



Psychedelics for Opioid and Other Substance Use Disorders: Design and Outcome Considerations

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Abuse liability & Risks 2018


- Can cause harm in people with psychosis or predisposition
- For anybody, can cause fear, panic, confusion and potentially dangerous behavior
- Moderate elevations in pulse & blood pressure
- Headaches in day following use
- Persisting perceptual changes
- No addiction



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Invited review

The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act

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ABSTRACT

This review assesses the abuse potential of medically-administered psilocybin, following the structure of the 8 factors of the US Controlled Substances Act (CSA). Research suggests the potential safety and efficacy of psilocybin in treating cancer-related psychiatric distress and substance use disorders, setting the occasion for this review. A more extensive assessment of abuse potential according to an 8-factor analysis would eventually be required to guide appropriate schedule placement.

Psilocybin, like other 5-HT_{2A} agonist classic psychedelics, has limited reinforcing effects, supporting marginal, transient non-human self-administration. Nonetheless, mushrooms with variable psilocybin content are used illicitly, with a few lifetime use occasions being normative among users. Potential harms include dangerous behavior in unprepared, unsupervised users, and exacerbation of mental illness in those with or predisposed to psychotic disorders. However, scope of use and associated harms are low compared to prototypical abused drugs, and the medical model addresses these concerns with dose control, patient screening, preparation and follow-up, and session supervision in a medical facility.

Conclusions: (1) psilocybin has an abuse potential appropriate for CSA scheduling if approved as medicine; (2) psilocybin can provide therapeutic benefits that may support the development of an approvable New Drug Application (NDA) but further studies are required which this review describes; (3) adverse effects of medical psilocybin are manageable when administered according to risk management approaches; and (4) although further study is required, this review suggests that placement in Schedule IV may be appropriate if a psilocybin-containing medicine is approved.

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Safety Guidelines 2008

- Assisted in the approval of psychedelic studies by new scientists and universities



Original Papers

Human hallucinogen research: guidelines for safety

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Abstract

There has recently been a renewal of human research with classical hallucinogens (psychedelics). This paper first briefly discusses the unique history of human hallucinogen research, and then reviews the risks of hallucinogen administration and safeguards for minimizing these risks. Although hallucinogens are relatively safe physiologically and are not considered drugs of dependence, their administration involves unique psychological risks. The most likely risk is overwhelming distress during drug action ('bad trip'), which could lead to potentially dangerous behaviour such as leaving the study site. Less common are prolonged psychoses triggered by hallucinogens. Safeguards against these risks include the exclusion of volunteers with personal or family history of psychotic disorders or other severe psychiatric disorders, establishing trust and rapport between session monitors and volunteer before the session, careful volunteer preparation, a safe physical session environment and

interpersonal support from at least two study monitors during the session. Investigators should probe for the relatively rare hallucinogen persisting perception disorder in follow-up contact. Persisting adverse reactions are rare when research is conducted along these guidelines. Incautious research may jeopardize participant safety and future research. However, carefully conducted research may inform the treatment of psychiatric disorders, and may lead to advances in basic science.

Key words

5-HT_{2A} agonists; adverse reactions; DMT; entheogens; hallucinogens; human research; LSD; mescaline; psilocybin; psychedelics; safety guidelines

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Ceremonial psychedelic use linked with addiction recovery

– Peyote and the Native American Church

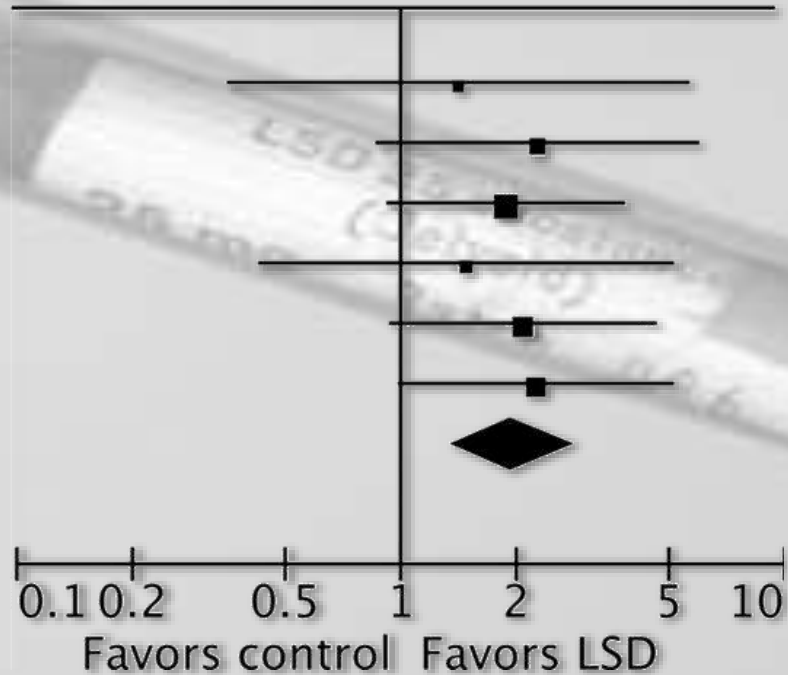
- Albaugh & Anderson, 1974; Bergman, 1971; Blum et al., 1977; Calabrese, 1997; Garrity, 2000; Menninger, 1971; Pascaro et al., 1976; Roy, 1973

– Ayahuasca ceremonies in South America and South American Religions

- Dobkin de Rios et al., 2002; Halpern et al., 2008

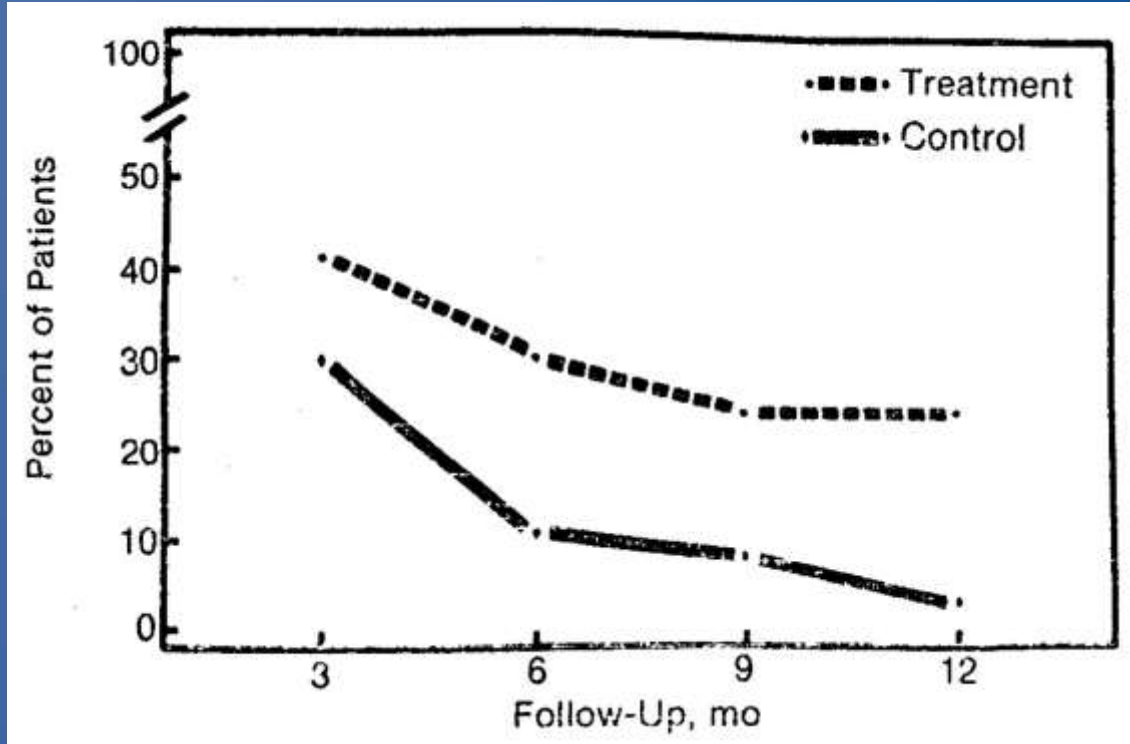
Krebs & Johansen (2012)

Across studies, LSD nearly doubled the odds that alcoholic patients would be improved at the 1st follow up (N=536)



Savage & McCabe (1973) Archives of General Psychiatry

LSD Treatment of Heroin Addicted Patients



Participant Comparing LSD to Heroin

“Heroin has a numbing-like effect on you. It tends to relax you and somewhat takes you out and away from your surroundings and yourself. LSD makes you more aware of yourself and puts you right into whatever has been troubling you.”

Smoking Cessation Pilot 2014

- Feasibility and safety



Original Paper

Pilot study of the 5-HT_{2A}R agonist psilocybin in the treatment of tobacco addiction

Matthew W Johnson¹, Albert Garcia-Romeu¹, Mary P Cosimano¹ and Roland R Griffiths^{1,2}

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ORIGINAL ARTICLE

Long-term follow-up of psilocybin-facilitated smoking cessation

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ABSTRACT

Background: A recent open-label pilot study ($N = 15$) found that two to three moderate to high doses (20 and 30 mg/70 kg) of the serotonin 2A receptor agonist, psilocybin, in combination with cognitive behavioral therapy (CBT) for smoking cessation, resulted in substantially higher 6-month smoking abstinence rates than are typically observed with other medications or CBT alone. **Objectives:** To assess long-term effects of a psilocybin-facilitated smoking cessation program at ≥ 12 months after psilocybin administration. **Methods:** The present report describes biologically verified smoking abstinence outcomes of the previous pilot study at ≥ 12 months, and related data on subjective effects of psilocybin. **Results:** All 15 participants completed a 12-month follow-up, and 12 (80%) returned for a long-term (≥ 16 months) follow-up, with a mean interval of 30 months (range = 16–57 months) between target-quit date (i.e., first psilocybin session) and long-term follow-up. At 12-month follow-up, 10 participants (67%) were confirmed as smoking abstinent. At long-term follow-up, nine participants (60%) were confirmed as smoking abstinent. At 12-month follow-up 13 participants (86.7%) rated their psilocybin experiences among the five most personally meaningful and spiritually significant experiences of their lives. **Conclusion:** These results suggest that in the context of a structured treatment program, psilocybin holds considerable promise in promoting

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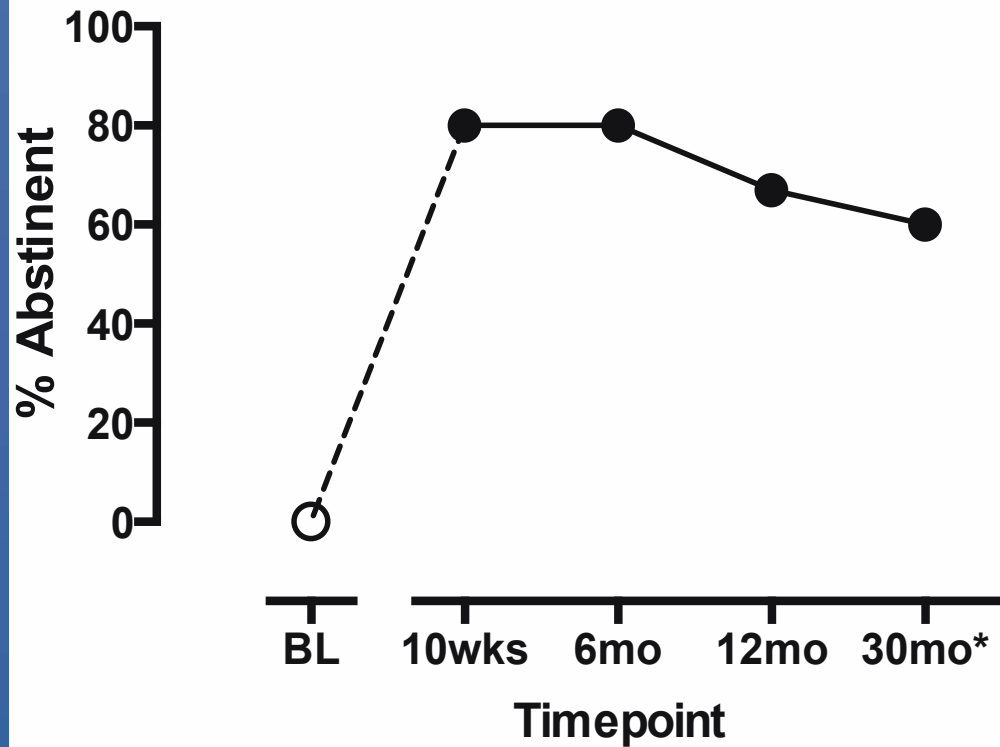
Hallucinogen; tobacco smoking cessation; addiction; psilocybin; psychedelic; mystical experience; spirituality

Pilot Study Timeline



- Participants smoked average of 31 years, 19 cigs/day
- 15 week protocol with weekly meetings
- Cognitive behavioral therapy
- 3 psilocybin sessions over 8 weeks (20-30 mg/70 kg)
- 1st Psilocybin session on target quit date

7-day Point Prevalence Abstinence (N = 15)



Mystical Experience in Smoking Cessation 2015

- Greater success in those who had mystical experience
- Mystical experience associated with craving reduction

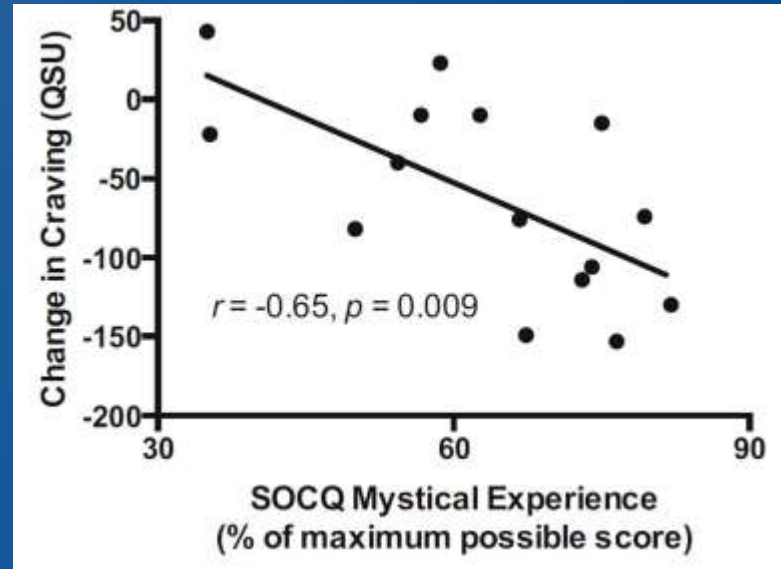


Psilocybin-Occasioned Mystical Experiences in the Treatment of Tobacco Addiction

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Qualitative analysis: Smoking Cessation, 2018

- Persisting sense of interconnectedness, awe, curiosity
- Reduced smoking withdrawal symptoms compared with previous quit attempts
- Psilocybin perceived as not addictive
- Other positive changes: Altruism, appreciation for aesthetics
- Insights: self-identity, smoking reasons

Original Paper

Psychedelic therapy for smoking cessation: Qualitative analysis of participant accounts

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Abstract

Background: Recent pilot trials suggest feasibility and potential efficacy of psychedelic-facilitated addiction treatment interventions. Fifteen participants completed a psilocybin-facilitated smoking cessation pilot study between 2009 and 2015.

Aims: The aims of this study were as follows: (1) to identify perceived mechanisms of change leading to smoking cessation in the pilot study; (2) to identify key themes in participant experiences and long-term outcomes to better understand the therapeutic process.

Methods: Participants were invited to a retrospective follow-up interview an average of 30 months after initial psilocybin sessions. Semi-structured interviews were conducted with 12 of the 15 participants. Data were analysed using thematic analysis.

Results: Participants reported gaining vivid insights into self-identity and reasons for smoking from their psilocybin sessions. Experiences of interconnectedness, awe, and curiosity persisted beyond the duration of acute drug effects. Participants emphasised that the content of psilocybin experiences overshadowed any short-term withdrawal symptoms. Preparatory counselling, strong rapport with the study team, and a sense of momentum once engaged in the study treatment were perceived as vital additional factors in achieving abstinence. In addition, participants reported a range of persisting positive changes beyond smoking cessation, including increased aesthetic appreciation, altruism, and pro-social behaviour.

Conclusions: The findings highlight the value of qualitative research in the psychopharmacological investigation of psychedelics. They describe perceived connections between drug- and non-drug factors, and provide suggestions for future research trial design and clinical applications.

Survey Study of Smoking Cessation/Reduction

- 1110 people claiming to have quit or reduced smoking as the result of a psychedelic experience
- 358 people > 1 year ago
- N=161 reported total abstinence for at least 6 months

Original Paper

An online survey of tobacco smoking cessation associated with naturalistic psychedelic use

Matthew W Johnson¹, Albert Garcia-Romeu¹, Patrick S Johnson² and Roland R Griffiths^{1,3}

Psychopharm

Journal of Psychopharmacology

1-10

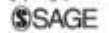
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Abstract

Data suggest psychedelics such as psilocybin and lysergic acid diethylamide (LSD) may hold therapeutic potential in the treatment of addictions, including tobacco dependence. This retrospective cross-sectional anonymous online survey characterized 358 individuals (52 females) who reported having quit or reduced smoking after ingesting a psychedelic in a non-laboratory setting ≥ 1 year ago. On average, participants smoked 14 cigarettes/day for 8 years, and had five previous quit attempts before their psychedelic experience. Of the 358 participants, 38% reported continuous smoking cessation after psychedelic use (quitters). Among quitters, 74% reported >2 years' abstinence. Of the 358 participants, 28% reported a persisting reduction in smoking (reducers), from a mode of 300 cigarettes/month before, to a mode of 1 cigarette/month after the experience. Among reducers, 62% reported >2 years of reduced smoking. Finally, 34% of the 358 participants (relapsers) reported a temporary smoking reduction before returning to baseline smoking levels, with a mode time range to relapse of 3–6 months. Relapsers rated their psychedelic experience significantly lower in personal meaning and spiritual significance than both other groups. Participants across all groups reported less severe affective withdrawal symptoms (e.g. depression, craving) after psychedelic use compared with previous quit attempts, suggesting a potential mechanism of action for psychedelic-associated smoking cessation/reduction. Changes in life priorities/values were endorsed as the most important psychological factor associated with smoking cessation/reduction. Results suggest psychedelics may hold promise in treating tobacco addiction as potentially mediated by spiritual experience, changed priorities/values, and improved emotional regulation.

Keywords

Hallucinogen, tobacco, smoking cessation, nicotine, addiction, psilocybin, psychedelic, mystical experience

Table 4. Withdrawal severity after psychedelic-associated smoking cessation or reduction in comparison with previous quit attempts. Modal responses shown in bold.

Withdrawal symptoms' severity (<i>n</i>) ^a	Much less severe, <i>n</i> (%)	Less severe, <i>n</i> (%)	Same, <i>n</i> (%)	More severe, <i>n</i> (%)	Much more severe, <i>n</i> (%)
Weight gain (258)	77 (29.8)	49 (19.0)	121 (46.9)	8 (3.1)	3 (1.2)
Increased eating (269)	71 (26.4)	61 (22.7)	121 (45.0)	14 (5.2)	2 (0.7)
Digestive problems (242)	69 (28.5)	40 (16.5)	127 (52.5)	6 (2.5)	0 (0)
Nausea (240)	74 (30.8)	41 (17.1)	118 (49.2)	7 (2.9)	0 (0)
Headaches (255)	84 (32.9)	54 (21.2)	106 (41.6)	9 (3.5)	2 (0.8)
Drowsiness (251)	80 (31.9)	42 (16.7)	123 (49.0)	6 (2.4)	0 (0)
Fatigue (257)	74 (28.8)	55 (21.4)	119 (46.3)	8 (3.1)	1 (0.4)
Insomnia (257)	76 (29.6)	51 (19.8)	122 (47.5)	5 (1.9)	3 (1.2)
Heart pounding/sweating (237)	78 (32.9)	29 (12.2)	125 (52.7)	4 (1.7)	1 (0.4)
Difficulty concentrating (268)	88 (32.8)	67 (25.0)	104 (38.8)	7 (2.6)	2 (0.7)
Anxiety (268)	93 (34.7)	72 (26.9)	93 (34.7)	6 (2.2)	4 (1.5)
Restlessness (272)	92 (33.8)	76 (27.9)	90 (33.1)	7 (2.6)	7 (2.6)
Depression/low mood (271)	114 (42.1)	69 (25.5)	80 (29.5)	7 (2.6)	1 (0.4)
Irritability (277)	118 (42.6)	73 (26.4)	73 (26.4)	10 (3.6)	3 (1.1)
Craving tobacco (284)	133 (46.8)	89 (31.3)	52 (18.3)	4 (1.4)	6 (2.1)

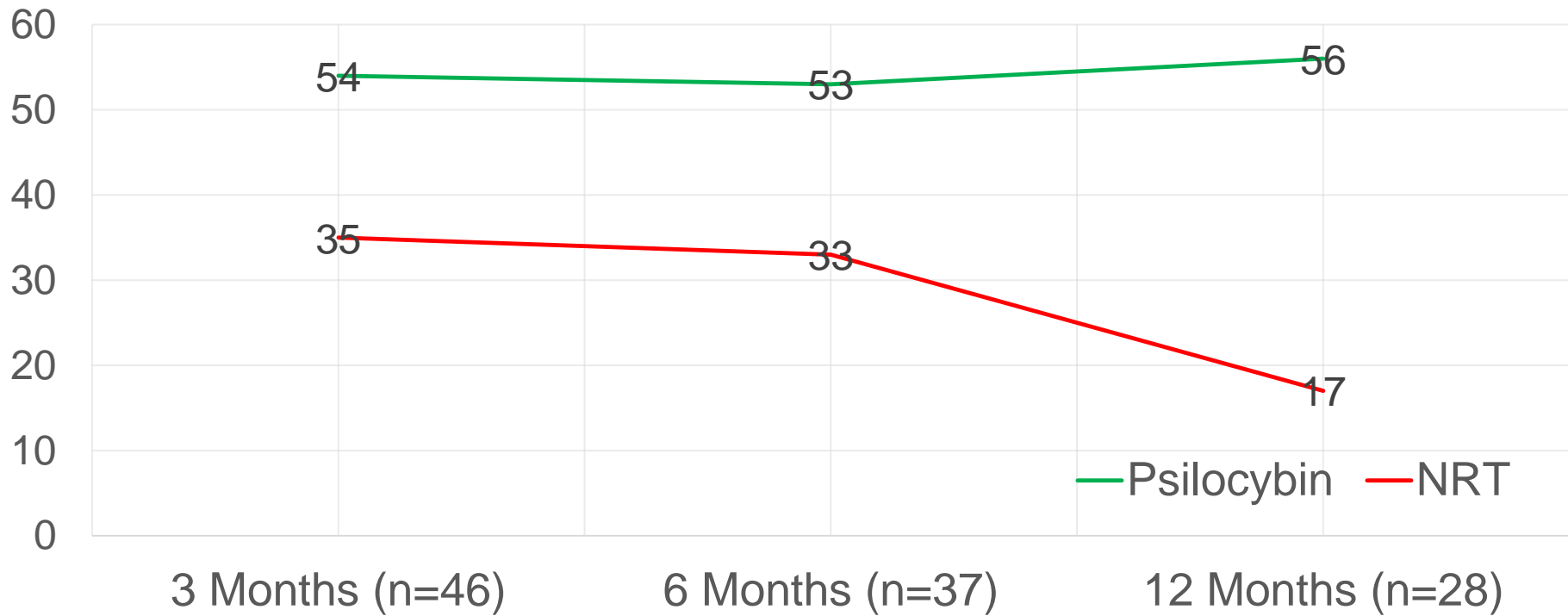
^aSample size varies by symptom (range = 237–284), as some participants reported no previous quit attempts as a basis for comparison, and others had never experienced particular withdrawal symptoms. Percentages were calculated based on the number of individuals who reported a particular withdrawal symptom.

Randomized Comparative Efficacy Trial



- 80 treatment-resistant smokers
- Randomized to psilocybin or nicotine patch
- Same cognitive behavior therapy
- 1 psilocybin session

7 Day Point Prevalence Biologically Confirmed % Abstinent – Completing Treatment Sample



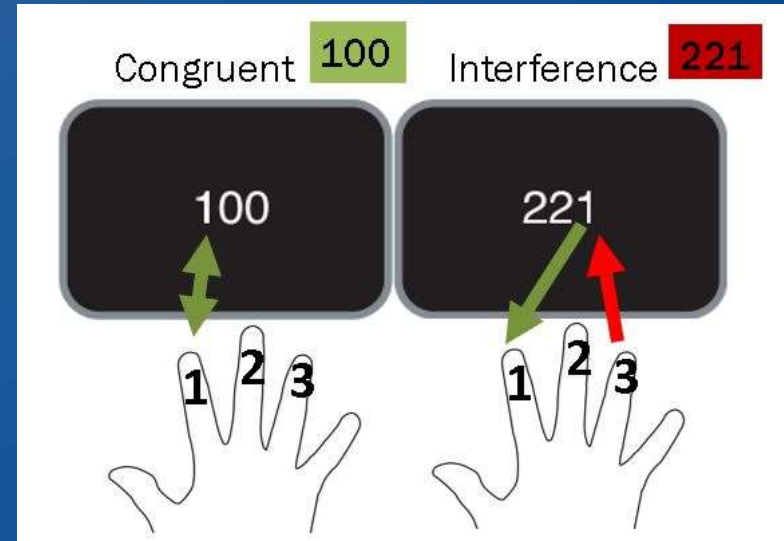
Psilocybin improves cognitive control and downregulates parietal cortex in treatment-seeking smokers



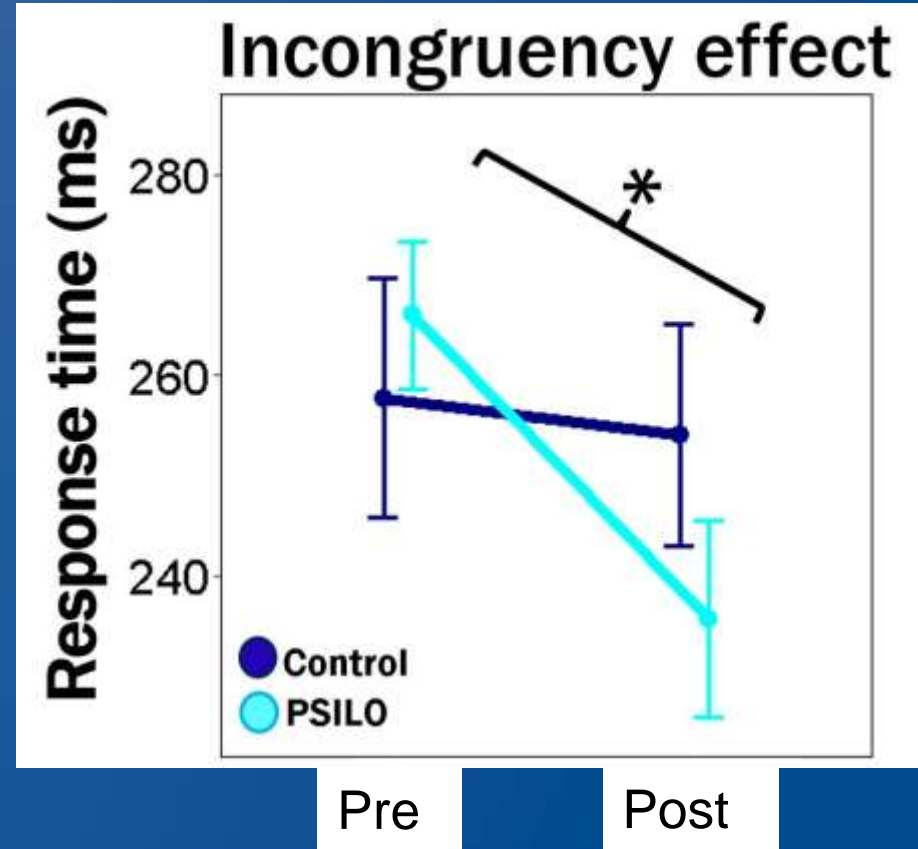
M. R. McKenna¹, J. R. Fedota¹, A. Garcia-Romeu², R. R. Griffiths², M. W. Johnson², and E. A. Stein¹
Neuroimaging Research Branch, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, Baltimore, MD¹
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD²

Preliminary Cognitive and fMRI Results (17 Psilocybin, 10 NRT)

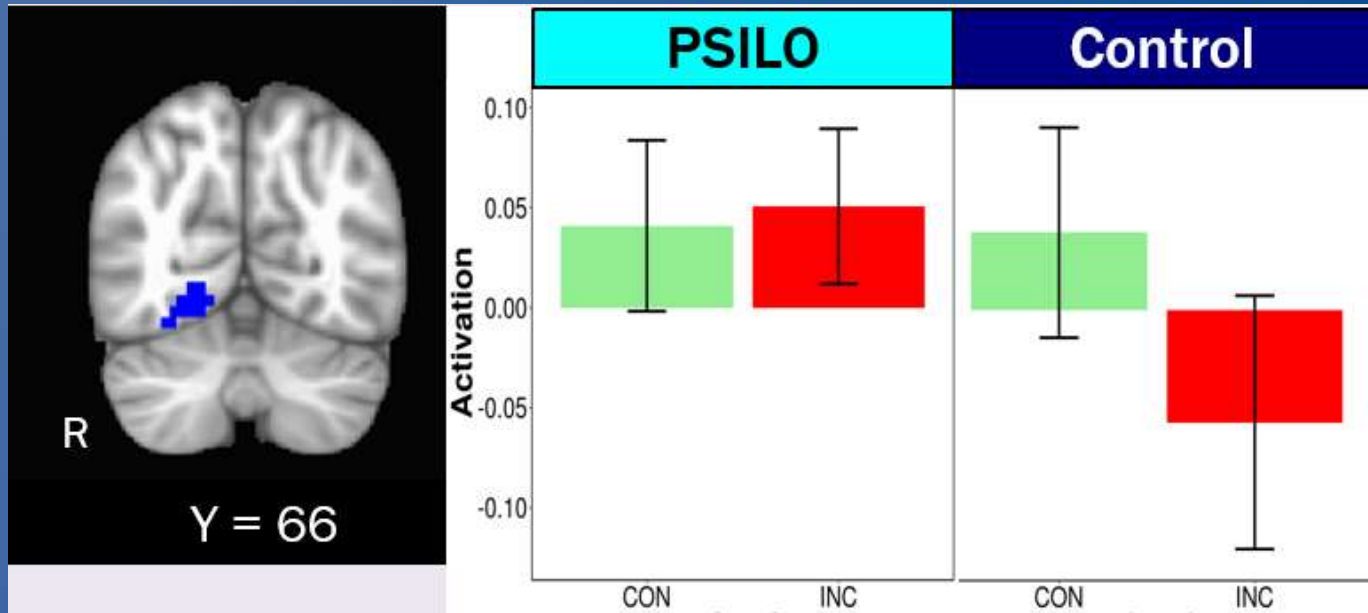
- Multi-Source Interference Task (MSIT) (Bush & Shin, 2006)
 - Cognitive interference
 - Congruency effect:
 - Reaction time of incongruent – congruent trials



Psilocybin group shows less
“cognitive interference” the day
after quitting



Normalization of task associated fMRI response in the right lingual gyrus the day after quitting for the psilocybin group



Alcohol Dependence Pilot

- 10 alcohol-dependent participants
- Motivational Enhancement Therapy
- 2 sessions of .3 mg/kg and .4 mg/kg psilocybin



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

Michael P Bogenschutz¹, Alyssa A Forcehimes¹, Jessica A Pommy¹,
Claire E Wilcox¹, PCR Barbosa² and Rick J Strassman¹



Survey Study of Alcohol Cessation/Reduction


- 343 people claiming to have quit or reduced alcohol as the result of a psychedelic experience
- 83% no longer qualified as having a alcohol use disorder

Original Paper

Cessation and reduction in alcohol consumption and misuse after psychedelic use

Albert Garcia-Romeu¹ , Alan K Davis¹, Fire Erowid², Earth Erowid², Roland R Griffiths^{1,3} and Matthew W Johnson¹



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Abstract

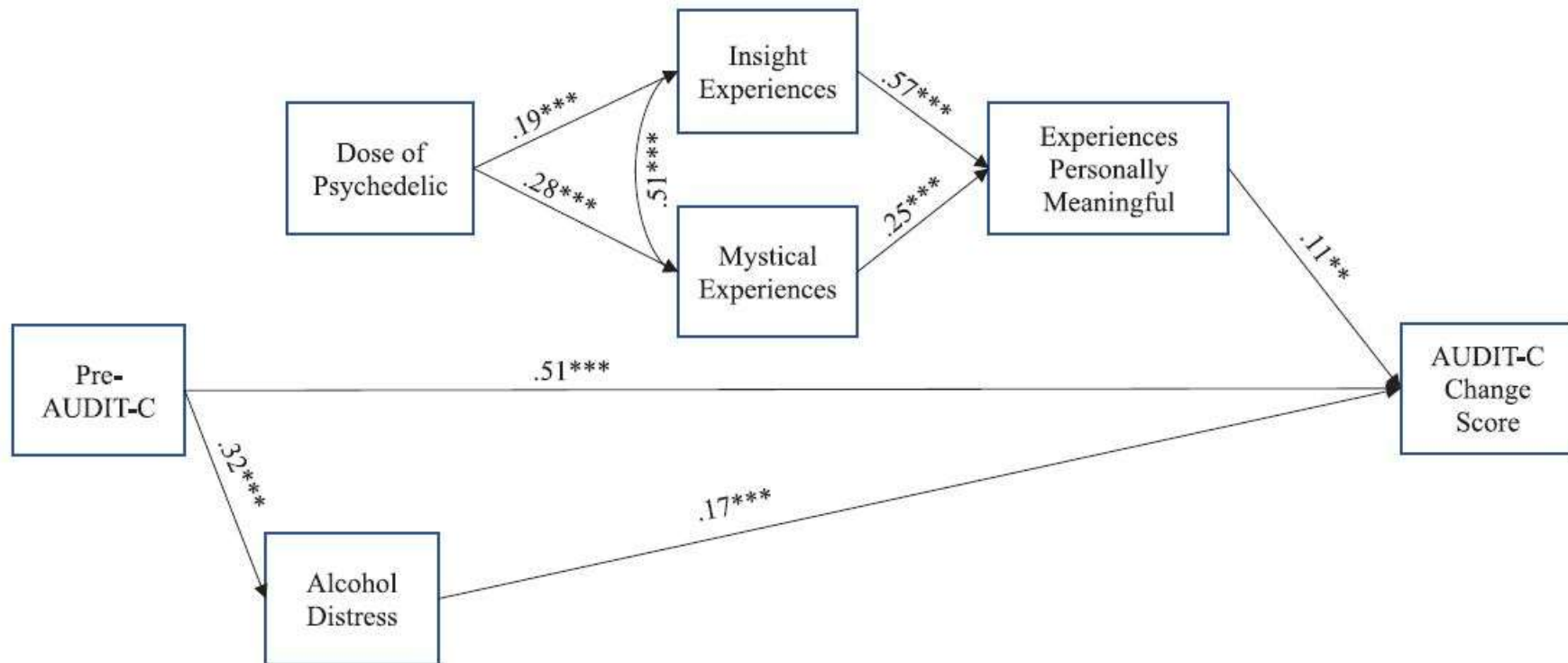
Background: Meta-analysis of randomized studies using lysergic acid diethylamide (LSD) for alcohol use disorder (AUD) showed large, significant effects for LSD efficacy compared to control conditions. Clinical studies suggest potential anti-addiction effects of LSD and mechanistically-related classic psychedelics for alcohol and other substance use disorders.

Aims: To supplement clinical studies, reports of psychedelic use in naturalistic settings can provide further data regarding potential effects of psychedelics on alcohol use.

Methods: An anonymous online survey of individuals with prior AUD reporting cessation or reduction in alcohol use following psychedelic use in non-clinical settings.

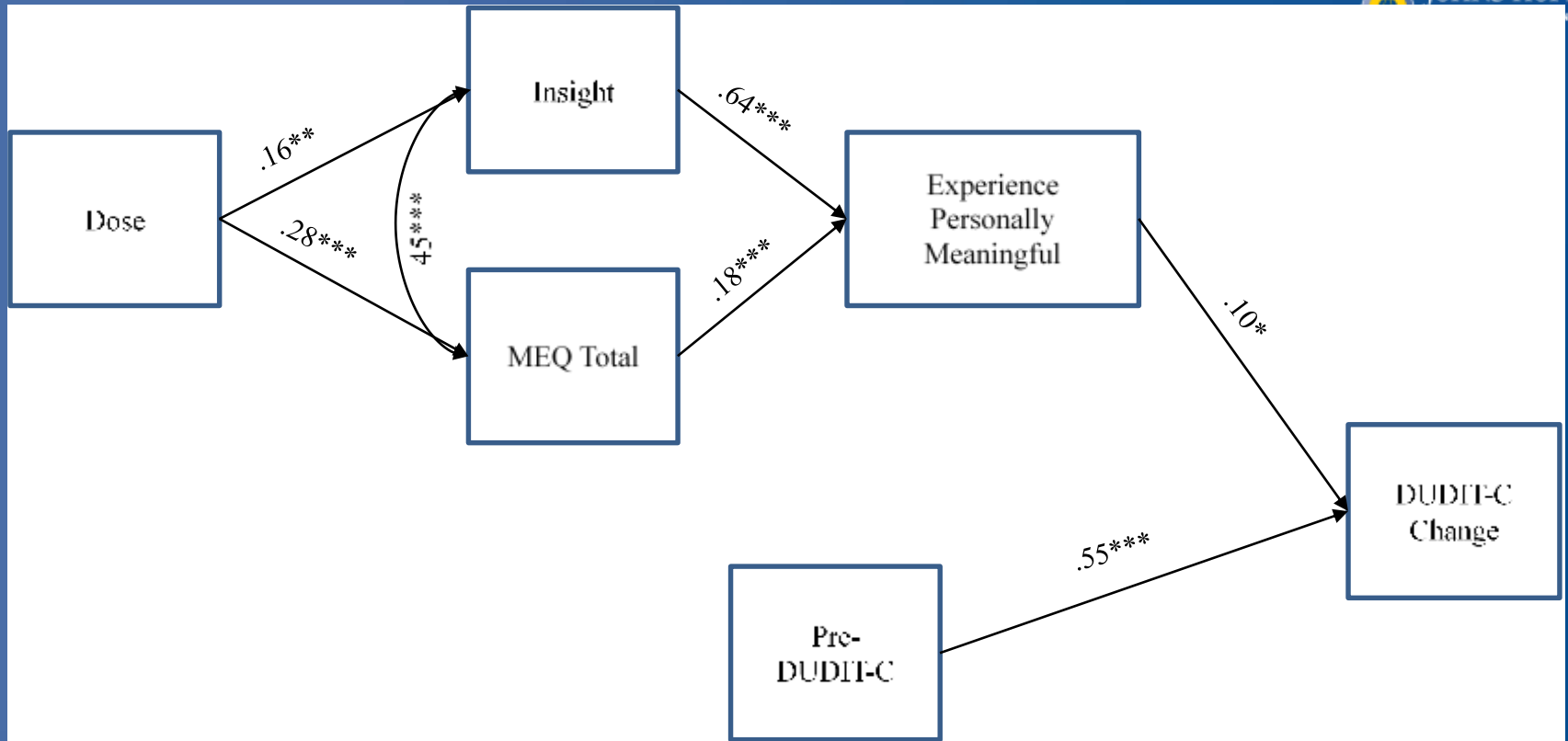
Results: 343 respondents, mostly White (89%), males (78%), in the USA (60%) completed the survey. Participants reported seven years of problematic alcohol use on average before the psychedelic experience to which they attributed reduced alcohol consumption, with 72% meeting retrospective criteria for severe AUD. Most reported taking a moderate or high dose of LSD (38%) or psilocybin (36%), followed by significant reduction in alcohol consumption. After the psychedelic experience 83% no longer met AUD criteria. Participants rated their psychedelic experience as highly meaningful and insightful, with 28% endorsing psychedelic-associated changes in life priorities or values as facilitating reduced alcohol misuse. Greater psychedelic dose, insight, mystical-type effects, and personal meaning of experiences were associated with a greater reduction in alcohol consumption, controlling for prior alcohol consumption and related distress.

Conclusions: Although results cannot demonstrate causality, they suggest that naturalistic psychedelic use may lead to cessation or reduction in problematic alcohol use, supporting further investigation of psychedelic-assisted treatment for AUD.



Survey Study of Opioid Cessation/Reduction

- 343 people claiming to have quit or reduced opioid use as the result of a psychedelic experience
- Large reductions in retrospectively assessed criteria for OUD



Designs and outcomes for psychedelic treatment for OUD



- Acute session measures
 - Mystical experience
 - Challenging experience
 - Meaningful nature of experience
 - Awe
- Assessment of persisting adverse effects
 - Life functioning
 - Perceptual disturbance

Designs and outcomes for psychedelic treatment for OUD



- Assessment of other persisting benefits and possible psychological mechanisms
 - Affect
 - Quality of life
 - Qualitative analysis
- Mechanistic outcome measures
 - Beyond receptor effects, e.g., brain network dynamics
 - Domains of executive function
 - Neuroplasticity
 - Inflammation

Overall Design Considerations

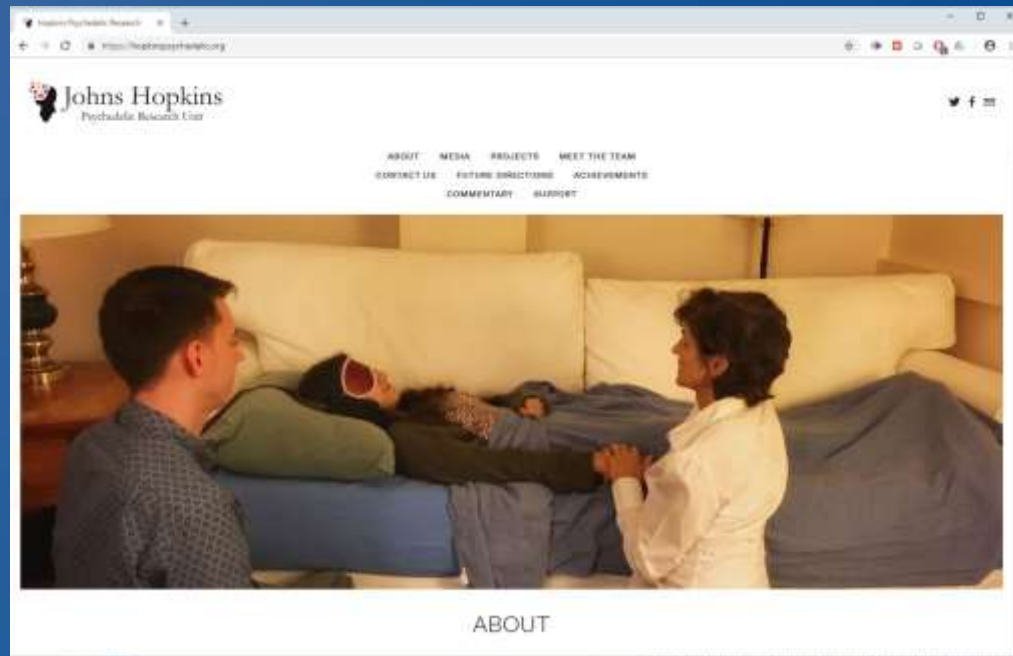
- Importance of preparation and rapport
- Unique risks and mitigation strategies
- Designs
 - Pilot studies, comparative efficacy studies, blinded studies
 - In blinded studies, nature of comparator:
 - placebo, active other compound, low or trivial dose
 - Comparative efficacy
- Long term assessment
- Concerns about opioid use lapse
- Navigating the true believers

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