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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
What are psychedelics?

• Tryptamines
  • (LSD, psilocybin, DMT/ayahuasca)
• Phenethylamines
  • (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 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 (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
Autonomic effects

Psilocybin

LSD

Bogenschutz *Psychopharmacology* 2015, Holze *Neuropsychopharmacology* 2021
Autonomic effects

Distinct acute effects of LSD, MDMA, and d-amphetamine
F Holze et al.
Safety, tolerability, pharmacokinetics, and pharmacodynamics of low dose lysergic acid diethylamide (LSD) in healthy older volunteers

Neiloufar Family¹  Emeline L. Maillet¹  Luke T. J. Williams¹  Erwin Krediet¹  Robin L. Carhart-Harris²  Tim M. Williams³  Charles D. Nichols⁴  Daniel J. Goble⁵  Shlomi Raz¹

Received: 12 March 2019 / Accepted: 27 November 2019 / Published online: 18 December 2019
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• 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
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
- Benefits may correlate with expectation

Kaertner, Sci Reports, 2021
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

<table>
<thead>
<tr>
<th></th>
<th>BDI</th>
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<td>Baseline</td>
<td>1 week</td>
<td>3 months</td>
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<td>Baseline</td>
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<td>Mean</td>
<td>34.5</td>
<td>11.8</td>
<td>19.2</td>
<td>19.5</td>
<td>68.6</td>
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<td>Difference vs baseline</td>
<td>–22.7</td>
<td>–15.3</td>
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<td>–12.2</td>
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<td>Cohen’s $d$</td>
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Carhart Harris, *Psychopharmacol* 2018
Psilocybin-assisted psychotherapy for treatment resistant depression

Table 2

<table>
<thead>
<tr>
<th></th>
<th>BDI (Baseline)</th>
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<th>BDI (3 months)</th>
<th>BDI (6 months)</th>
<th>STAI (Baseline)</th>
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<th>STAI (3 months)</th>
<th>STAI (6 months)</th>
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Carhart Harris, *Psychopharmacol* 2018
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\(^{1,2}\)


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

Davis et al, 2020
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
History

• Synthesized and patented by Merck, 1912, then shelved ("Safrylmethylamin")

• Military research (CHATTER, MK ULTRA) into mescaline for "behavior manipulation" and "ego depressant" effects

• Mescaline derivatives re-synthesized by Army 1950-1952, shelved when Army research swung towards LSD exclusively
History

• 1976, rediscovered by chemist Alexander Shulgin
• By early 1980s, emerging case reports using MDMA within psychotherapy for PTSD and social anxiety
• Rapid popularity as "club drug"
• Emergency DEA meeting in 1985 led to Schedule I classification, effectively shutting down research for two decades
History

• 1986 – Multidisciplinary Association for Psychedelic Studies (MAPS) founded by Rick Doblin, PhD

• 2004 – MAPS, along with renewed interested in "prosocial" drugs, led to FDA's approval of MDMA as an IND, leading to several small trials

• Aug 2017 – Breakthrough Therapy designation by FDA for 2 Phase III clinical trials
Effects

• Usually taken orally
• Study doses usually 80 – 125mg (recreational doses usually within similar range)
• Time to onset ~30 min
• Average duration of effect 2-6 hours, with peak effect around 1-2 hours after ingestion
• Mild elevations in BP, HR, and core temp
Effects

- Euphoria
- Increased well-being
- Increased feelings of connectedness to others
- Self-confidence
- Extroversion
- Heightened sensory experience
MDMA - Pharmacology

Re-uptake inhibitors

Bind to transporter protein, but not themselves transported
Block transporter-mediated re-uptake of monoamines from extracellular space
Elevate extracellular monoamine levels

Substrate-type releasers

Promote efflux of monoamine by transporter-mediated exchange
Increase cytoplasmic levels of monoamines by disrupting storage of transmitter in vesicles
This increases availability of transmitter for exchange
Can be blocked by re-uptake inhibitors (which block exchange)
MDMA - Pharmacology

Methylenedioxypheynethylamines

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?

Why PTSD?

• For effective psychotherapy in PTSD, patient must be engaged but not overwhelmed
• PTSD patients suffer from both under-arousal (numbing) and over-arousal (intense emotions, anxiety, dissociation)
• MDMA may widen this window by reducing fear response and increasing capacity for tolerating negative emotions and memories
Correspondence

It is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group

To the Editor:

There is an urgent need to address a critical lack of advancement in the psychopharmacologic treatment of posttraumatic stress disorder (PTSD). The clinical, social, and financial burden of ineffectively treated PTSD is enormous (1–6). The impact of PTSD morbidity and mortality is further magnified by its substantial disruptions in family, workplace, and societal contexts (7). For the Department of Veterans Affairs (VA) and Department of Defense (DoD), i.e., institutions that are vehicles for the expression of the national debt to military personnel who developed PTSD as a consequence of their military service, the need to help these people has taken on significant priority. One in 10 VA healthcare users have the diagnosis of PTSD, which includes one in four treatment-seeking veterans of the recent wars in Iraq and Afghanistan (8). The prevalence of PTSD in the general population for lifetime is approximately 8% (8) and just under 4% for the current year, making it the fifth most prevalent mental disorder in the United States (9–11). Despite this high prevalence and costly

Why PTSD?

- FDA approval only for sertraline and paroxetine, most treatment is off label
- Psychotherapy efficacy (CPT, exposure) 49-70% show improvement, but in military populations 60-72% retain PTSD diagnosis
- Treatment, when successful, takes weeks to months
MDMA-assisted psychotherapy for PTSD

2018 study (Mithoefer, *Lancet Psychiatry*)
- 26 veterans and 1\textsuperscript{st} 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)
Informed written consent and screening with SCID, CAPS-IV, neuropsychological measures, physical exam, blood tests, and ECG

Three 90-min preparatory sessions with co-therapy team

Two 8-h MDMA or comparator experimental sessions, approximately 1 month apart; overnight stay with attendant; 90-min integration session morning after; and daily phone contact during following week

Two non-drug integration sessions after each experimental session, approximately weekly

Primary endpoint (1 month after second experimental session)

Blind broken

125 mg group

One open-label (125 mg) session with three integration sessions

Stage 2 (open-label crossover)

30 mg and 75 mg groups

Preparatory session: two open-label (100–125 mg) sessions with three integration sessions

Secondary endpoint (1 month after second experimental session)

One open-label experimental session with three integrative sessions

End of stage endpoint (2 months after third MDMA session)

12-month follow-up

<table>
<thead>
<tr>
<th>Primary efficacy measure</th>
<th>30 mg MDMA plus psychotherapy (n=7)</th>
<th>75 mg MDMA plus psychotherapy (n=7)</th>
<th>125 mg MDMA plus psychotherapy (n=12)</th>
</tr>
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<tbody>
<tr>
<td>Mean CAPS-IV total score</td>
<td>87.4 (14.1)</td>
<td>82.4 (17.3)</td>
<td>89.7 (17.3)</td>
</tr>
<tr>
<td>Baseline</td>
<td>76.0 (23.4)</td>
<td>24.1 (17.2)</td>
<td>45.3 (33.8)</td>
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<tr>
<td>After two experimental</td>
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<tr>
<td>sessions of MDMA</td>
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<tr>
<td>Change†</td>
<td>-11.4 (12.7)</td>
<td>-58.3 (9.8)</td>
<td>-44.3 (28.7)</td>
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<th>Secondary efficacy measures</th>
<th>30 mg MDMA plus psychotherapy (n=7)</th>
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<th>125 mg MDMA plus psychotherapy (n=12)</th>
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<tr>
<td>Number of participants who</td>
<td>5 (71%)</td>
<td>1 (14%)</td>
<td>5 (42%)</td>
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<tr>
<td>met CAPS-IV PTSD</td>
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<td>diagnostic criteria (primary endpoint)</td>
<td>2 (29%)</td>
<td>6 (86%)</td>
<td>7 (58%)</td>
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<td>Number of participants who</td>
<td>2 (29%)</td>
<td>7 (100%)</td>
<td>8 (67%)</td>
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<td>had more than 30% decrease</td>
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<td>in CAPS-IV total score</td>
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<td>0</td>
<td>4 (33%)</td>
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<td>Mean BDI-II score</td>
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<tr>
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<td>p value‡</td>
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- 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)

Fig. 3: Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, \(n = 46\); placebo, \(n = 44\)).

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

Responders (clinically significant improvement, defined as a \(\geq 10\)-point decrease on CAPS-5), loss of diagnosis (specific diagnostic measure on CAPS-5), and remission (loss of diagnosis and a total CAPS-5 score of \(<11\)) were tracked in both groups. Non-response is defined as a \(<10\)-point decrease on CAPS-5. Withdrawal is defined as a post-randomization early termination.
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
Psychedelics as drugs of abuse
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.

NOTES and COMMENT

The Efficacy of LSD in the Treatment of Alcoholism

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 lack of control groups, follow-up and objective measurements of change characterized psychiatric research into both pharmacological methods (3, 4). This general lack of methodological effort attempts to exam

LSD in Psychotherapy and Alcoholism

Edited by Harold A. Abramson, M.D.

Introduction by Frank Fremont-Smith, M.D.
Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials

Teri S Krebs¹,² and Pål-Ørjan Johansen¹,²

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 (I² = 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

Bogenschutz et al 2015, J Psychopharmacol.
A double blind trial of psilocybin-assisted treatment of alcohol dependence

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<td>Allocation</td>
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<td>Intervention Model</td>
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<td>Masking</td>
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<tr>
<td>Primary Purpose</td>
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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,³ David Nutt³

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
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.”
IBOGAINE
Ibogaine

- Derived from bark of *Tabernanthe iboga* shrub in W. Africa
- Used ceremonially for thousands of years
- Elicits powerful psychedelic experience, described as qualitatively different from "classical" psychedelics
Ibogaine

• Shares tryptamine structure w/ classical psychedelics
• Multiple pharmacologic targets
  – NMDA-R antagonist
  – SRI
  – kappa opioid agonist and (weak) mu opioid receptor agonist/partial agonist
• Cardiac risk: bradycardia, QTc prolongation
  – 19 fatalities reported 1998 — 2008*
  – Harm reduction: CV disease, EKG, LFTs
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?

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

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

Fernanda Palhano-Fontes, Katia C. Andrado, 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

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

Lorenzo Pasquini¹,* Fernanda Palhano-Fontes²,* and Draulio B Araujo²

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 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 also increase openness to experience and 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. Reff, M.D., Elon E. Richman, M.D., Charles B. Nemeroff, M.D., Ph.D., Linda I. Carpenter, M.D.,
Alk 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 psychoactive
Drugs in psychiatric disorders.

and July 1, 2019. A total of 1603 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

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 addiction,
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
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Director, MGH Chemical Neurobiology Laboratory, Center for Genomic Medicine
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Sharmin Ghaznavi MD, PhD
Associate Director
Director of Clinical Studies
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Franklin King MD
Director of Training and Education
Psychiatrist, Massachusetts General Hospital
Instructor of Psychiatry, Harvard Medical School

www.mghcme.org
Thank you!