PSYCHEDELIC PSYCHIATRY

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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

What are psychedelics?

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  - **(mescaline, MDMA)**

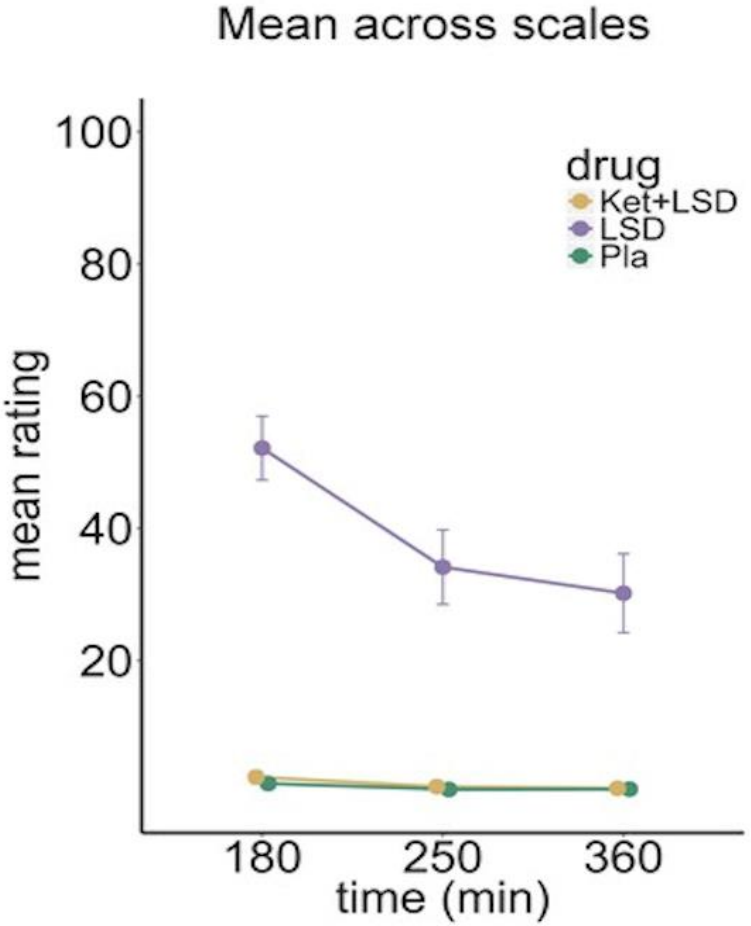
- **[Ibogaine]**

- Ketamine

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 agonists or agonists at 5HT-1A & 5HT-2C
- 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

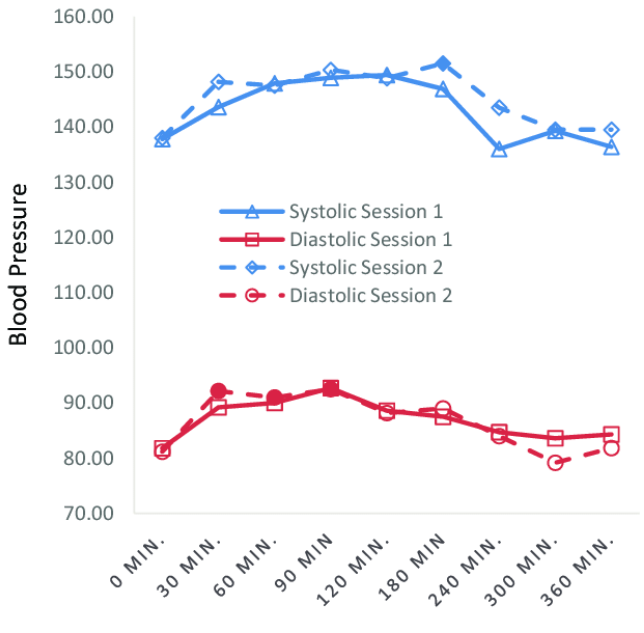
Nichols *Pharmacol Rev* 2016

Safety & physiologic effects

- Negative effects (dose dependent):
  - Headache, nausea, fatigue most common (<50%)
- Sympathetic changes:
  - ↑BP, ↑HR (mild), ↑temperature (mild)
  - 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

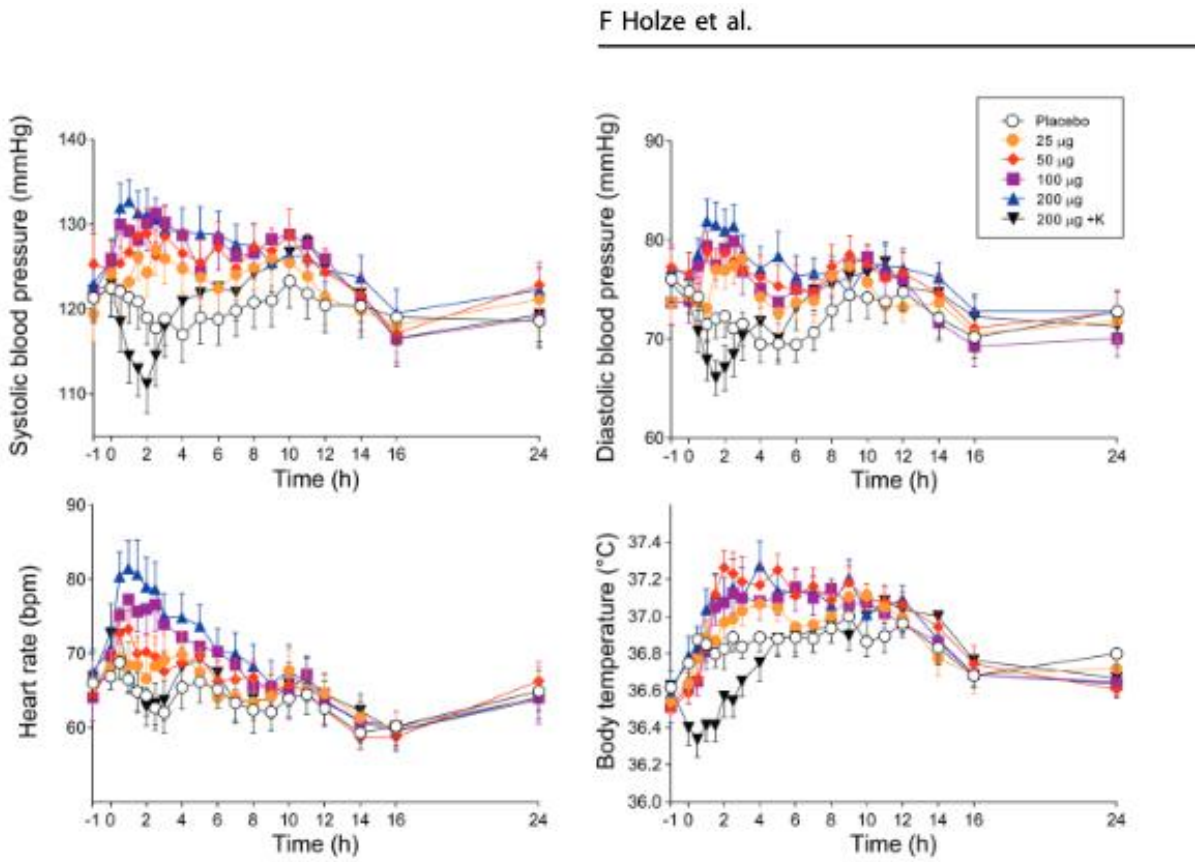
Passie *CNS Neuroscience and Therapeutics* 2008

Autonomic effects



Psilocybin ☝

LSD 👇



Bogenschutz *Psychopharmacology* 2015, Holze *Neuropsychopharmacology* 2021

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]

Received: 12 March 2019 / Accepted: 27 November 2019 / Published online: 18 December 2019

- 48 healthy older adults (55-75 yo; mean = 62.9)
- Randomly assigned to placebo or 5µg, 10µg, or 20µg LSD Q4days for 6 doses, monitored for 8-12 hours post-dosing
- No statistical difference between groups on measures of cognition, balance or proprioception
- Only adverse effect = headaches in 10µg group

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 vs 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 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

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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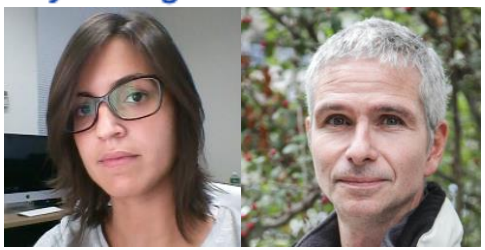
Carhart Harris, *Psychopharmacol* 2018

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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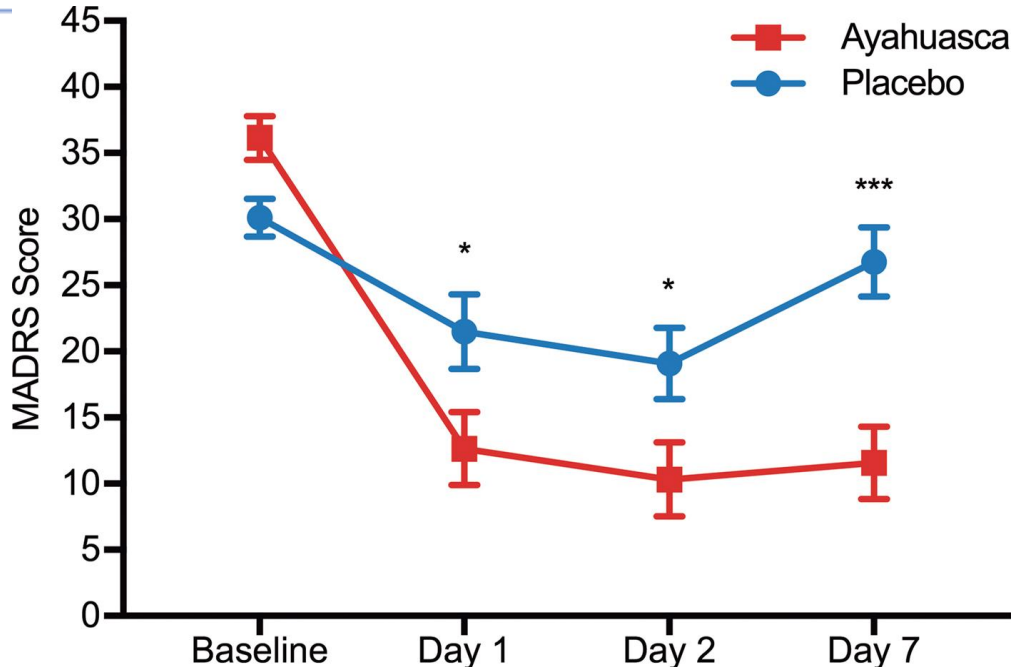
Accepted: 24 April 2018

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).



Effects of psilocybin-assisted therapy on major depressive disorder

- Waitlist control, 27 subjects enrolled
- Waitlist controlled
- 2 psilocybin sessions
- Significant reductions in depression scores from baseline
- Remission from depression in 58% at week 1 and 54% at week 4

Figure 3. Comparison of GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores Between the Delayed Treatment and Immediate Treatment Groups

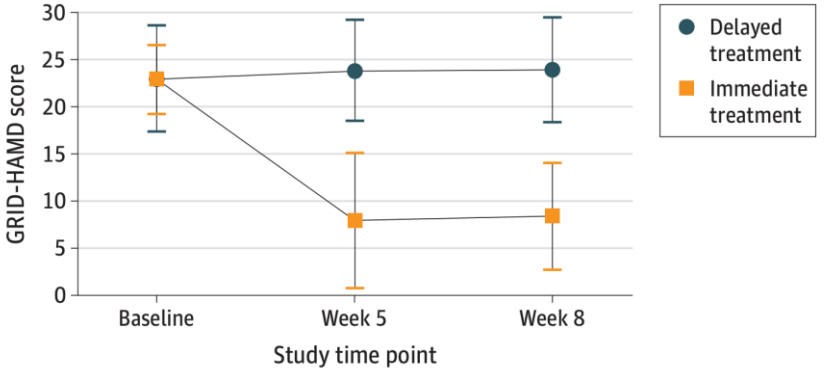
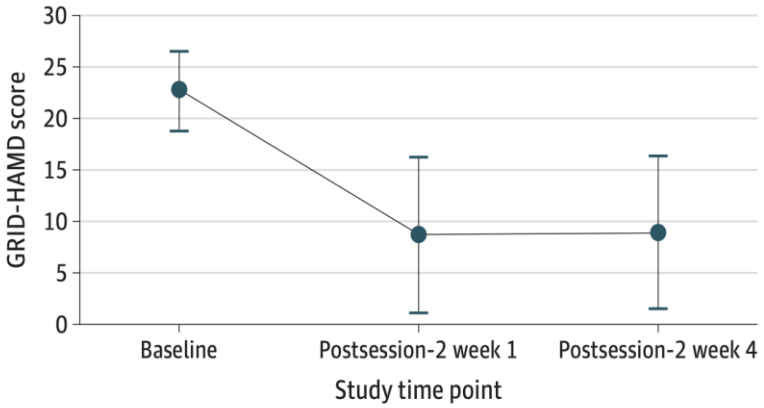


Figure 4. Decrease in the GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores at Week 1 and Week 4 Postsession-2 Follow-up in the Overall Treatment Sample



Davis et al, 2020

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

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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MDMA-ASSISTED PSYCHOTHERAPY

MDMA - Pharmacology

Methylenedioxyphenethylamines

MDMA, MDA, MDEA, MBDB, MMDA

Binds to SERT, NET, and >>> DAT (reuptake inhibition)

Also substrate for monoamine transporters (releasing agent)

Mild 5HT-2A agonism

Effects

Euphoria, enhanced well-being, extraversion, connection to others, trust

Toxicity (?)

Early studies focused exclusively on neurotoxicity in animals, extremely high doses

Neurocognitive effects from recreational use?

Retracted article (Ricaurte et al, *Science*, 2003

MDMA-assisted psychotherapy for PTSD

2018 study (Mithoefer, *Lancet Psychiatry*)

26 veterans and 1st responders with treatment-resistant PTSD

CAPS mean = 86.5

Randomized to 30mg/75mg/125mg. Each received 2 rounds of MAP

Significant reduction in CAPS, with sustained reduction at 12 month follow up (71% no longer met criteria for PTSD)

2021 study (Mitchell, *Nature Medicine*)

90 participants with severe PTSD

Randomized to either 3 rounds of MAP versus placebo with therapy

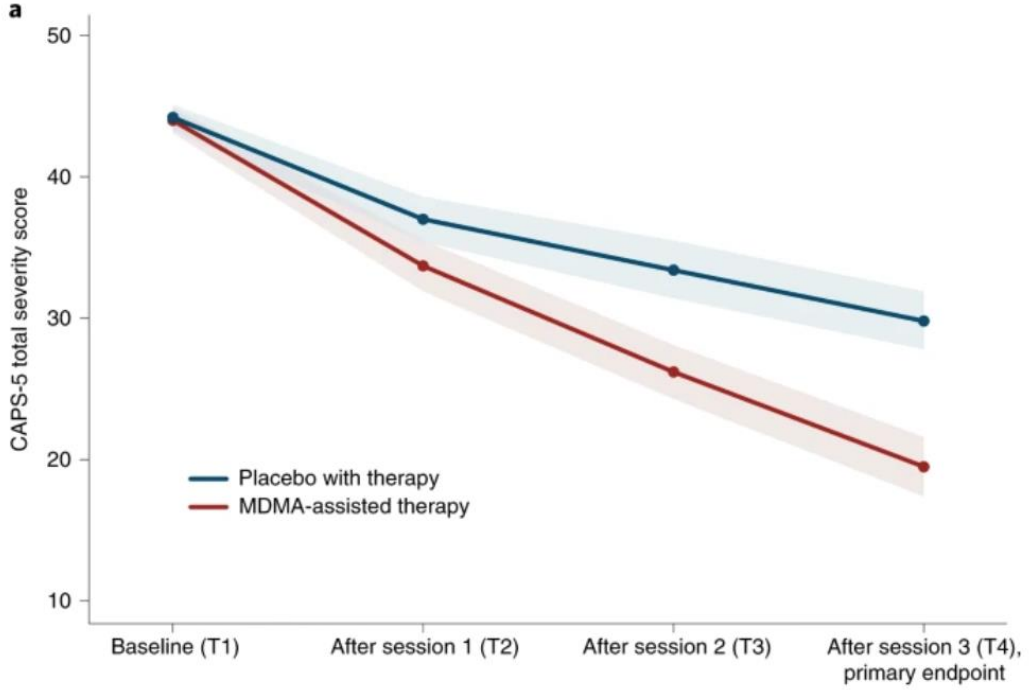
Significant reductions in CAPS (MDMA= -24.5; placebo = -13.9)

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)
Primary efficacy measure			
Mean CAPS-IV total score			
Baseline	87·4 (14·1)	82·4 (17·3)	89·7 (17·3)
After two experimental sessions of MDMA	76·0 (23·4)	24·1 (17·2)	45·3 (33·8)
Change†	−11·4 (12·7)	−58·3 (9·8)	−44·3 (28·7)
p value‡	NA	0·0005	0·004
Secondary efficacy measures			
Number of participants who met CAPS-IV PTSD diagnostic criteria (primary endpoint)			
Yes	5 (71%)	1 (14%)	5 (42%)
No	2 (29%)	6 (86%)	7 (58%)
Number of participants who had more than 30% decrease in CAPS-IV total score (primary endpoint)			
Yes	2 (29%)	7 (100%)	8 (67%)
No	5 (71%)	0	4 (33%)
Mean BDI-II score			
Baseline	30·4 (13·7)	24·7 (12·6)	36·6 (10·5)
After two experimental sessions of MDMA	25·9 (11·2)	9·3 (6·8)	12·0 (9·0)
Change†	−4·6 (8·8)	−15·4 (9·5)	−24·6 (10·6)
p value‡	NA	0·052	0·0003

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., & Doblin, R. (2018). *The Lancet Psychiatry*, 5(6), 486-497.

Mitchell, *Nature Medicine*, 2021

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



- No difference in efficacy for dissociative vs non-dissociative subtypes of PTSD

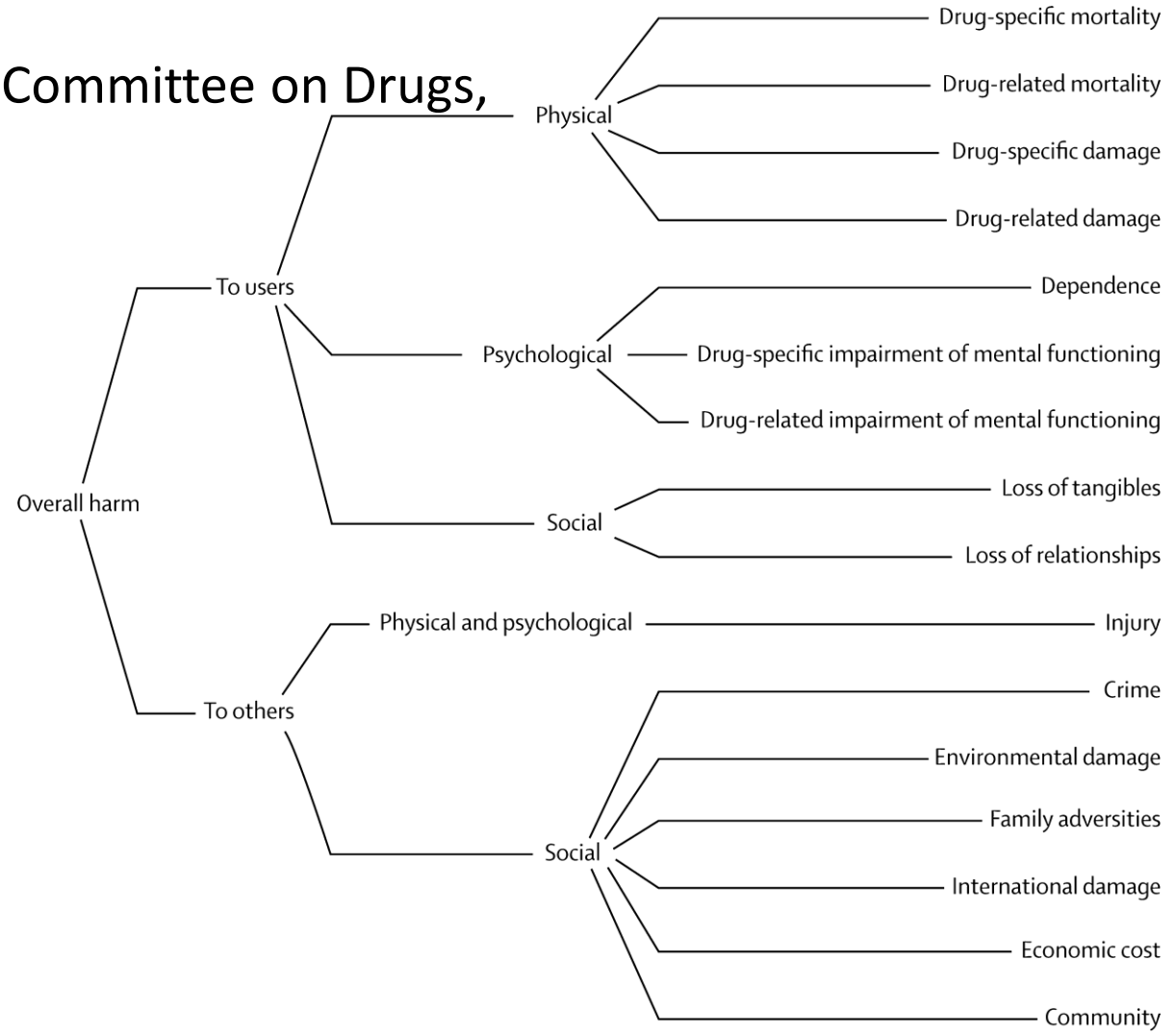
- Equally effective in participants with comorbidities a/w treatment resistance (eg AUD, SUDs, severe childhood trauma)

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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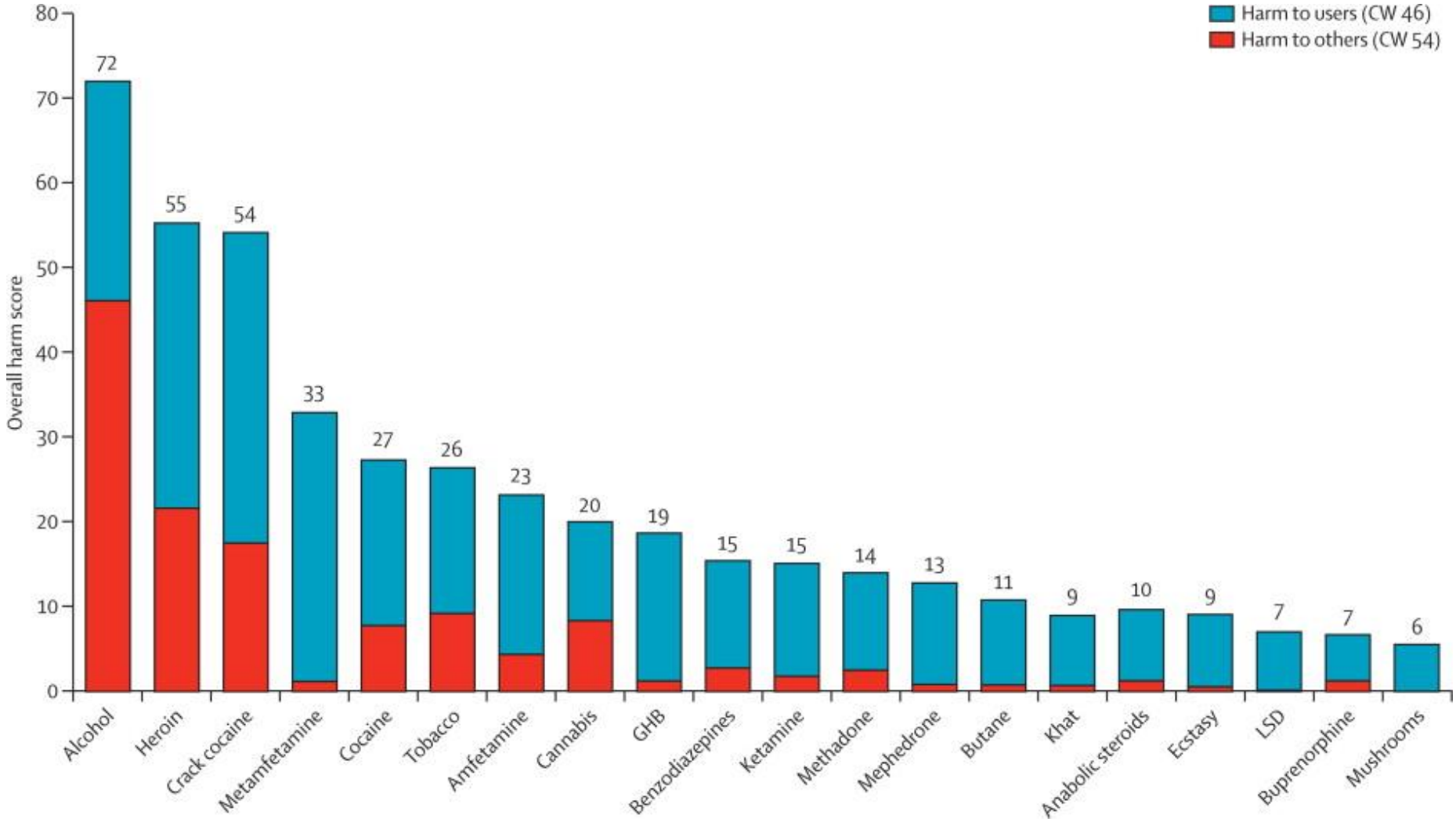


Alcohol Use Disorder

- 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

LSD-assisted therapy for alcoholism

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

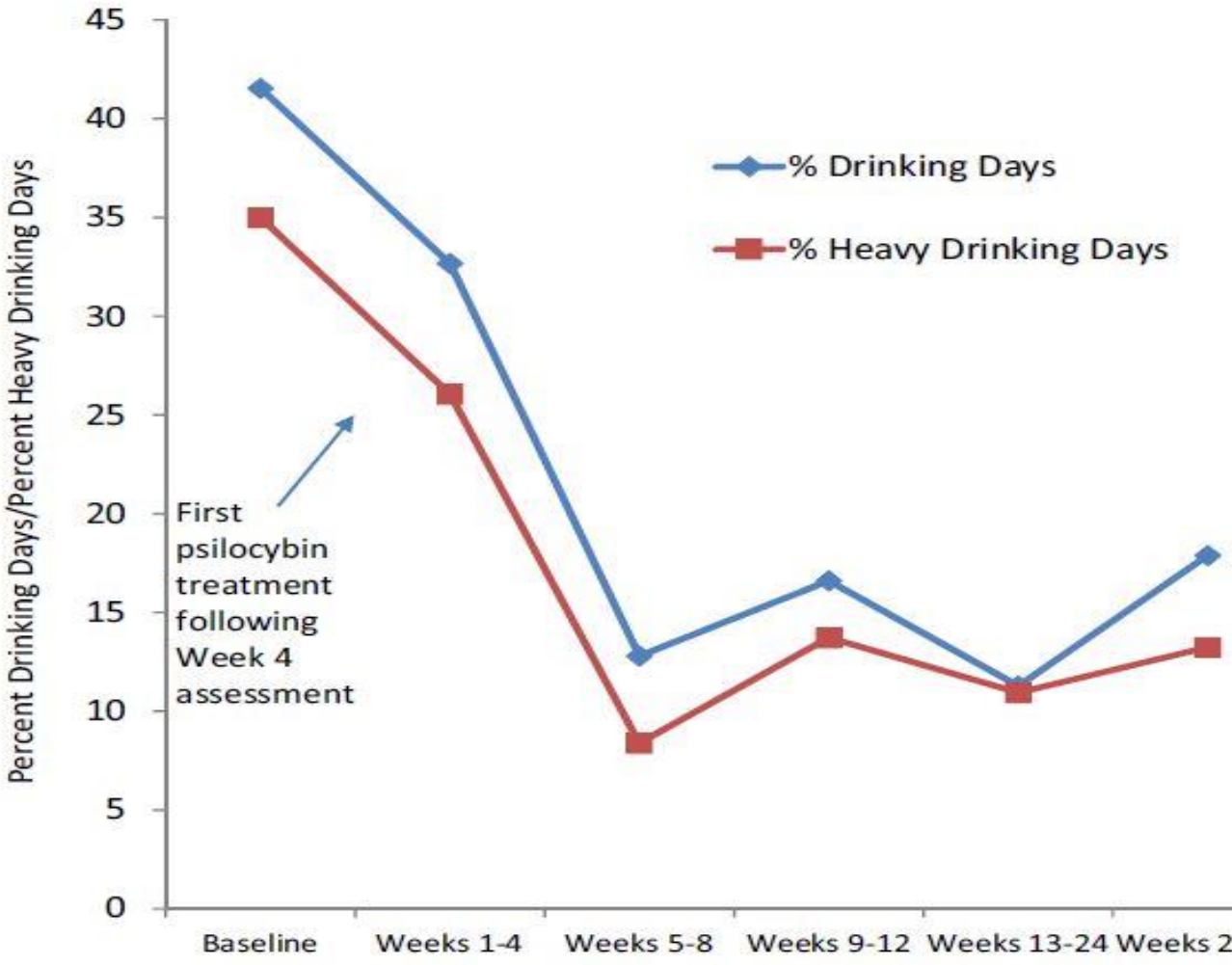
2012 meta-analysis of 6 1950s-60s studies found an odds ratio of 1.96 for beneficial effect on alcohol “misuse”

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

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*

IBOGAINE

Ibogaine

- Some evidence ibogaine reduces symptoms of acute opioid withdrawal
- 50% (15/30) reporting abstinence at 30 days (Brown, observational, Mexico)
- 65% (9/14) abstinent at 30 days (Noller, open label prospective, New Zealand)
- **18-MC:** possibly less cardiotoxic, no psychedelic effects, ?as effective for SUDs?

Brown, *Am J Drug Alcohol Abuse* 2018; 44(1):24-36.
Noller, *Am J Drug Alcohol Abuse* 2018 ;56(1):37-46.

V. 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
- Aberrant DMN patterns associated with craving and relapse in SUDs
- Decreased DMN activity by 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, Zhang Neuroimag 2019

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

Journal of Psychopharmacology
1–13

DOI: 10.1177/0269881120909409
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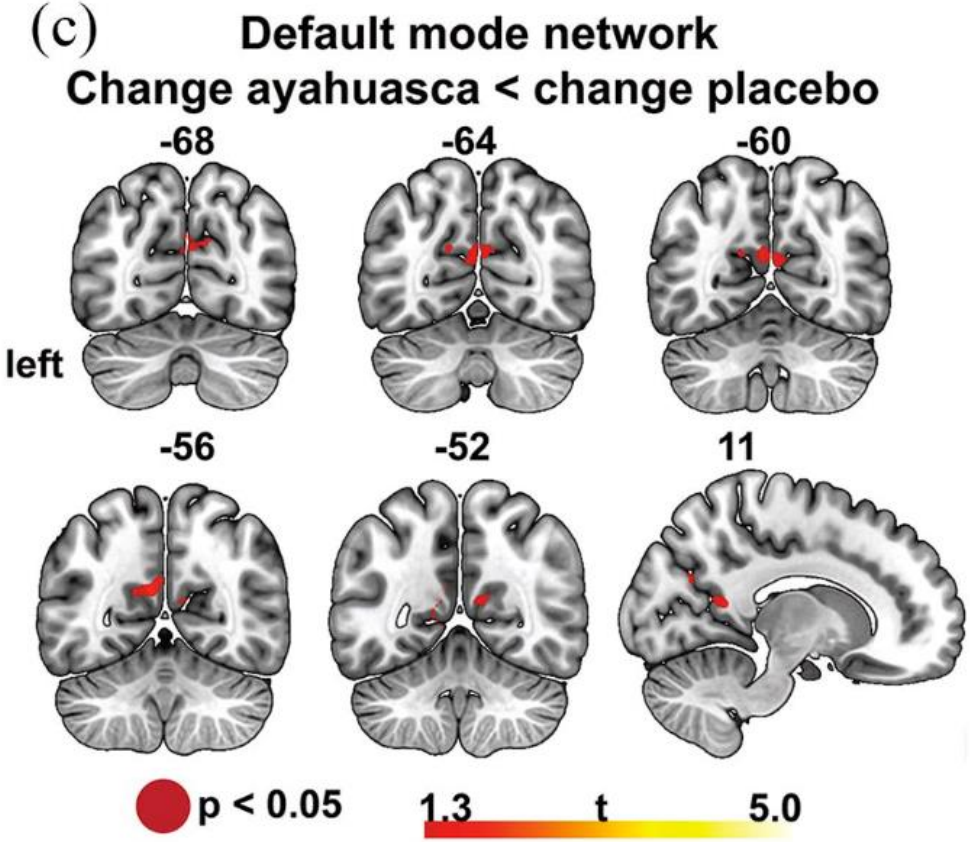

Participants: 50 healthy volunteers, ayahuasca naïve

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

Psychological mechanisms - neuroticism

- Psychedelics may decrease neuroticism
- Increased susceptibility to stress, negative affect, anxiety, somatization
- Association with development of depression, anxiety, PTSD, and SUDs
- Association with psychosomatic/functional disorders
- Psychedelics may also increase openness to experience and extraversion

VI. HARM REDUCTION

Harm Reduction

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

Thank you!