-Coelho[5,11], Bruno Lobão-Soares[5,12], Jaime E. C. Hallak[4,5], Emerson Arcoverde[2,3,5], João P. Maia-de-Oliveira[2,3,5] and Dráulio B. Araújo[1,2]

- **Methods**: RCT, double-blinded. N=29 patients with treatment-resistant depression. Primary endpoint Day 7.
- **Results**: Significant response rate in intervention group at Day 1, 2 and 7. Remission rate showed trend toward significance at Day 7 (p = 0.054).



Use in end of life-related depression and anxiety

- **Grob et al 2011/UCLA: 30% decrease in BDI, significant decrease in trait anxiety sustained at 6 months**
  - N=12, dx=advanced stage cancer/acute stress, GAD, adjustment disorder, or anxiety secondary to cancer
  - Psilocybin 14 mg/70 kg vs niacin placebo
- **Gasser et al 2014/University of Bern: trend toward decreased state anxiety sustained at 12 months**
  - N=12, dx=life threatening medical illness/anxiety associated with medical illness
  - Randomized, open-label crossover; 200 µg vs 20 µg LSD
- **Griffiths et al 2016/Hopkins: 80% of subjects with significant decreases in anxiety and depression at 6 months**
  - N=51, dx=life threatening cancer/depression or anxiety
  - Randomized crossover design; 22 mg/70 kg psilocybin vs 1 mg (placebo)
- **Ross et al 2016/NYU: 60-80% response rate for anxiety and depression at 6 months**
  - N=29, dx=cancer (2/3 with advanced cancer)/anxiety disorder (GAD 10%, adjustment 90%)
  - Randomized, crossover design; psilocybin 21 mg/70 kg vs niacin placebo

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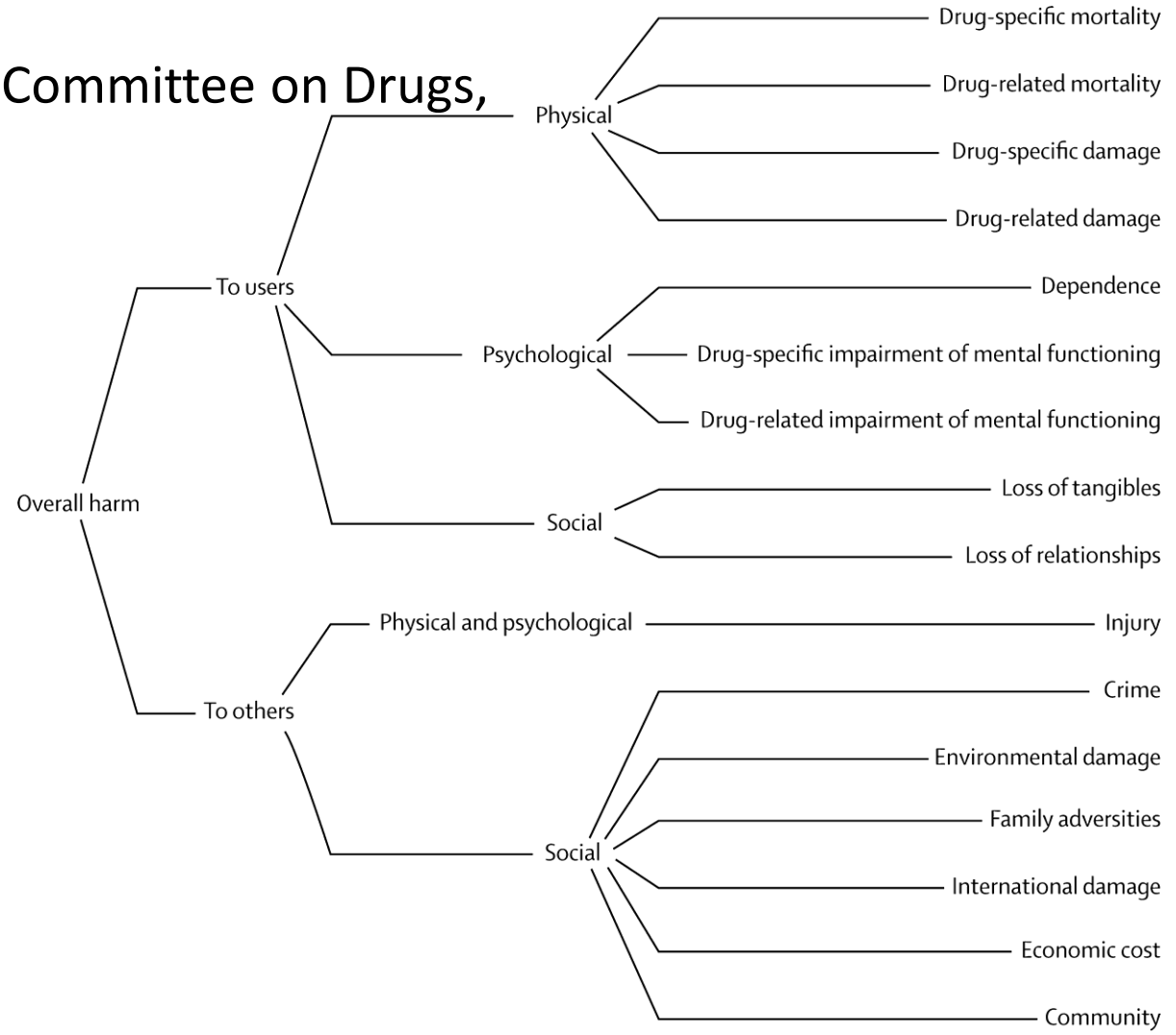
IV. SUBSTANCE USE DISORDERS

Psychedelics as drugs of abuse

- Independent Scientific Committee on Drugs, UK, 2009

- Multicriteria decision analysis modelling to a range of drug harms



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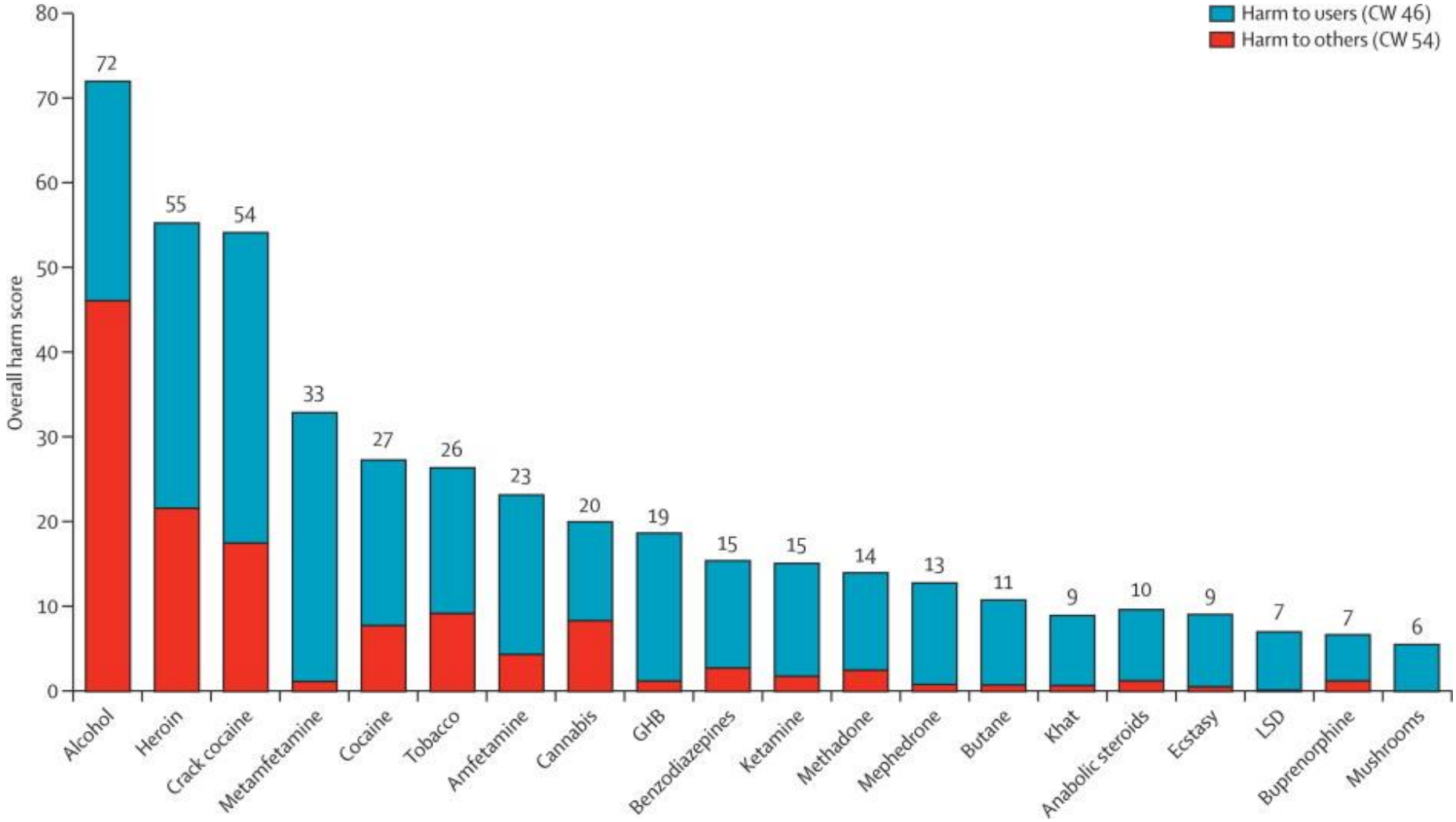
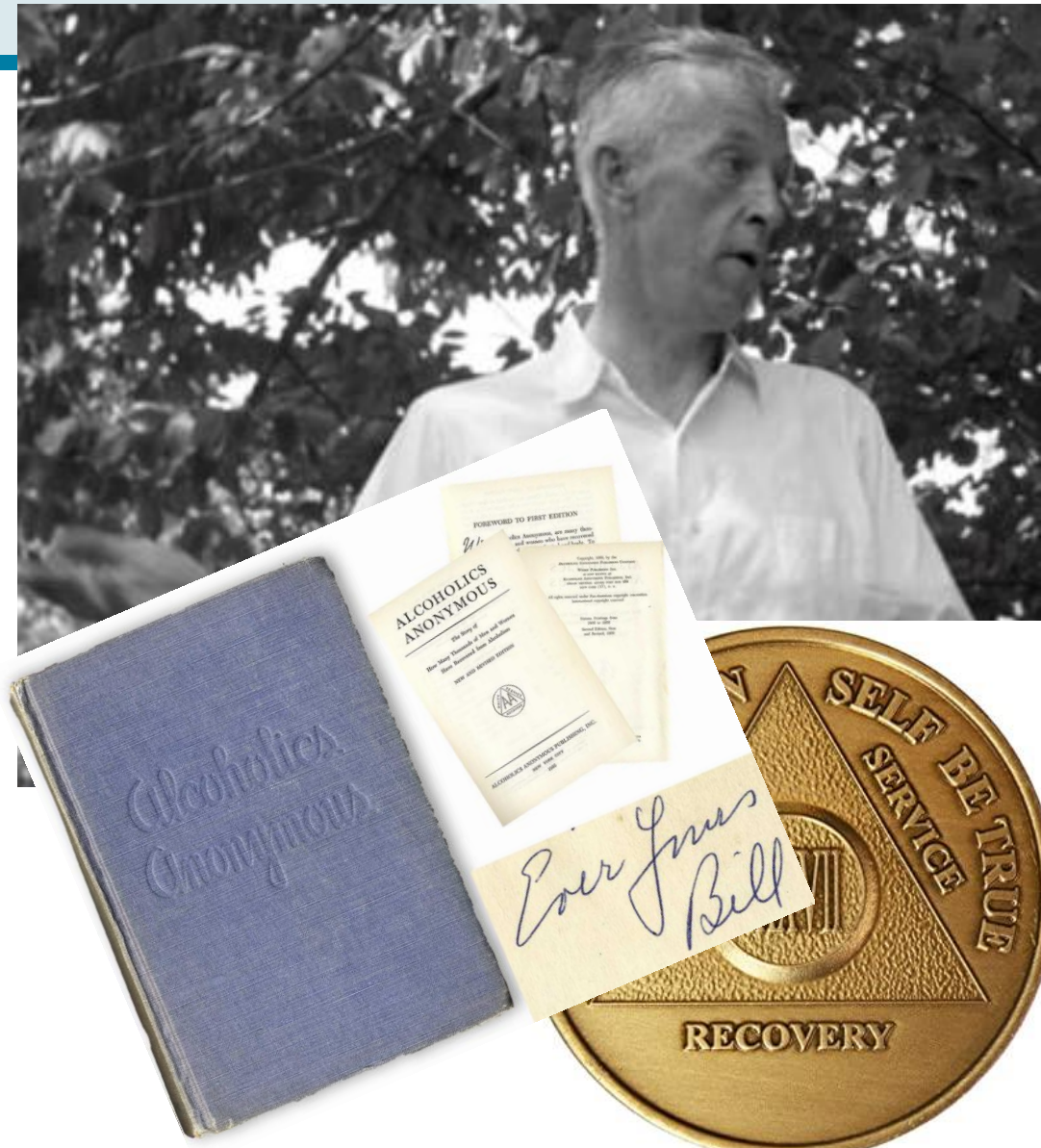


Alcohol Use Disorder

- Early research using LSD in 1950s Saskatchewan under Abram Hoffer
- Initially based on theory that LSD mimicked delirium tremens
- Bill Wilson of AA given LSD in 1956

Alcohol Use Disorder

- After learning of Hoffer's work in Canada, became proponent of using LSD to catalyze spiritual breakthroughs in resistant patients:
- *"I don't believe [LSD] has any miraculous property of transforming spiritually and emotionally sick people into healthy ones overnight. It can set up a shining goal on the positive side, after all it is only a temporary ego-reducer… The vision and insights given by LSD could create a large incentive – at least in a considerable number of people."*



Psychedelic Therapy Utilizing LSD in the Treatment of the Alcoholic Patient: A Preliminary Report

BY ALBERT A. KURLAND, M.D., SANFORD UNGER, PH.D., JOHN W. SHAFFER, PH.D., AND CHARLES SAVAGE, M.D.

The rationale of psychedelic therapy with alcoholic patients is focused on the alienation-breaking potential of "peak" or psychedelic experiences induced with the aid of LSD. An exemplary LSD session report and MMPI data on 69 pilot patients are presented for illustration. While all present results indicate that psychedelic therapy does add significantly to presently available alcoholic rehabilitation resources, it is emphasized that safe and effective use of LSD requires specialized training.

the chronic alcoholic patient and the then extant several reports on the drug's usefulness, we launched our own explorations with patients hospitalized in the Alcoholic Rehabilitation Unit of the Spring Grove State Hospital in Baltimore, Md.

From the very beginning, our approach to the use of this potent compound was marked by extreme respect. We started by implementing a treatment effort, called the psychedelic procedure, which consisted of approximately three weeks of intensive psychotherapy incorporating one high-dose

Quart.J.Stud.Alcohol 25, 333-338 (1964). LSD 1288

NOTES and COMMENT

The Efficacy of LSD in the Treatment of Alcoholism[1]

Reginald G. Smart and Thomas Storm

Comment has often been made (1, 2) on the low scientific standard which prevail in routine clinical trials of new drugs. In fact, the lac of control groups, follow-up and objective measurements of chan characterized psychiatric research into both pharmacologi methods (3, 4). This general lack efforts to exam

LSD in Psychotherapy and Alcoholism

Edited by Harold A. Abramson, M.D.

Introduction by Frank Fremont-Smith, M.D.

Was LSD-assisted therapy effective?

Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials

Teri S Krebs[1,2] and Pål-Ørjan Johansen[1,2]

Psychopharm

Journal of Psychopharmacology
26(7) 994–1002

DOI: 10.1177/0269881112439253
jop.sagepub.com
SAGE

Abstract

Assessments of lysergic acid diethylamide (LSD) in the treatment of alcoholism have not been based on quantitative meta-analysis. Hence, we performed a meta-analysis of randomized controlled trials in order to evaluate the clinical efficacy of LSD in the treatment of alcoholism. Two reviewers independently extracted the data, pooling the effects using odds ratios (ORs) by a generic inverse variance, random effects model. We identified six eligible trials, including 536 participants. There was evidence for a beneficial effect of LSD on alcohol misuse (OR, 1.96; 95% CI, 1.36–2.84; $p = 0.0003$). Between-trial heterogeneity for the treatment effects was negligible ($I^2 = 0\%$). Secondary outcomes, risk of bias and limitations are discussed. A single dose of LSD, in the context of various alcoholism treatment programs, is associated with a decrease in alcohol misuse.

Keywords

Alcoholism, alcohol-related disorders, hallucinogens, meta-analysis, psychedelics, substance-related disorders

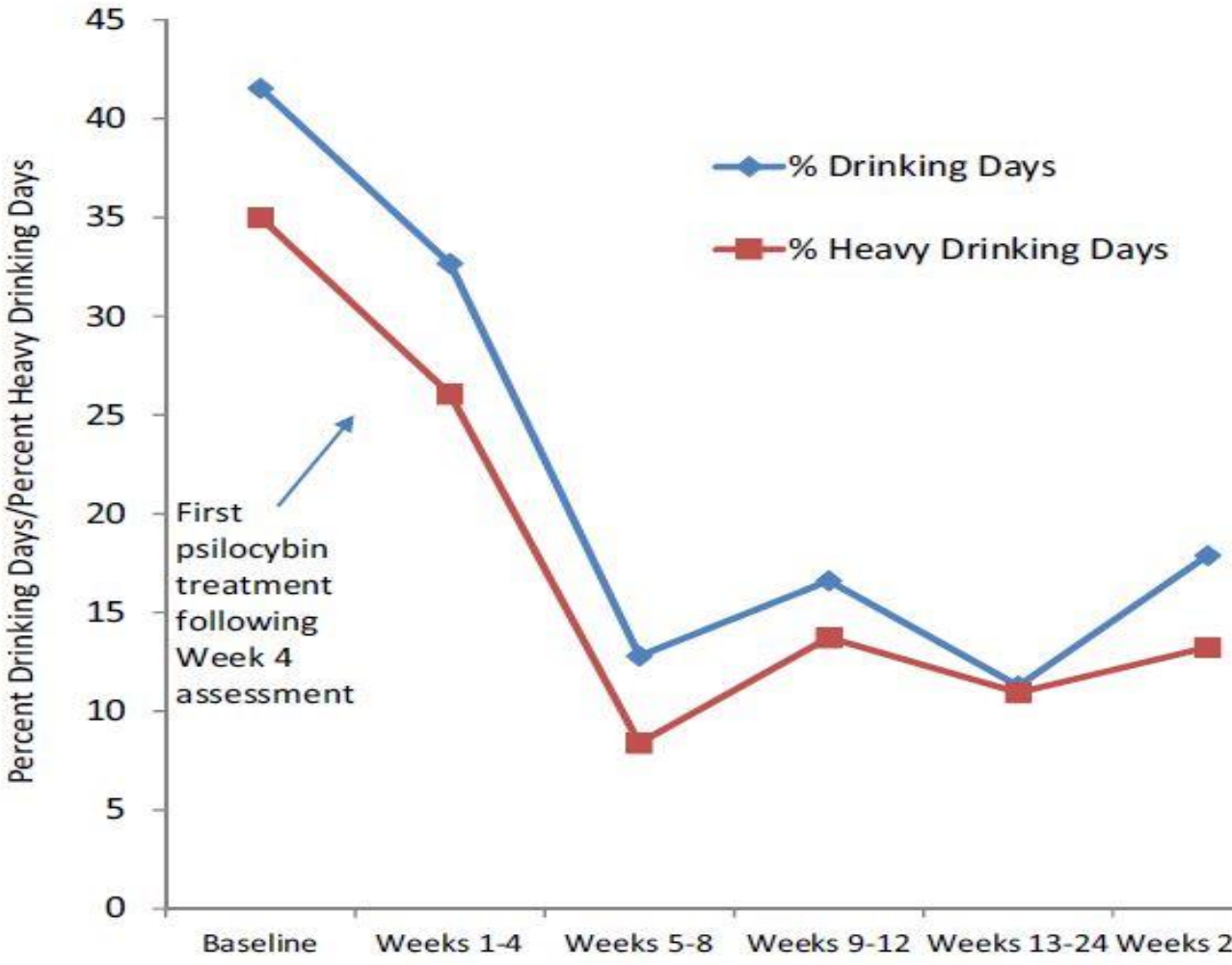
2012 meta-analysis of 6 1950s-60s studies found an odds ratio of 1.96 for beneficial effect on alcohol “misuse”

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

- 10 participants (60% male, mean age = 40) with alcohol dependence received psilocybin in 1-2 sessions
- Primary drinking outcome: % heavy drinking days
- Received Motivational Enhancement Therapy (12-week manualized intervention), also preparatory and debriefing therapy sessions
- First psilocybin dose at week 4, second dose at week 8
- Two therapists present during psilocybin sessions delivering supportive therapy

Bogenschutz et al 2015, *J Psychopharmacol.*

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



Drinking Days

Baseline vs.		
Weeks 1-4	$p = .164$	$d = 0.490$
Weeks 5-8	$p = .009$	$d = 1.194$
Weeks 9-12	$p = .015$	$d = 1.033$
Weeks 13-24	$p = .006$	$d = 1.332$
Weeks 25-36	$p = .007$	$d = 1.187$
Weeks 1-4 vs.		
Weeks 5-8	$p = .016$	$d = 1.109$
Weeks 9-12	$p = .033$	$d = 0.869$
Weeks 13-24	$p = .014$	$d = 1.163$
Weeks 25-36	$p = .013$	$d = 1.036$

Heavy Drinking Days

Baseline vs.		
Weeks 1-4	$p = .158$	$d = 0.492$
Weeks 5-8	$p = .007$	$d = 1.249$
Weeks 9-12	$p = .019$	$d = 0.985$
Weeks 13-24	$p = .010$	$d = 1.161$
Weeks 25-36	$p = .004$	$d = 1.383$
Weeks 1-4 vs.		
Weeks 5-8	$p = .022$	$d = 1.046$
Weeks 9-12	$p = .059$	$d = 0.750$
Weeks 13-24	$p = .038$	$d = 0.876$
Weeks 25-36	$p = .018$	$d = 1.040$

Bogenschutz et al 2015, *J Psychopharmacol.*

A double blind trial of psilocybin-assisted treatment of alcohol dependence

Study Design

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	180 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Double-Blind Trial of Psilocybin-Assisted Treatment of Alcohol Dependence
Study Start Date :	June 2014
Estimated Primary Completion Date :	October 2020
Estimated Study Completion Date :	October 2020

CASE REPORT

First study of safety and tolerability of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with alcohol use disorder: preliminary data on the first four participants

Ben Sessa,[1] Chloe Sakal,[2] Steve O'Brien,[1] David Nutt[1]

Participant 3: Better than other treatments, including inpatient detox … I enjoyed every moment of it. Thrilled to be part of the study … I feel energised … The treatment has worked for me, done me a lot of good. I've got a lot of confidence out of it. I'm calmer … It's given me what I wanted; to be cured, to not have the cravings, to look at life differently. I'm not so angry at everything … Being under MDMA was beautiful. It showed me the real me; the me without alcohol.

Participant 4: A weight has been lifted off my shoulders. I haven't felt like that for a long time. There are no nagging doubts. I'm getting my life back on track … Everything is so much clearer. It's like a smog has been removed. I can see myself moving forward … It makes me think: why was I drinking that rubbish? I was just being stupid, idiotic, killing myself. There's no reason to be doing that … Taking part in this study has helped me focus more on life and my goals … An uplifting experience that I would recommend to anyone.

Learning points

- An 8-week course of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy can be safely delivered to this population of patients with alcohol use disorder (AUD).
- Patients with AUD tolerate the medicine and the psychotherapy course well, with no acute or lasting negative changes in physiological data up to 8 weeks.
- Demonstrable improvements in quality of life, mindfulness, self-compassion, anxiety and depression scores were observed in all participants following the 8-week course of MDMA therapy.
- This study forms the basis of further plans for a randomised double-blind placebo-controlled study testing the efficacy of MDMA-assisted psychotherapy as a treatment for AUD.

Sessa et al, BMJ Case Reports, 2019

Nicotine

Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction

- Open label, moderate (20 mg) and high dose (30 mg) dose psilocybin within 15-week smoking cessation program
- Target quit date set for 1st psilocybin session (week 5)
- High dose psilocybin given at week 7 and 13 (optional)
- N = 15, 2/3 male, 6 previous quit attempts
- 12/15 (80%) abstinent at 6 months
- 67% abstinent at 12 months, 60% abstinent at 30 months

Johnson et al 2014, *J Psychopharmacol*

Qualitative results

"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 don't know if I really learned – it was more like letting back in stuff that I had blocked out?... I don't think I changed my values, just remembered more of them. Or just remembered to honour them more, or...allow them more."

"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."

Noorani 2018, *J. Psychopharmacol.*

V. MULTIPLE MECHANISMS

Why 5HT2A?

- 5HT2A receptors may facilitate plasticity as a stress response
- Amygdala is rich in 5HT2A receptors, connecting it widely across the neocortex, role in salience of sensory stimuli
- Prefrontal cortex also regulates amygdala “tone” directly and indirectly via 5HT2A

Kraehenmann *Neuroimag Clin* 2015

Modulation of default mode network (DMN)

- DMN involved in experience of sense of self/embodiment, retrieval of autobiographical memory, daydreaming
- Balance between internally and externally directed thought
- Increased DMN activity in pathological rumination in depression
- Decreased DMN activity shown psilocybin, LSD, ayahuasca
- Magnitude of deactivation correlates with subjective effects

Carhart Harris 2011 *PNAS*, Palhano-Fontes 2015 *PLOS ONE,* Carhart Harris 2017 *Sci Rep, Müller* Neuroimag Clin 2018

PLOS ONE

OPEN ACCESS PEER-REVIEWED

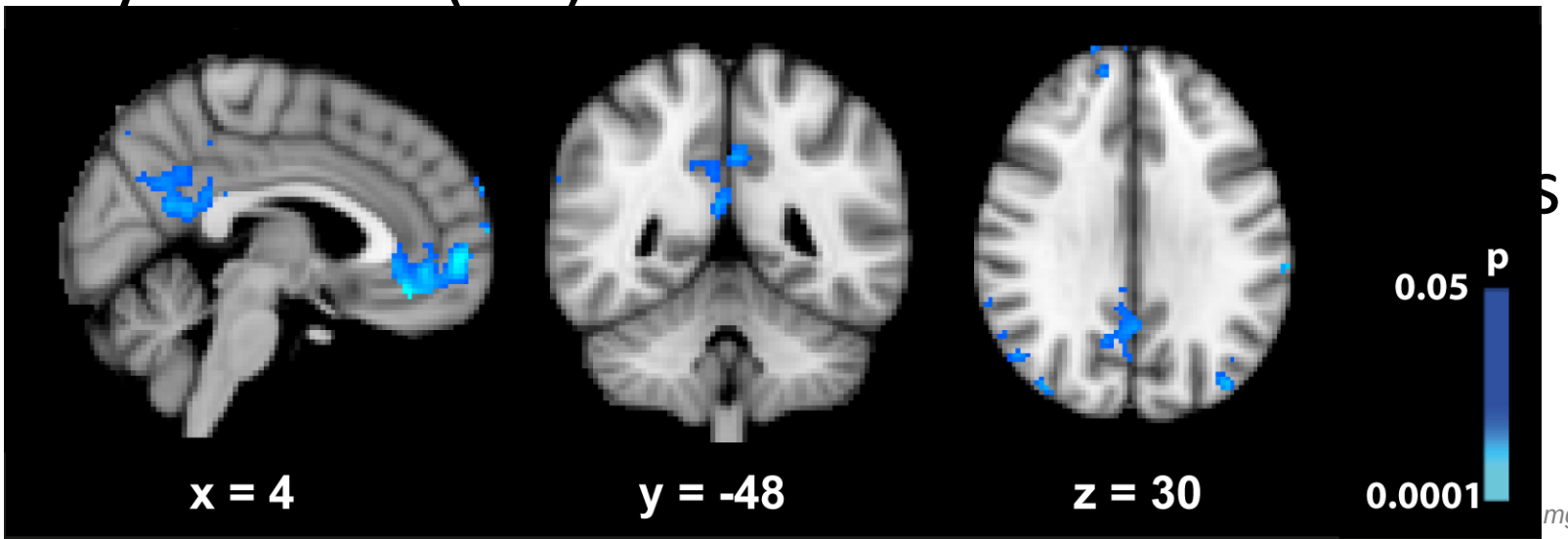
RESEARCH ARTICLE

The Psychedelic State Induced by Ayahuasca Modulates the Activity and Connectivity of the Default Mode Network

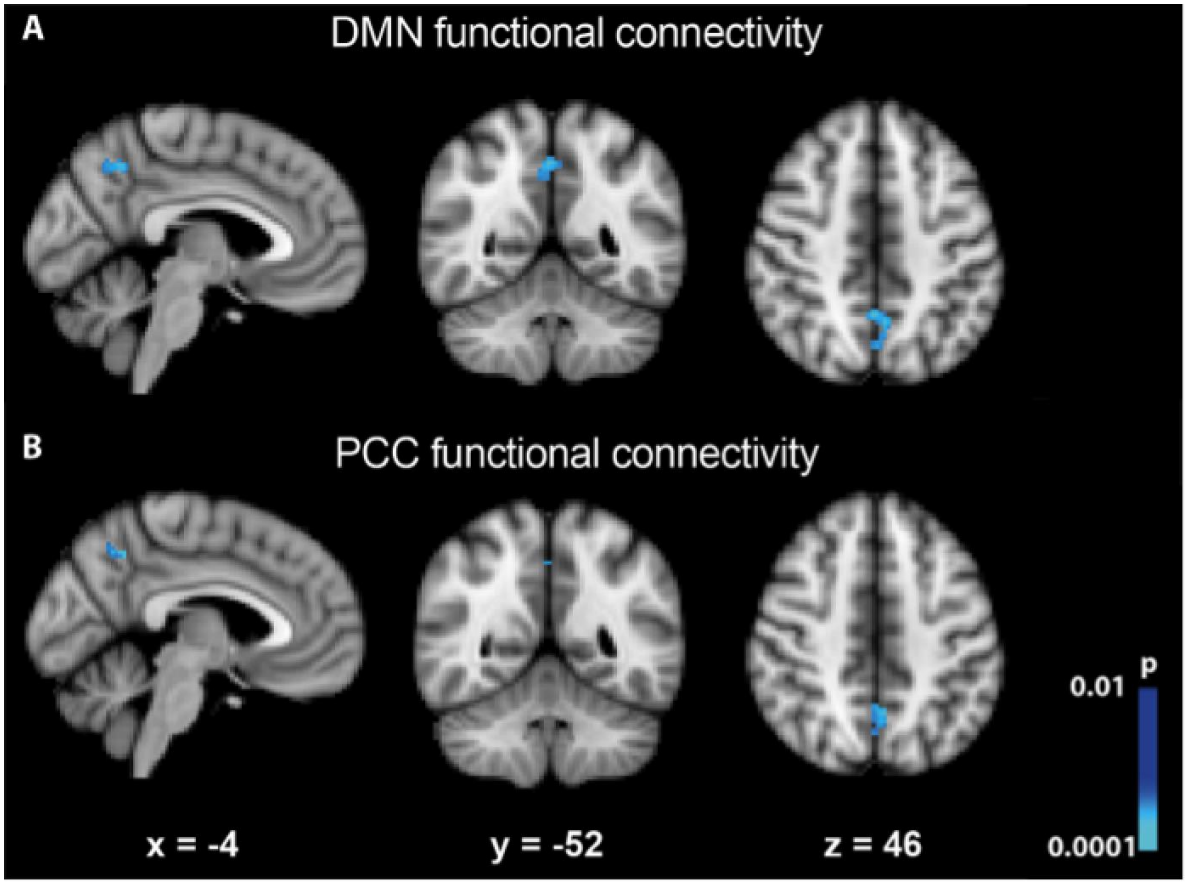
Fernanda Palhano-Fontes, Katia C. Andrade, Luis F. Tofoli, Antonio C. Santos, Jose Alexandre S. Crippa, Jaime E. C. Hallak, Sidarta Ribeiro, Draulio B. de Araujo

Published: February 18, 2015 • https://doi.org/10.1371/journal.pone.0118143

- 10 healthy subjects, all ayahuasca experienced
- 2 fMRI sessions, before and 40min after ayahuasca (PO)



Reduction in DMN connectivity under ayahuasca



- Reduced functional connectivity within the DMN
- Driven largely by PCC/precuneus
- Psilocybin, but not ayahuasca, also caused decreased PCC-mPFC connectivity

Palhano-Fontes 2015 *PLOS ONE,* Carhart-Harris 2012, *PNAS*

Original Paper

Subacute effects of the psychedelic ayahuasca on the salience and default mode networks

Lorenzo Pasquini[1,*], Fernanda Palhano-Fontes[2,*] and Draulio B Araujo[2]

Psychopharm

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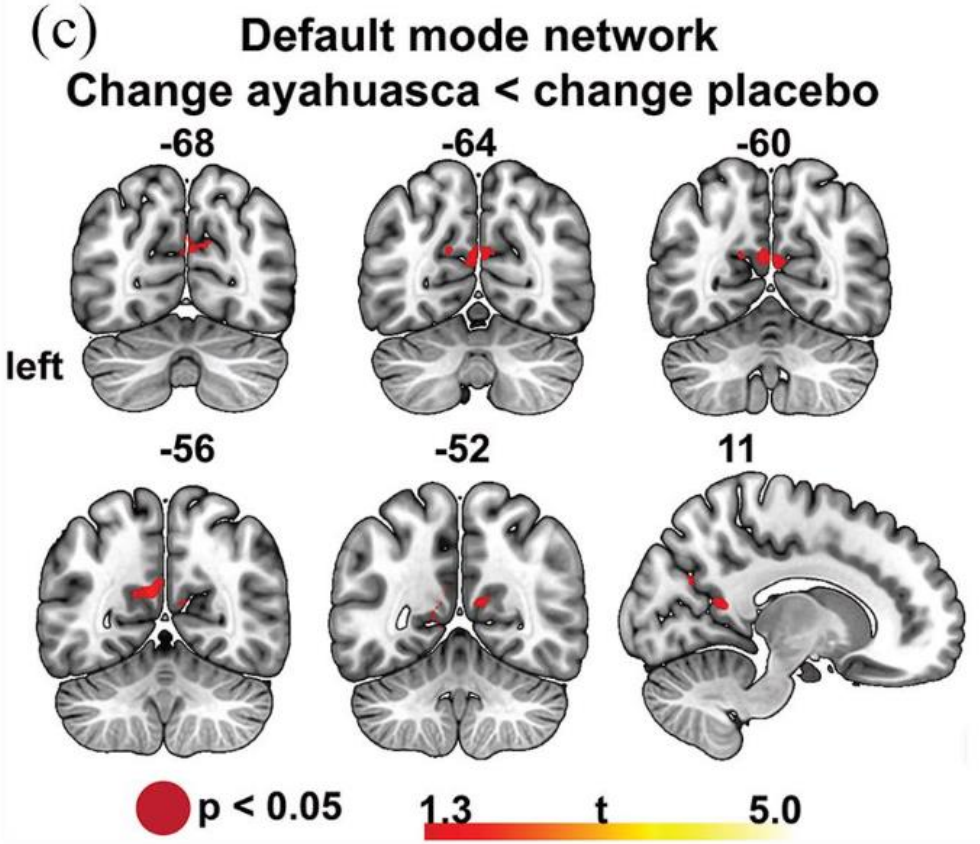

Participants: 50 healthy volunteers, ayahuasca naïve

Results: Significant default mode network functional connectivity decreases within the posterior cingulate cortex for the ayahuasca compared to the placebo group.

Psychological mechanisms

- Decreased neuroticism:
- Increased susceptibility to stress, negative affect, anxiety, somatization
- Association with development of depression, anxiety, PTSD
- Association with psychosomatic/functional disorders
- Increased openness to experience, increased extraversion

VI. FUTURE DIRECTIONS

Harm Reduction

- Non-clinical settings ≠ risk-free
- Legality
- Drug purity
- Multidisciplinary Association for Psychedelic Studies
- DanceSafe
- RollSafe

Future directions

REVIEWS AND OVERVIEWS

Psychedelics and Psychedelic-Assisted Psychotherapy

Collin M. Reiff, M.D., Elon E. Richman, M.D., Charles B. Nemeroff, M.D., Ph.D., Linda L. Carpenter, M.D., Alik S. Widge, M.D., Ph.D., Carolyn I. Rodriguez, M.D., Ph.D., Ned H. Kalin, M.D., William M. McDonald, M.D., and the Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research

Objective: The authors provide an evidenced-based summary of the literature on the clinical application of psychedelic drugs in psychiatric disorders.

Methods: Searches of PubMed and PsycINFO via Ovid were conducted for articles in English, in peer-reviewed journals, reporting on "psilocybin," "lysergic acid diethylamide," "LSD," "ayahuasca," "3,4-methylenedioxymethamphetamine," and "MDMA," in human subjects, published between 2007 and July 1, 2019. A total of 1,603 articles were identified and screened. Articles that did not contain the terms "clinical trial," "therapy," or "imaging" in the title or abstract were filtered out. The 161 remaining articles were reviewed by two or more authors. The authors identified 14 articles reporting on well-designed clinical trials investigating

Results: The most significant database exists for MDMA and psilocybin, which have been designated by the U.S. Food and Drug Administration (FDA) as "breakthrough therapies" for posttraumatic stress disorder (PTSD) and treatment-resistant depression, respectively. The research on LSD and ayahuasca is observational, but available evidence suggests that these agents may have therapeutic effects in specific psychiatric disorders.

Conclusions: Randomized clinical trials support the efficacy of MDMA in the treatment of PTSD and psilocybin in the treatment of depression and cancer-related anxiety. The research to support the use of LSD and ayahuasca in the treatment of psychiatric disorders is preliminary, although promising. Overall, the database is insufficient for FDA ap-

WORLD'S FIRST CENTER FOR PSYCHEDELICS RESEARCH OPENS IN UK

HUB

Johns Hopkins launches center for psychedelic research

The center, believed to be the first and largest of its kind, will use study the mind and identify therapies for diseases such as addic Alzheimer's

MGH Center for Neuroscience of Psychedelics

Jerrold Rosenbaum MD

Director

Psychiatrist-in-Chief Emeritus

Director, Center for Anxiety and Traumatic Stress Disorders

Professor of Psychiatry, Harvard Medical School

Bruce Rosen MD, PhD

Scientific Director Clinical Neuroscience and Neuroimaging

Director of the Athinoula A. Martinos Center for Biomedical Imaging

Professor of Radiology, Harvard Medical School

Steven Haggarty PhD

Scientific Director

Chemical Neurobiology

Director , MGH Chemical Neurobiology Laboratory, Center for Genomic Medicine

Stuart & Suzanne Steele Research Scholar Associate Professor of Neurology, Harvard Medical School

Sharmin Ghaznavi MD, PhD

Associate Director

Director of Clinical Studies

Director of the Cross Program Research Initiative on Rumination

Instructor of Psychiatry, Harvard Medical School

Franklin King MD

Director of Training and Education

Psychiatrist, Massachusetts General Hospital

Instructor of Psychiatry, Harvard Medical School

Thank you!