PSYCHAE

DMT and addiction treatment

A/Prof Daniel Perkins

Jun 2023

The return of psychedelics?

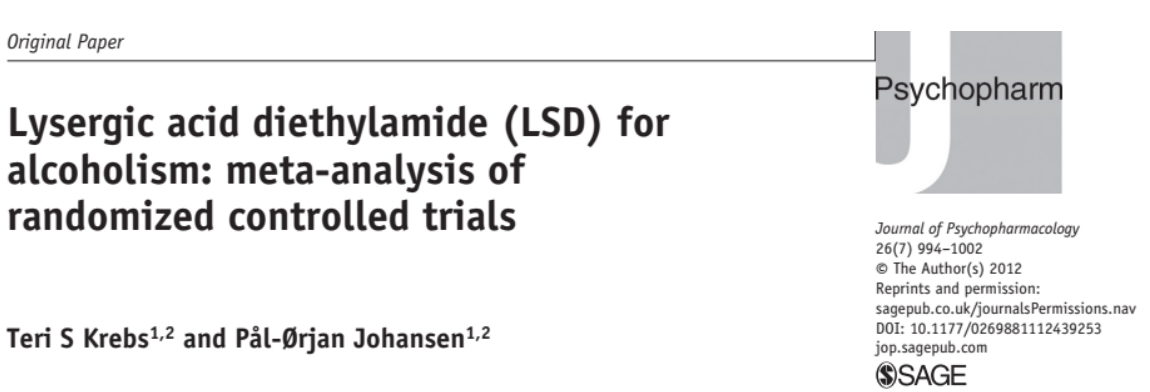
Significant research undertaken between 1950s and 1970s

- Encouraging but methodically limited
- Halted due to the ‘war on drugs’

Current resurgence of interest

- Unmet medical need, changing attitudes, contemporary studies

- Primary focus is ‘classics’ psychedelics: psilocybin, ayahuasca (DMT), LSD
- Also strong interest in the entactogen MDMA



Original Paper

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

Psychopharm

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

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.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 21 January 2020
doi: 10.3389/fpsyt.2019.00943

Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials

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Lysergic acid diethylamide (LSD) was studied from the 1950s to the 1970s to evaluate behavioral and personality changes, as well as remission of psychiatric symptoms in various disorders. LSD was used in the treatment of anxiety, depression, psychosomatic

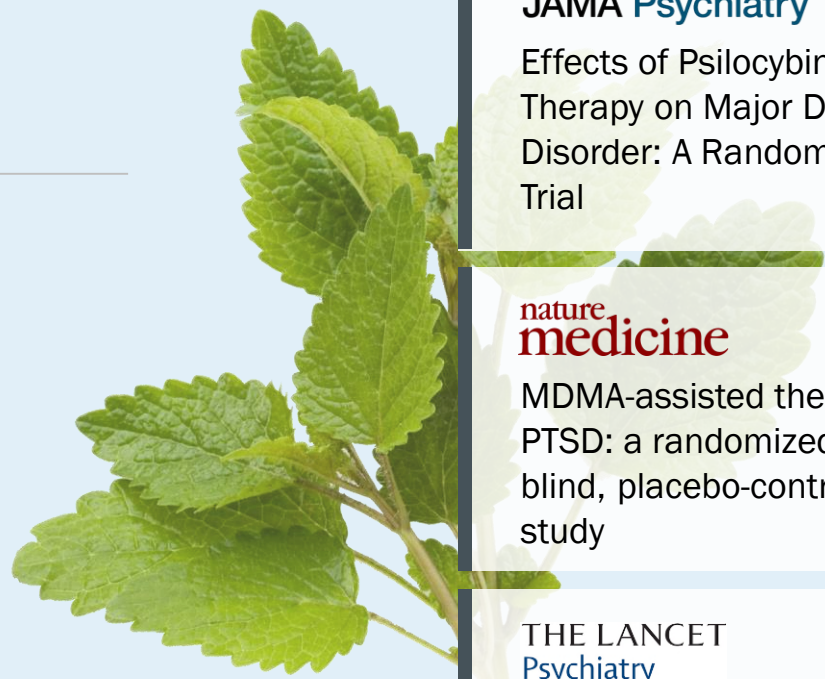
Psychedelics promise a new paradigm of mental health treatment

Evidence of **substantially increased efficacy,** rapid and enduring effects and an excellent safety profile

Very strong patient interest, large numbers seeking treatment in underground settings

Growing policy and regulatory acceptance.

- Recent Australian down scheduling enables clinical use to commence 1 July 2023
- Establishes non-registered medicine market access pathway for psychedelics
- Access pathways also establishing in other countries - e.g. Canada, Switzerland.



JAMA Psychiatry

Effects of Psilocybin Assisted Therapy on Major Depressive Disorder: A Randomized Control Trial

nature medicine

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

THE LANCET Psychiatry

Turn on and tune in to evidence-based psychedelic research

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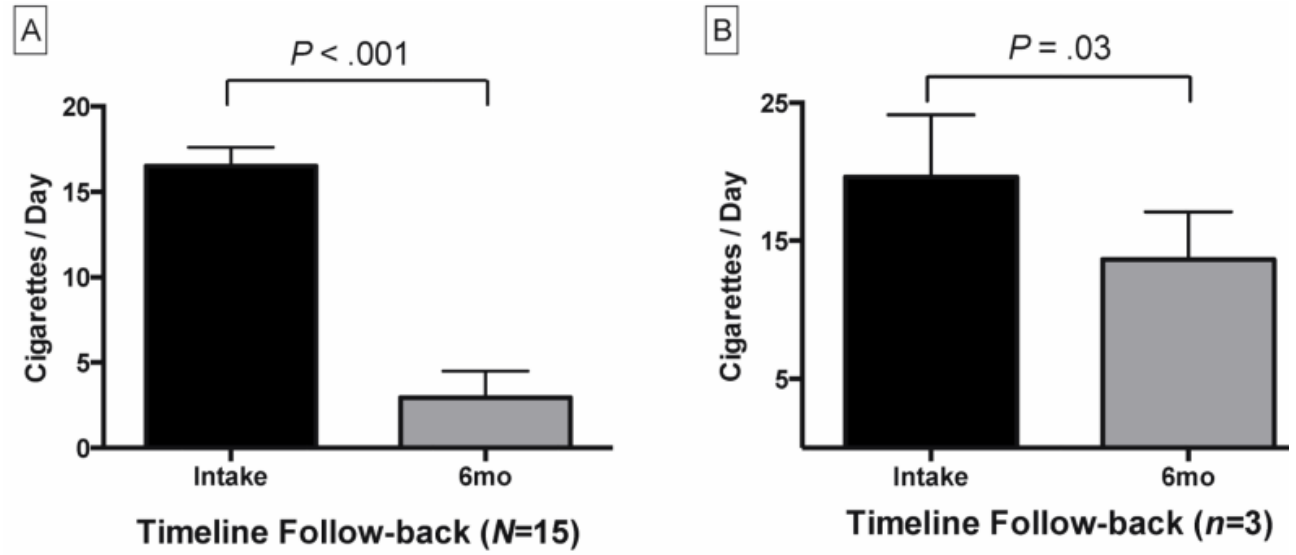
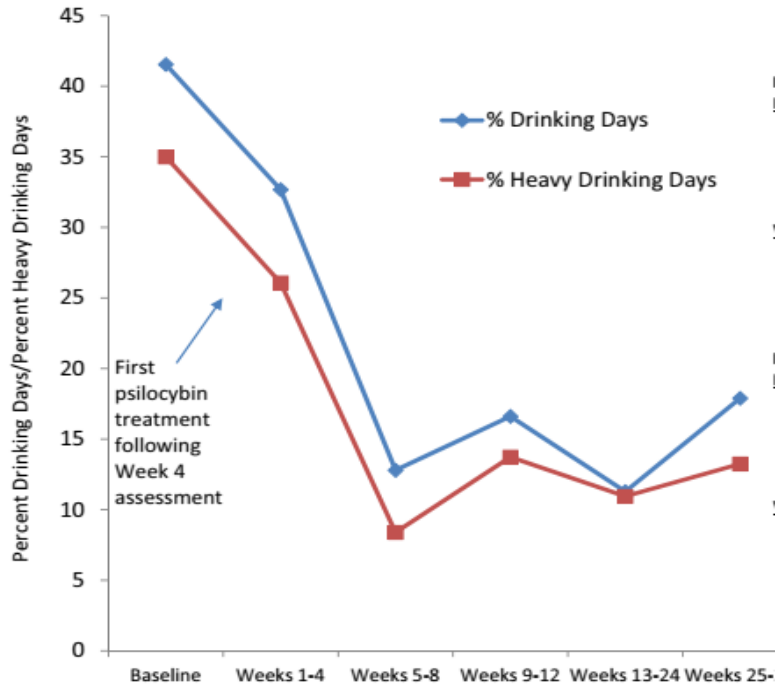
Recent studies

- Tobacco addiction (Johnson et al. 2014)
  - Open label, n=15, mean 31 years smoking
  - 80% verified tobacco free at 6 months
  - 67% at 12 months
  - 87% rated as among 5 most meaningful experiences
- Alcohol use disorder (Bogenschutz et al. 2015)
  - Open label, n=10, mean AUD 15.1 years
  - Improvement in drinking (large effects sizes) and related psychological measures to 36 weeks
  - Subjective mystical experience predictive
  - Treatment related AEs mild & transient
- Current clinical studies
  - AUD, methamphetamine, methadone, opioids, tobacco, cocaine



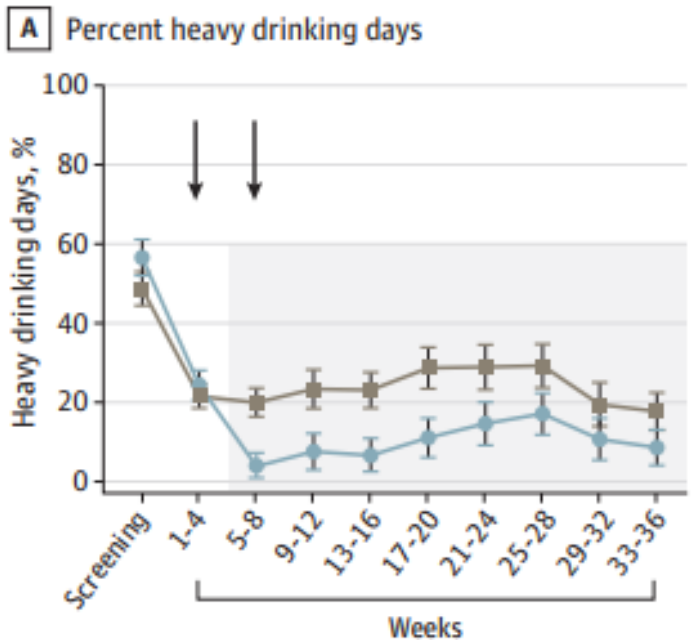


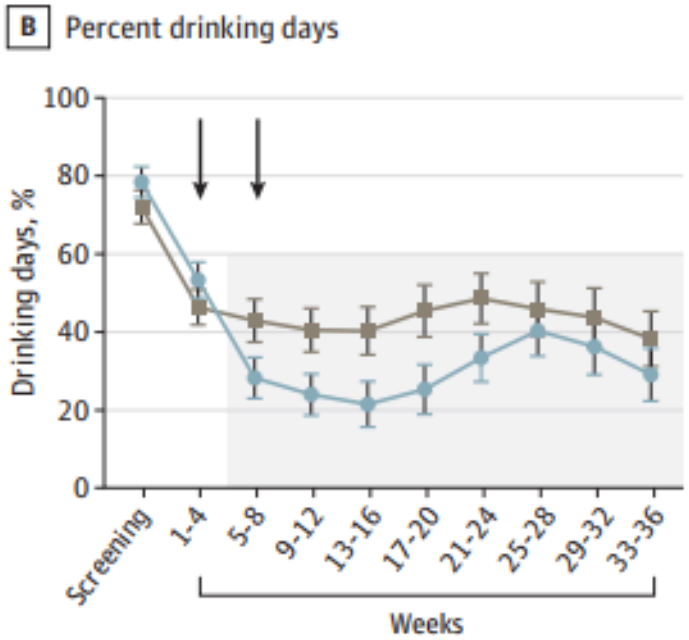
JAMA Psychiatry | Original Investigation

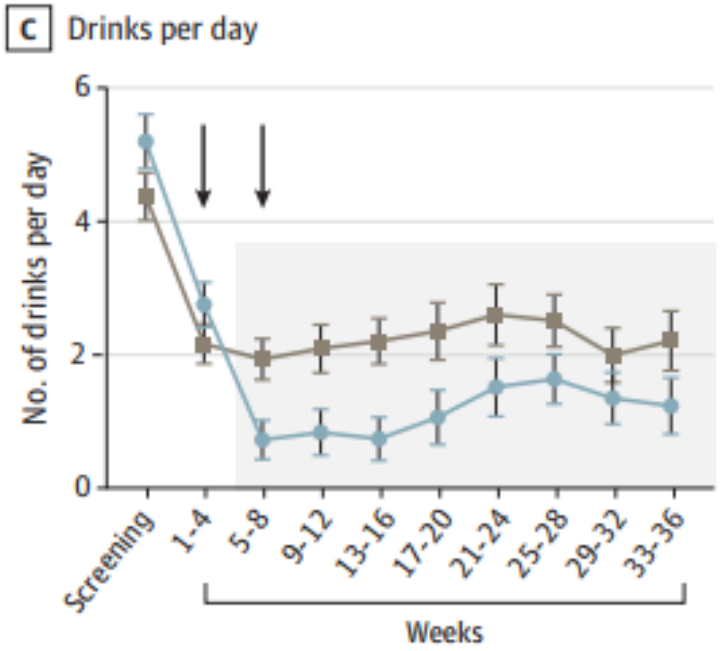
Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder

A Randomized Clinical Trial

Heavy drinking days during the 32 weeks were 9.7% vs 23.6%







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Ayahuasca and DMT

Background

- Ayahuasca a traditional medicine from the Amazon rainforest (or analogues globally)
- Decoction of two plants containing DMT and three harmala alkaloids (harmine, tetrahydroharmine, harmaline)
- Unlike other psychedelics almost always used for therapeutic or spiritual purposes in facilitated settings
- Large number of Westerners accessing via travel to South America or underground neo-shamanic ceremonies
- Several veteran focused NGOs established to facilitate veteran access

Therapeutic effects

- Compelling pre-clinical, observational & early clinical data
- Unique and transformative psychotherapeutic effects
- Rapid & enduring therapeutic benefit reported in depression, alcohol/substance use, PTSD, anxiety, and grief
- Broader wellbeing benefits: emotional regulation, cognitive flexibility, mindfulness, self-efficacy, personality effects
- Good long-term safety profile

Psychological Medicine

Rapid Antidepressant Effects of the Psychedelic Ayahuasca in Treatment-Resistant Depression:
A Randomized Placebo-controlled trial

Psychopharm

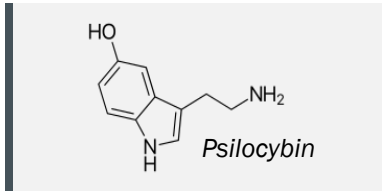
Changes in inflammatory biomarkers are related to the antidepressant effects of Ayahuasca

Translational Psychiatry

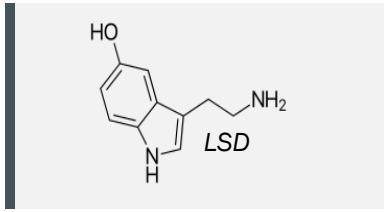
N,N-dimethyltryptamine compound found in the hallucinogenic tea ayahuasca, regulates adult neurogenesis in vitro and in vivo

PSYCHAE

The DMT-harmala pharmacology



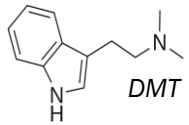
Psilocybin



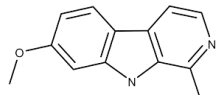
LSD

Psilocybin, LSD, or related analogues

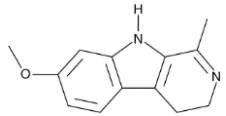
- Single active, single target
- Primary mechanism of action (shared with DMT) via serotonin 5-HT2A receptors
  - induces brain network modulation, neurogenesis and anti-inflammatory effects



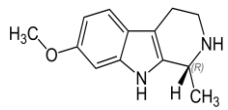
DMT



Harmine



Harmaline



Tetrahydroharmine

DMT-harmala combination products

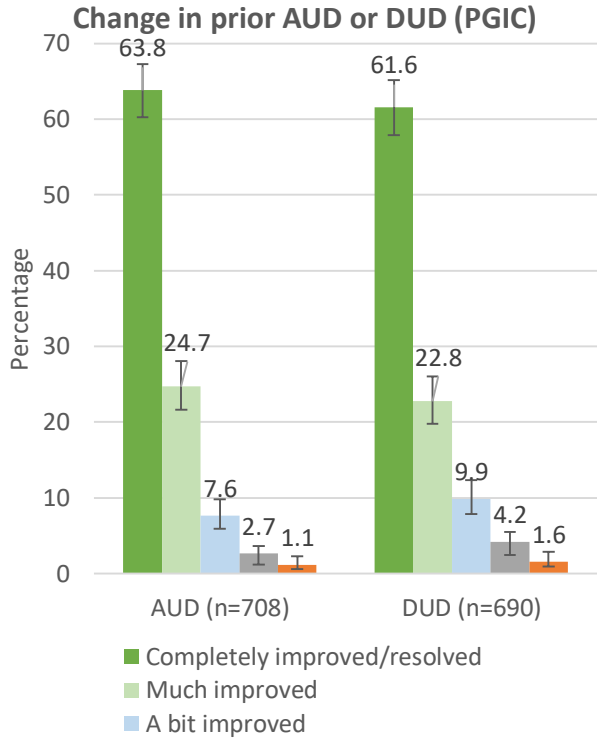
- Multiple actives with differing & synergistic pharmacokinetic, psychotropic & therapeutic profiles via multiple pathways – a **multi-target drug**
- DMT - shares primary 5-HT2A receptor pathway and associated effects with psilocybin/LSD
- Additional therapeutic mechanism via Sigma-1 and TAAR receptors (↑ neuroplasticity, role in addiction behaviours, depression, anxiety and fear extinction)
- Harmala alkaloids enhance the acute psychedelic experience, and provide further antidepressant, anxiolytic, and anti-addictive effects via multiple mechanisms including:
  - inducing brain plasticity and neurogenesis; increased BDNF; MAOI, serotonergic, and SSRI effects; modulating the dopaminergic system; and upregulating serotonin receptor density.

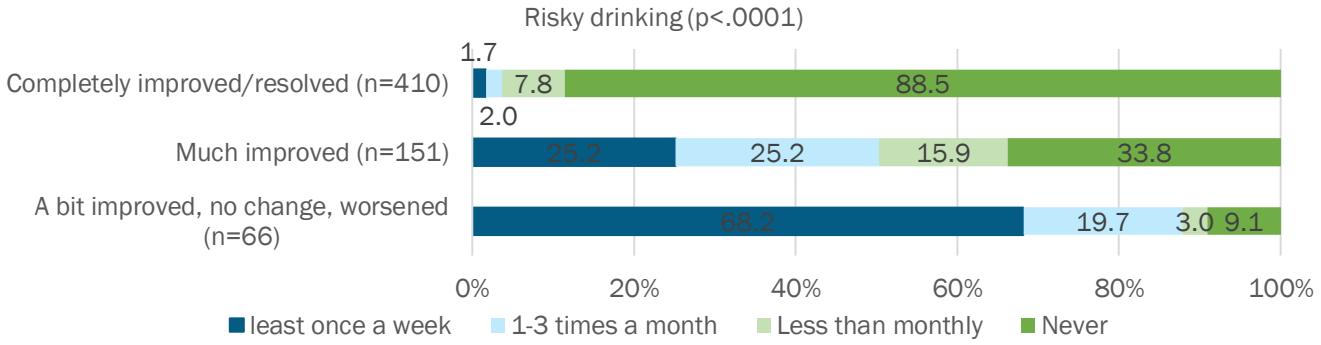
PSYCHAE

Drug and Alcohol REVIEW
APSAD
Drug and Alcohol Review (January 2022), 41, 265–274
DOI: 10.1111/dar.13348

Associations between ayahuasca consumption in naturalistic settings and current alcohol and drug use: Results of a large international cross-sectional survey

- Study of 8,629 participants
- Number of times ayahuasca had been drunk strongly associated with:
  - never or rarely drinking alcohol
  - never or rarely engaging in 'risky drinking'
  - not having consumed illicit drugs in the past month
  - lower odds of recent use of a range of drugs: cocaine, methamphetamine, cannabis, MDMA
- Effects were stronger for those with a prior substance use disorder compared to those without
- The subjective spiritual experience, number of personal self-insights were associated with lower alcohol/drug use





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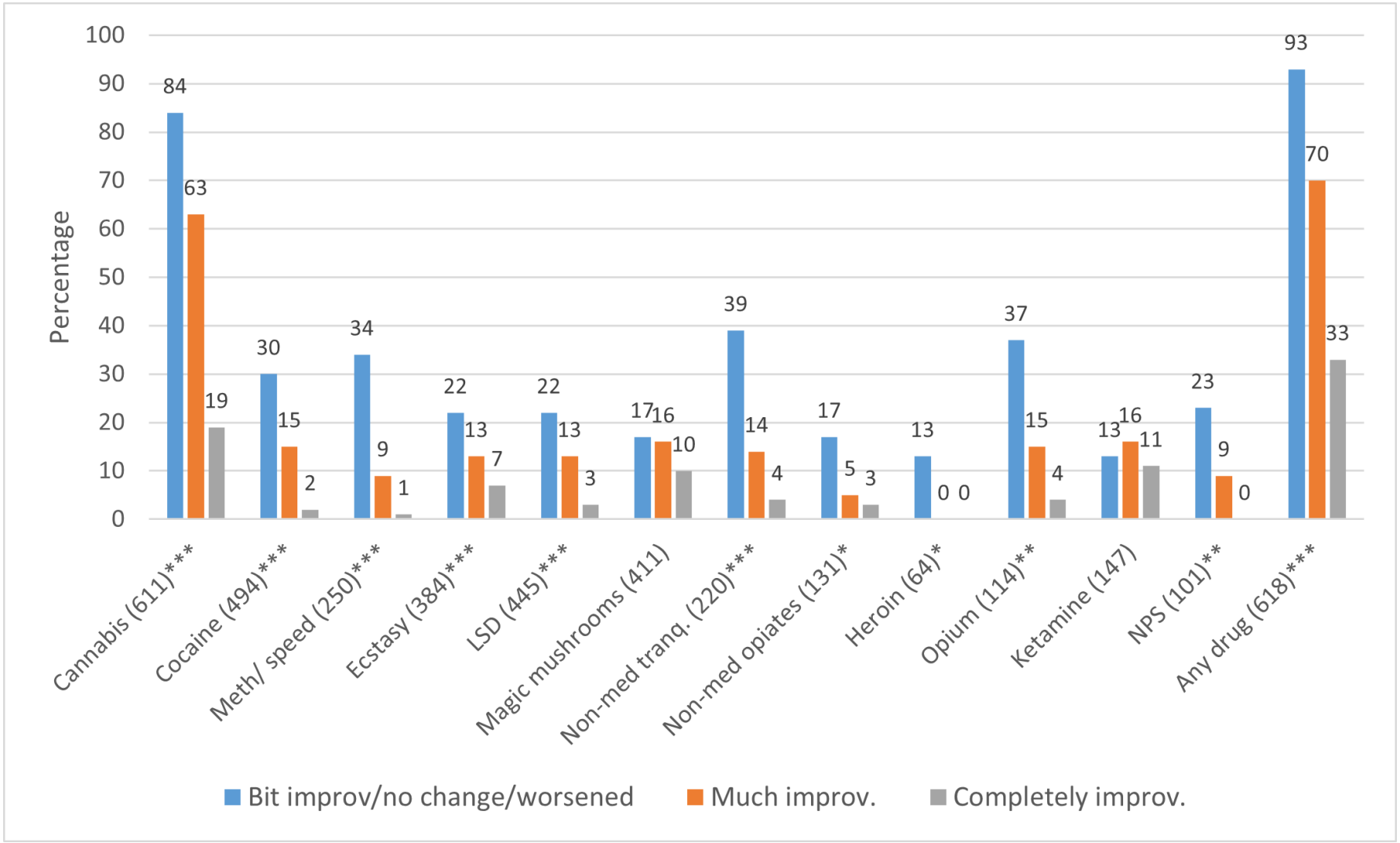
DUD group reporting 30-day use (%)



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Participant descriptions

I hardly ever drink alcohol anymore, quite smoking cigarettes, don't eat any junk food and exercise (yoga, walking running) almost daily. I am so much more aware of how different things I put into my body makes me feel

It has released deep and profound childhood trauma that affected my adult life, by cheating, stealing, being unfaithful with my girlfriend, nervous or unstable with friends, and always wanting to consume soft drugs.

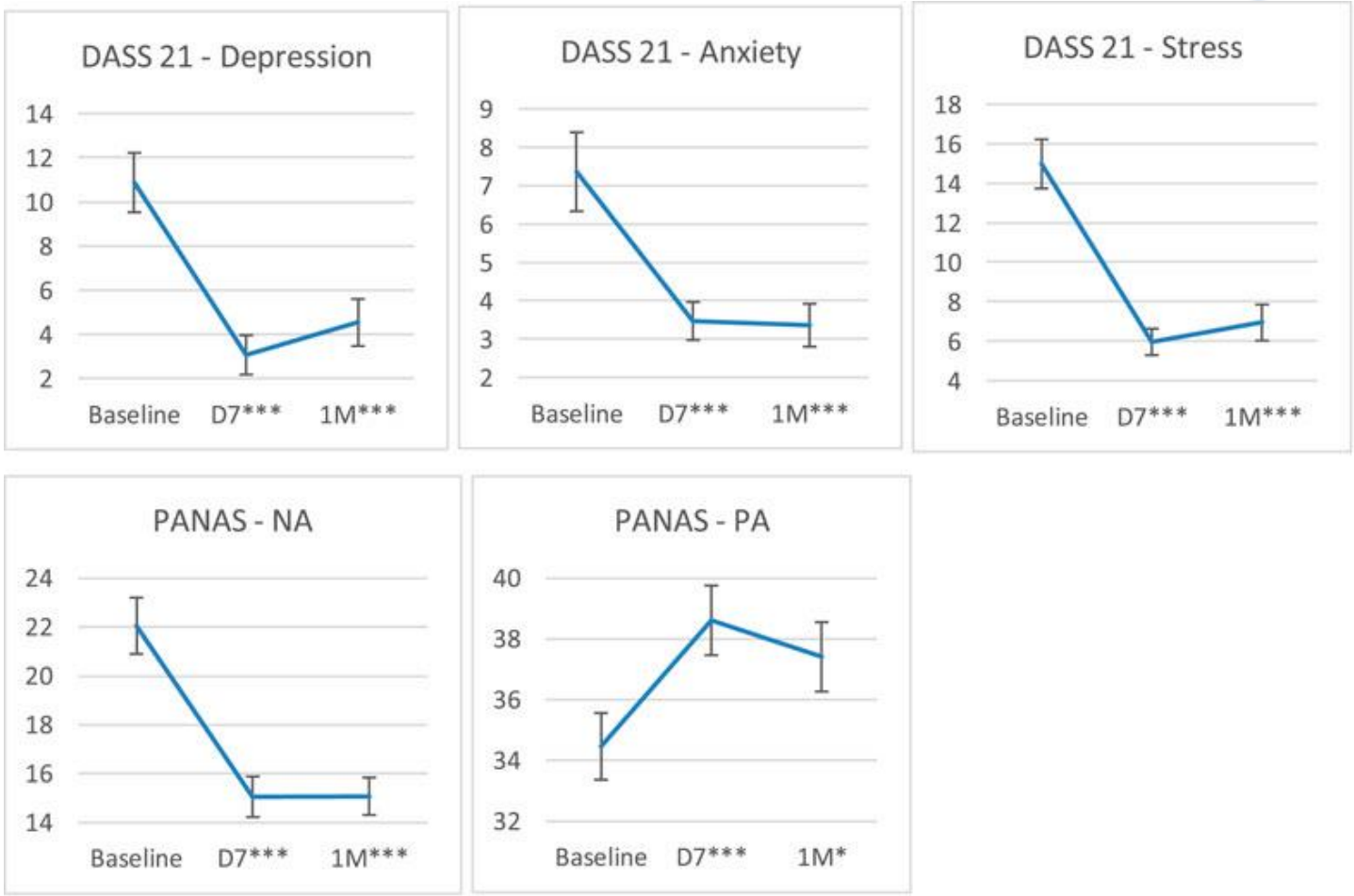
I have been given insight into what has driven my behavior since almost day one. I've been shown where I need to go and how to get there. No amount of counseling could compare to the results.

It became totally apparent to be that my alcohol consumption was causing harm to myself and my family. I have eliminated alcohol from my diet.

frontiers | Frontiers in Pharmacology
TYPE Original Research
PUBLISHED 26 October 2022
DOI 10.3389/fphar.2022.884703

Changes in mental health, wellbeing and personality following ayahuasca consumption: Results of a naturalistic longitudinal study

- 53 ayahuasca naïve participants
- Poor initial mental health, rapid improvements sustained at 1 month
- ↓ alcohol & cannabis use
- ↑ Generalised Self-Efficacy, personal spirituality, personal authenticity
- Personality change: ↓ neg emotionality; ↑ open-mindedness, extraversion, agreeableness
- ↓ body dissociation



[a] DASS 21 = Depression Anxiety and Stress Scale; PANAS= Positive and Negative Affect Scale (NA= negative affect, PA = positive affect). Asterisks indicate p values (*p <.05; **p <.01; ***p < .001) between baseline and day 7, and baseline and 1 month. Change between day 7 an was not significant for any item displayed.

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Perkins, D., B. A. Pagni, J. Sarris, P. C. R. Barbosa and R. Chenhall (2022). "Changes in mental health, wellbeing and personality following ayahuasca consumption: Results of a naturalistic longitudinal study." Frontiers in Pharmacology **13.**

PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE

Adverse effects of ayahuasca

Side effects common, but usually transient, not severe and an inherent part of the ayahuasca psychotherapeutic process

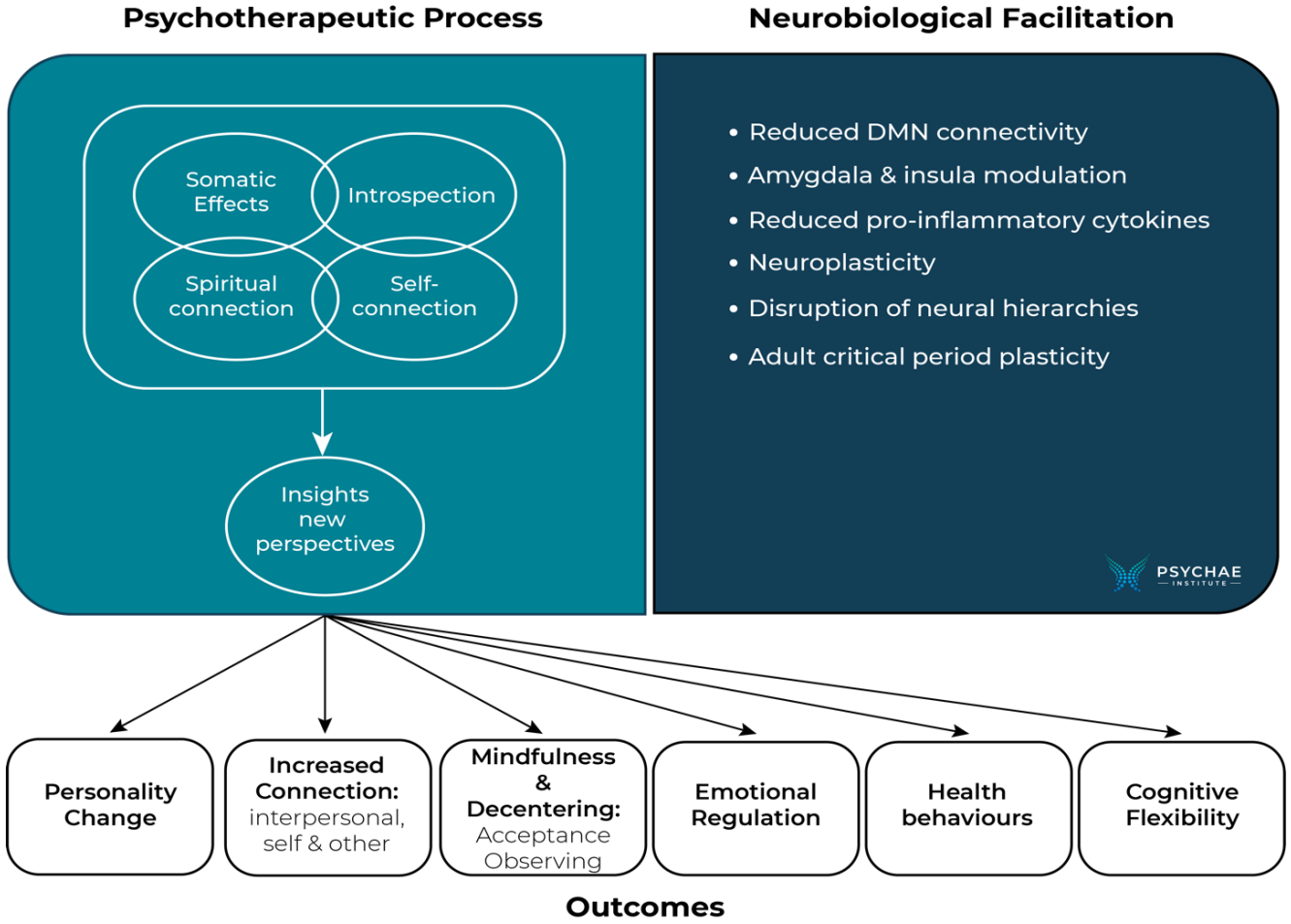
Adverse physical effect[1,2]	5,742 (69.9)
General symptom adverse effect[1,3]	5,603 (68.2)
Vomiting/nausea	5,097 (62.0)
Headache	1,460 (17.8)
Abdominal pain	1,052 (12.8)
Breathing difficulties	599 (7.3)
Chest pains	384 (4.7)
Arthromyalgical adverse effect[1,4]	883 (10.7)
Aching muscles	617 (7.5)
Coughing/wheezing	273 (3.3)
Stiff/swollen joints	182 (2.2)
Neurological adverse effect[1,5]	416 (5.1)
Fainting	335 (4.1)
Fits or seizures	106 (1.3)

	Adverse effects	Severe adverse effects
	n (%)	n (%)
Adverse mental health effects[1,2]	4,341 (55.4)	
Emotional-cognitive adverse effects[1,3]	3,293 (42.0)	
Feeling disconnected or alone	1,650 (21.0)	233 (3.0)
Nightmares, disturbing thoughts, feelings, or sensations	1,506 (19.2)	175 (2.2)
Feeling nervous, anxious, or on edge	1,483 (18.9)	247 (3.2)
Feeling down, depressed, or hopeless	1,300 (16.6)	149 (1.9)
Not being able to stop or control worrying	1,201 (15.3)	185 (2.4)
Little interest or pleasure in doing things	1,160 (14.8)	134 (1.7)
Difficulty knowing what is real and not real	1,011 (12.9)	167 (2.1)
Altered perception adverse effects[1,4]	3,004 (38.3)	
Hearing or seeing things that other people do not hear or see	2,236 (28.5)	251 (3.2)
Feeling "energetically attacked" or a harmful connection with a "spirit world"	1,186 (14.9)	191 (2.4)
Visual distortions	2,236 (15.1)	342 (4.4)

Bouso, J. C., Ó. Andión, J. J. Sarris, M. Scheidegger, L. F. Tófoli, E. S. Opaleye, V. Schubert and D. Perkins (2022). "Adverse effects of ayahuasca: Results from the Global Ayahuasca Survey." PLOS Global Public Health **2(11).**

Implications for potential clinical use

- Evidence of broad and enduring mental health and wellbeing benefits
- Psychotherapeutic and neurobiological processes at play
- Adaptable across contexts: safety, support, preparation, and integration important
- Context: treated as powerful and sacred ritual
- Psychedelic treatment models likely to be most effective if tailored to ayahuasca's specific effects
- Good safety/tolerability profile in controlled administration



frontiers | Frontiers in Neuroscience

Psychotherapeutic and neurobiological processes associated with ayahuasca

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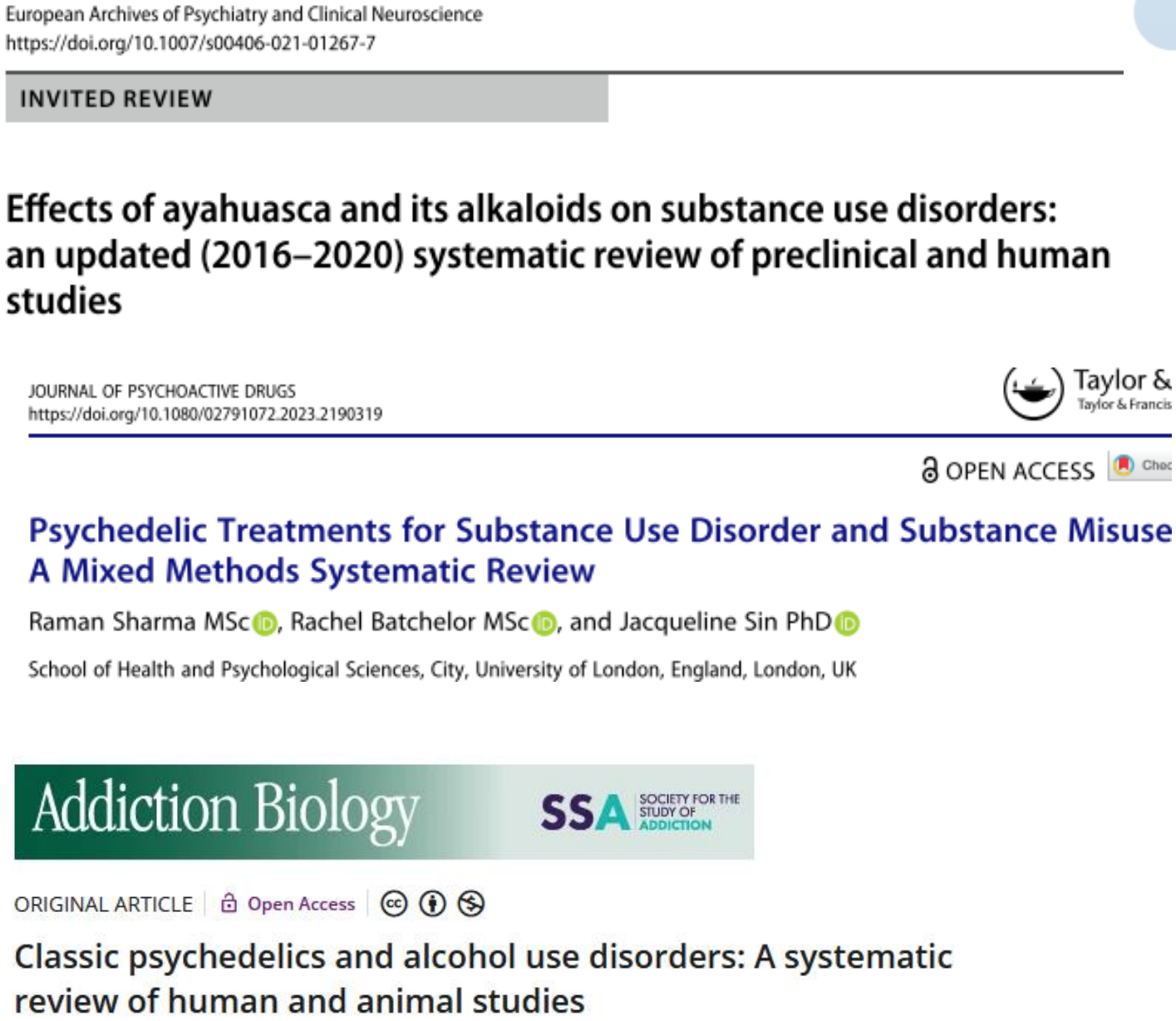
Recent systematic reviews

- Encouraging data, BUT issues with:
  - Translation of preclinical data to humans
  - Observational studies cannot show causality
  - Lack of dose standardization
  - Context of use confounders
  - Methodological weaknesses
  - Unclear biological and/or psychological mechanisms
- Data not adequate to recommend treatment
- Further controlled studies required



European Archives of Psychiatry and Clinical Neuroscience
https://doi.org/10.1007/s00406-021-01267-7

INVITED REVIEW

Effects of ayahuasca and its alkaloids on substance use disorders: an updated (2016–2020) systematic review of preclinical and human studies

JOURNAL OF PSYCHOACTIVE DRUGS
https://doi.org/10.1080/02791072.2023.2190319

Taylor & Taylor & Francis

OPEN ACCESS

Psychedelic Treatments for Substance Use Disorder and Substance Misuse A Mixed Methods Systematic Review

Raman Sharma MSc, Rachel Batchelor MSc, and Jacqueline Sin PhD

School of Health and Psychological Sciences, City, University of London, England, London, UK

Addiction Biology

SSA SOCIETY FOR THE STUDY OF ADDICTION

ORIGINAL ARTICLE | Open Access

Classic psychedelics and alcohol use disorders: A systematic review of human and animal studies

PSYCHAE

$14.8 million for innovative mental health clinical trials

Seven clinical trials testing the use of potential breakthrough combination therapies to treat debilitating mental illnesses will receive a total of almost $15 million from the Australian Government's Medical Research Future Fund (MRFF)

Medical Research Future Fund

N,N Dimethyltryptamine (DMT)-Assisted Psychological Therapy for Treatment-Resistant Major Depression, Alcohol Use Disorder, and Dual Diagnosis

STUDY AIM & SUMMARY:

We will assess the efficacy and safety of a GMP produced psychedelic formulation of DMT and harmala alkaloids, alongside a psychological intervention to achieve a long-term reduction or abstinence from alcohol use and/or reducing depressed mood

Study design is a 12-week phase IIb triple-blind, placebo-controlled innovative 'basket' trial (n=60)

The basket design will stratify recruitment according to two distinct diagnoses: 1) Chronic Alcohol Use Disorder; 2) Treatment-resistant Major Depressive Disorder

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Thank you

A/Prof Daniel Perkins