

RESEARCH INTO PSYCHEDELIC COMPOUNDS FOR SUBSTANCE USE DISORDERS

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Integrated Opioid & Addiction Care ECHO
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PROTEA

Program for Research, Outreach, Therapeutics
& Education in the Addictions



School of Medicine
and Public Health

UNIVERSITY OF WISCONSIN-MADISON

Disclosures

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Significance

- Substance use disorders (SUDs) are common
 - 15-20% lifetime prevalence in general U.S.
 - 30+% in primary care/hospital samples
- Cost estimates range \$200 billion to \$1.4 trillion
- < 10% access needed treatment
- Challenges in current treatments
 - Relapse 40-90% (3 mo-2 yr)
 - Treatment retention (~40-50%)

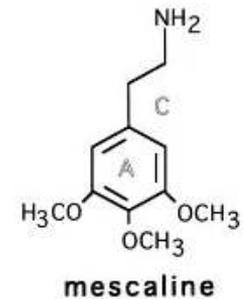
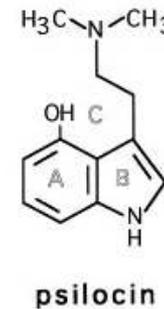
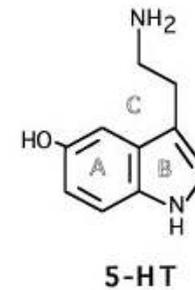
National Survey on Drug Use & Health 2019

NIDA Drug Addiction Treatment Outcomes Study (e.g. Schoenthaler et al 2015. J Reward Deficienc)

Andersson et al 2019. Addict Beh.

Classic Psychedelics

- Common site of action at 5HT_{2A} receptors
 - Subj effects blocked by ketanserin
- “Mystical” or “transformative” experience
 - Ineffability
 - Noetic quality/”special knowledge”
 - Conscious unity/ego dissolution
 - Time/space transcendence
 - Deeply felt positive mood
 - Sense of sacredness



Aghajanian G 1999. Neuropsychopharm

Richards WA. 2018. *Sacred Knowledge: Psychedelics & Religious Experience*

Theoretical Basis for Consideration of Psychedelics

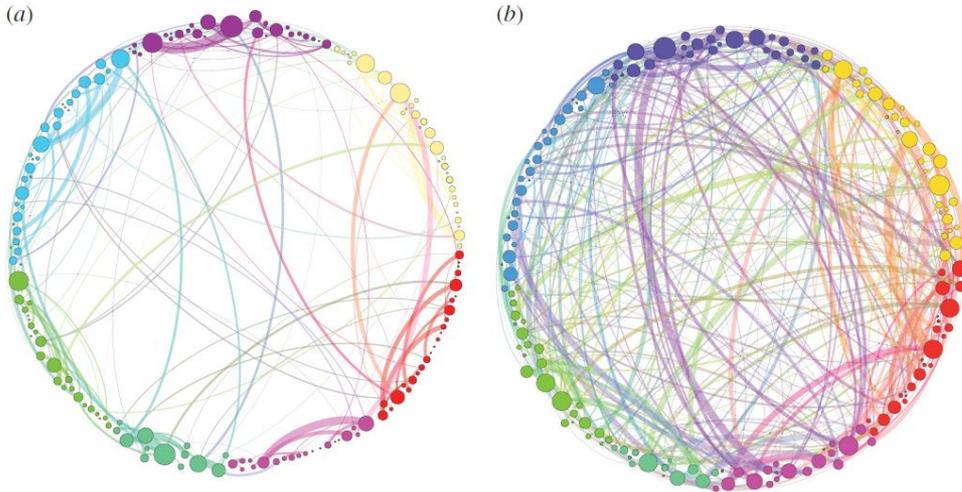
- Cathartic emotional experience
- Mystical/spiritual experience, “awe”
 - “Some of my AA friends and I have taken the material (LSD) frequently and with much benefit.”
 - “My original spontaneous spiritual experience . . .was enacted with wonderful splendor and conviction.”
 - Bill W, AA founder, in letters to Carl Jung, 1961
- Impact on personality structure (e.g. extraversion, openness)

Bogenschutz & Johnson 2016. Prog Neuropsych & Biol Psychiatry.

Erritzoe et al 2018. Acta Psych Scand.

Hendricks 2018. Int Rev Psychiatry.

Greater whole brain communication



- **Greater communication between various major brain hub networks**
- **Decreased communication within hubs.**

- **Default mode network which together represents self-related functioning**
- **Self-referential processing, self-awareness, metacognition**
- **Decreased activity correlates with degree of ego dissolution**

Carhart-Harris et al. (2014). Frontiers in Human Neuroscience



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Population Data

– Classic psychedelic use

- No increase in mental illness (lower rates for some Sx)
- Reduced odds of past-month psychological distress, past year suicidal thinking, past-year suicidal planning, or past-year suicide attempt
- Decreased rate of supervision failure among criminal justice-involved

Psilocybin in Research: Safety

- No evidence of neurotoxic effects
- Transient ↑ BP/HR
- Possible headache within 24 hours after dosing
- Impairs judgement thus context, support, and preparation are important
- No withdrawal
- Low risk of hallucinogen persisting perceptual disorder (HPPD)
- Possible negative interaction with serious psychiatric diagnoses (e.g. psychosis, bipolar)

Dosing

- **Typical: 0.28-0.43 mg/kg**
- **UW Study: 0.3-0.6 mg/kg
(18.8-59.2 mg)**
- **Oral onset: ~30-60 min**
- **Peak effects: ~2 hours**
- **1-5 doses /4-6 weeks**
- **Total duration: 4-8 hours**



Psilocybin Protocol

- Comprehensive psychological & medical screening
- 2 facilitators (mental health professionals)
- 6-8 hours of pre-dosing preparation before initial dose
- Eye-shades, headphones for pre-set music playlist
- May stay overnight or discharge under care of their support person
- Integration sessions



The UW SETTING



Set: person's psychological state

- Pre-dose preparation
- Careful screening
- Expectations/concerns
- Integration

Setting: environment & context

- Interpersonal support
- Safe & secure room
- Room with comfortable & positive décor
- Personal objects if possible



Psilocybin Session

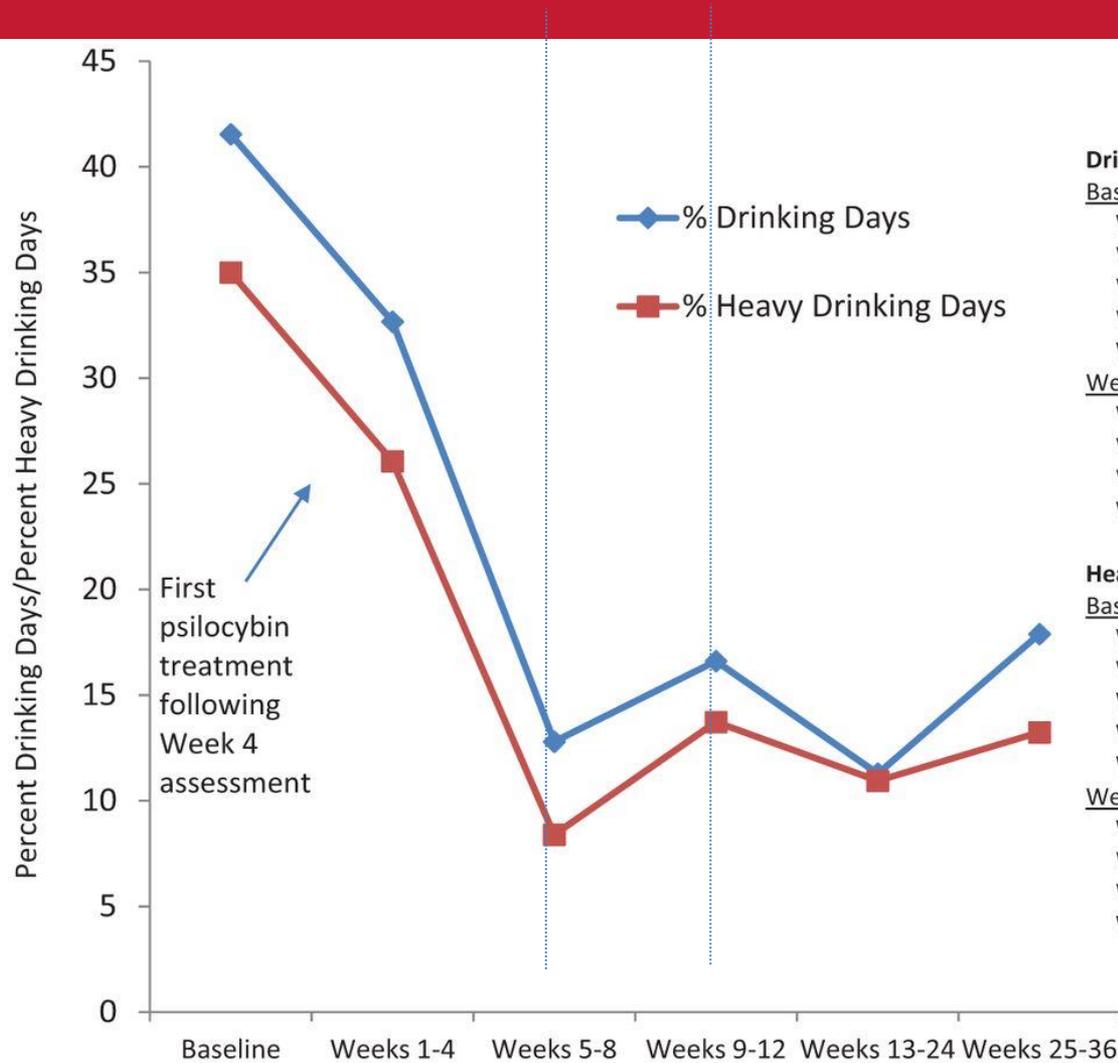
- Non-directive approach, guiding when necessary
- Lay down and relax into their experience
- Emotional support and reassurance
- Agreement that they would let us know if they need help
- Help participant be curious about their experience (“Trust, Let Go, Be Open”)
- Challenging Experience (“In and through”)



Johns Hopkins Treatment room courtesy of MAPS

Studies of Psychedelics in SUDs

- Alcohol use disorders
 - 30 publications 1950s-70s w/ LSD
 - Meta-analysis (Krebs, Johansen 2012) of 6 RCTs
 - 325 participants
 - Single dose sessions (210-800 mcg)
 - Consistent treatment effect for 'misuse' vs placebo (OR 1.96, $p = 0.0003$)
 - Bogenschutz et al 2015 J Psychopharm
 - Single arm, $n = 10$
 - 12-week, 14-session manualized intervention (MET)
 - 2 open-label psilocybin dosing sessions (0.3mg/kg, 0.4mg/kg)
 - Drinking days & heavy drinking days both significantly reduced v baseline out to 36 wk ($d = 1.2, 1.4$)



Drinking Days

Baseline vs.

Weeks 1-4	<i>p</i> = .164	<i>d</i> = 0.490
Weeks 5-8	<i>p</i> = .009	<i>d</i> = 1.194
Weeks 9-12	<i>p</i> = .015	<i>d</i> = 1.033
Weeks 13-24	<i>p</i> = .006	<i>d</i> = 1.332
Weeks 25-36	<i>p</i> = .007	<i>d</i> = 1.187

Weeks 1-4 vs.

Weeks 5-8	<i>p</i> = .016	<i>d</i> = 1.109
Weeks 9-12	<i>p</i> = .033	<i>d</i> = 0.869
Weeks 13-24	<i>p</i> = .014	<i>d</i> = 1.163
Weeks 25-36	<i>p</i> = .013	<i>d</i> = 1.036

Heavy Drinking Days

Baseline vs.

Weeks 1-4	<i>p</i> = .158	<i>d</i> = 0.492
Weeks 5-8	<i>p</i> = .007	<i>d</i> = 1.249
Weeks 9-12	<i>p</i> = .019	<i>d</i> = 0.985
Weeks 13-24	<i>p</i> = .010	<i>d</i> = 1.161
Weeks 25-36	<i>p</i> = .004	<i>d</i> = 1.383

Weeks 1-4 vs.

Weeks 5-8	<i>p</i> = .022	<i>d</i> = 1.046
Weeks 9-12	<i>p</i> = .059	<i>d</i> = 0.750
Weeks 13-24	<i>p</i> = .038	<i>d</i> = 0.876
Weeks 25-36	<i>p</i> = .018	<i>d</i> = 1.040



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Other Substance Use Disorders

- Very limited study
 - Ludwig et al 1965 Am J Psychother
 - 70 “post-narcotic drug addicts” at US PHS Public Health Service Hospital, Lexington
 - Randomized to one of 5 treatments
 - Outcome = psychopathology via questionnaire at 2 wk and 2 mo after 140mcg LSD
 - All groups improved; greatest improvement in “hypnodelic” group
 - Savage & McCabe 1973 Arch Gen Psych
 - 78 incarcerated males with opioid addiction
 - Random assignment: abstinence-based care vs. 4-6 wk residential care + 300-500mcg LSD (in addition to 24 hr prep + 1-wk integration)
 - 25% vs 5% abstinence in intervention vs control at 12 mo



HEFFTER
RESEARCH INSTITUTE

HEFFTER OPIOID USE DISORDER INVESTIGATION (HOUDI)



PROTEA Psychedelic Trials Team



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HOUDI: Rationale

- Treatment retention and ongoing use during treatment is a major issue
- Without medication MOUD, opioid overdose = major risk
- Psilocybin under appropriate conditions might facilitate engagement in recovery/treatment and reduce craving
- Interaction b/t psilocybin and MOUD remains uninvestigated in scientifically rigorous study in humans

HOUDI: Proposed Study Aims

Primary

In patients with OUD, characterize effects of adding psilocybin to buprenorphine regimen

Secondary

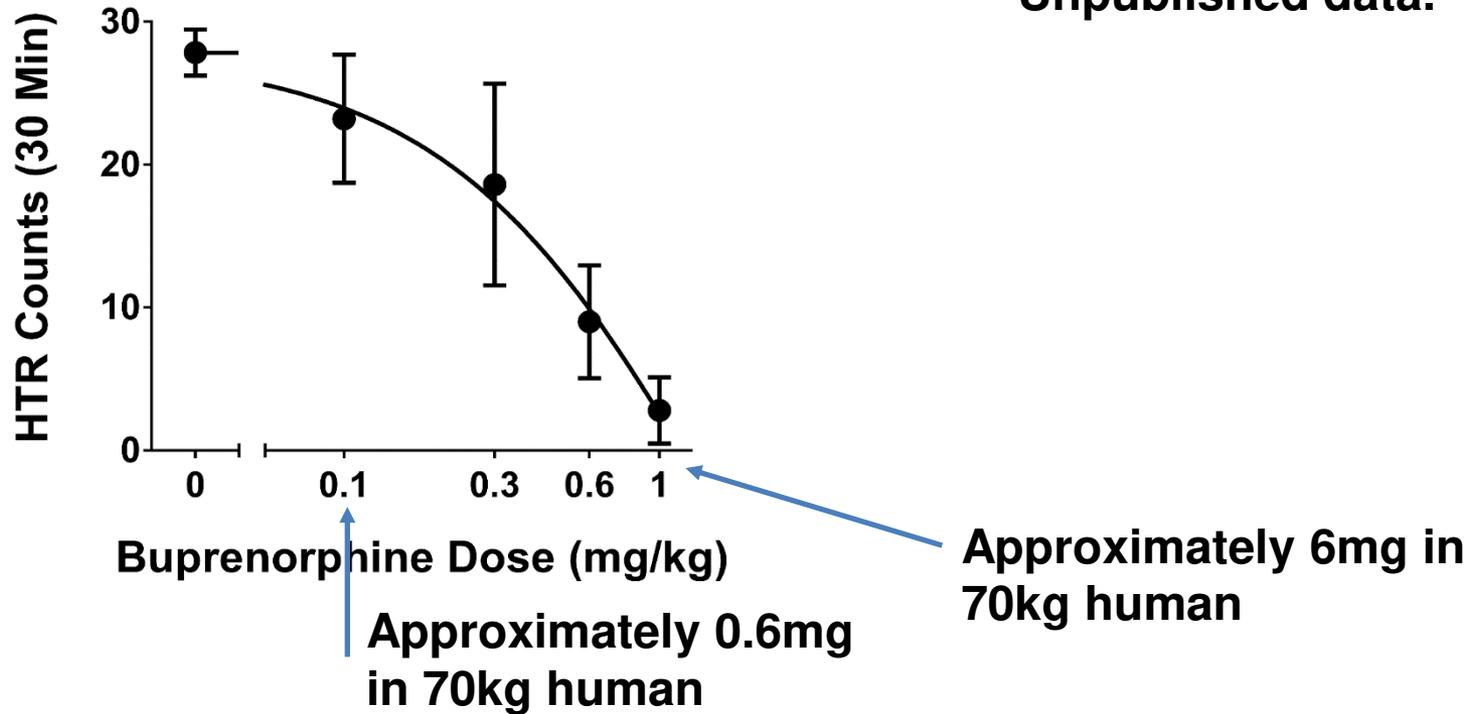
Demonstrate that after one or two doses of psilocybin, neither opioid craving nor illicit opioid use will increase

Exploratory

Observation of depressive and anxiety symptoms, quality of life, treatment retention during observation period

Data from Mouse Model

Halberstadt, A. 2018.
Unpublished data.



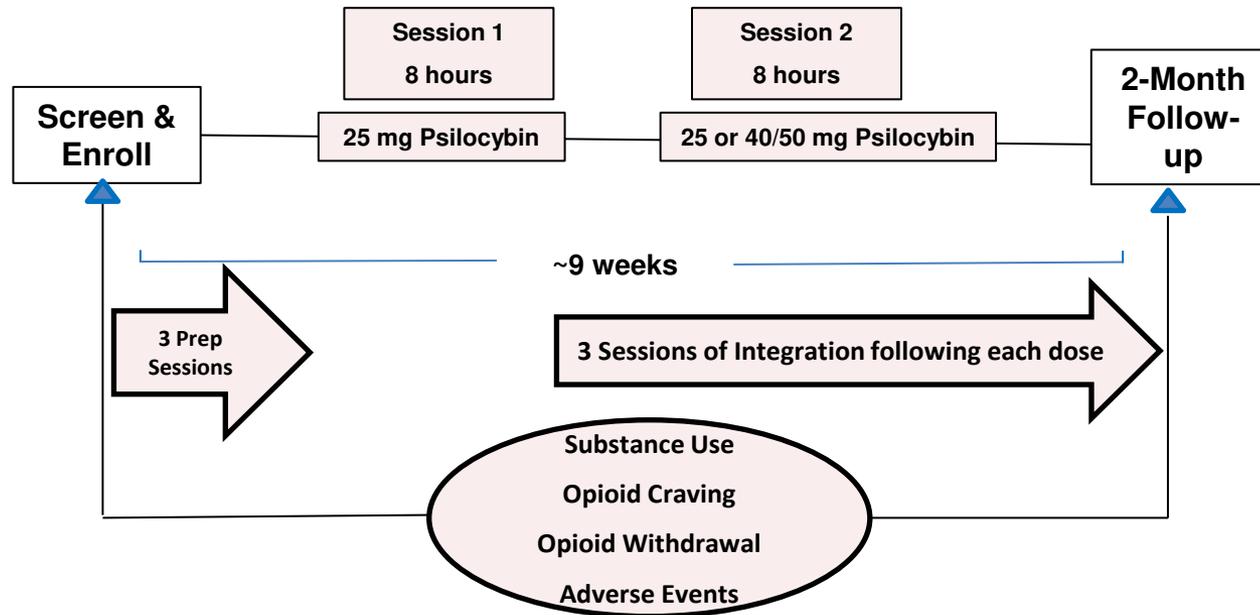
HOUDI: Methods

- Single arm, open label n = 10
- Recruitment via local MOUD prescribers (transitioning to community-based recruitment of people who currently use)
- Key Inclusion Criteria (HOUDI 1)
 - age 21-55 years
 - OUD in early or sustained recovery
 - ≤ 20 mg daily buprenorphine

HOUDI: Methods

- Key Exclusion Criteria
 - creatinine clearance < 30ml/min
 - personal history of primary psychotic disorder (SCID)
 - 1st degree relative with primary psychotic disorder
 - urine drug testing + stimulant, opioid, sedative
 - cardiac conduction abnormality/ischemic heart disease
 - uncontrolled hypertension
 - physical exam findings of concern

Design

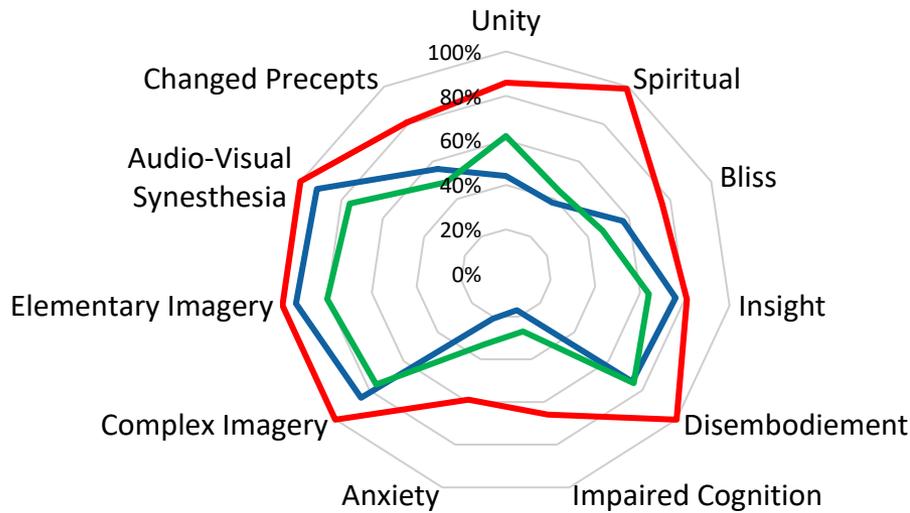


- N=10, adults with Opioid Use Disorder stabilized on MOUD (buprenorphine)
- Supportive therapy with 2 facilitators
- ECG/Vitals monitored throughout each dosing session

Altered States of Consciousness (94 items)

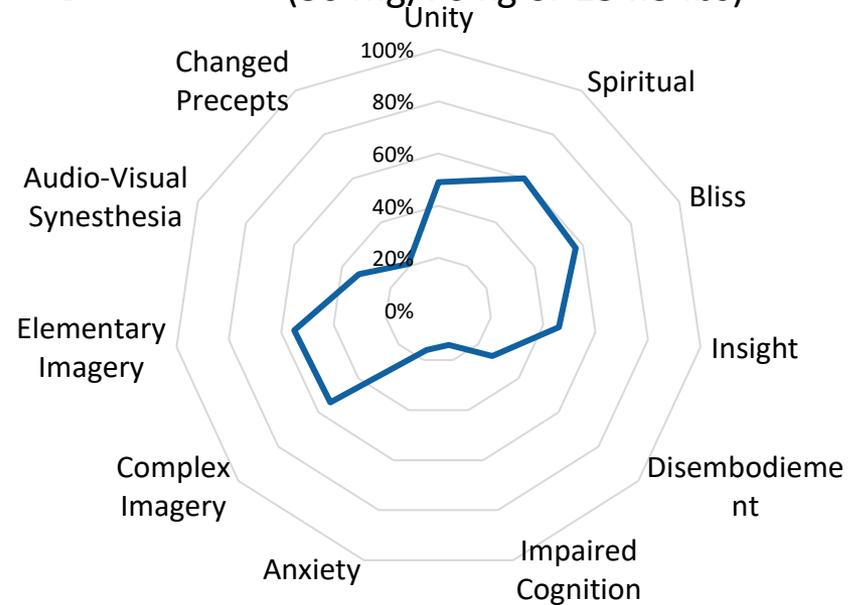
Opioid Study (N = 2)

— P1 Dose 2 (25 mg; 74.8 kg) — P2 Dose 1 (25 mg; 90.3 kg)
— P2 Dose 2 (50 mg)



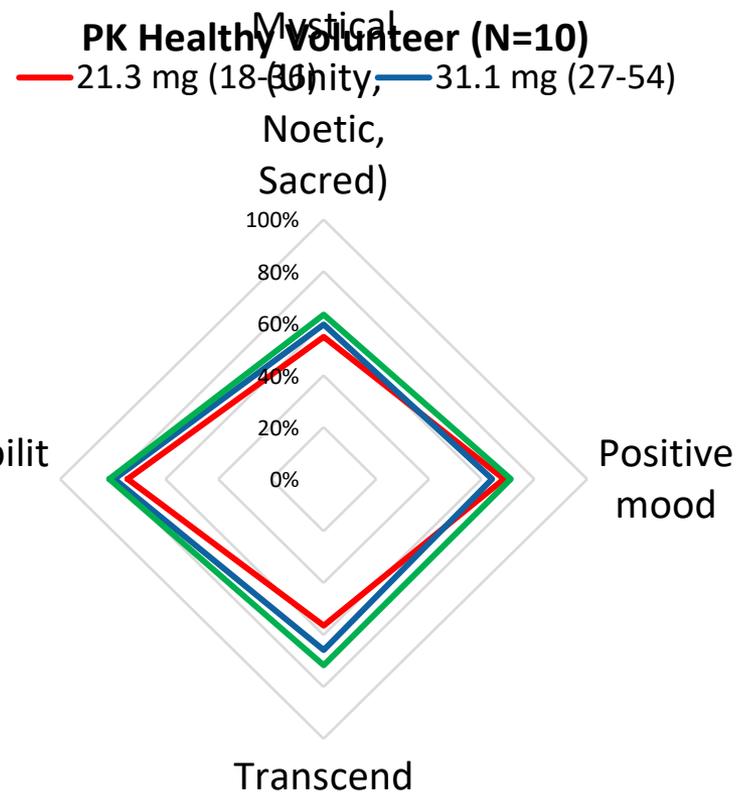
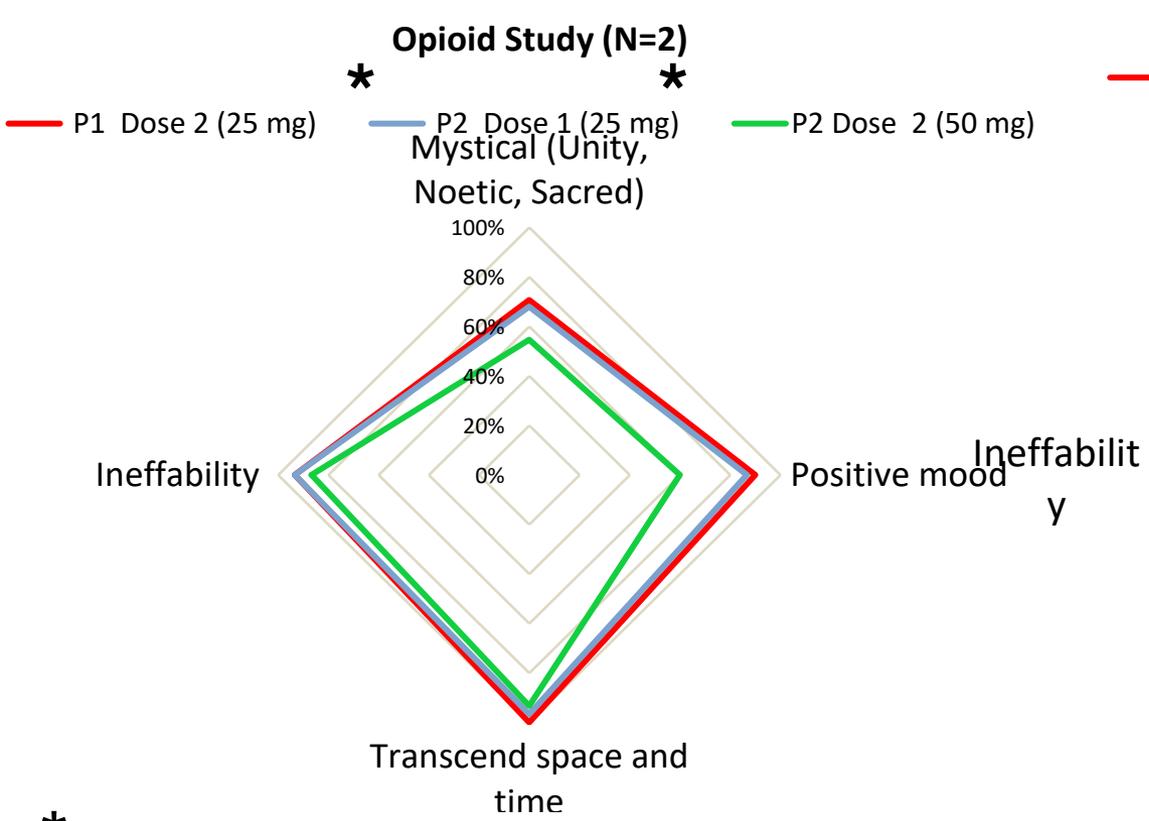
Normative Adult Sample (N = 20)*

(30 mg/70 kg or 154.3 lbs)



*Carbanaro, 2018, Psychopharmacology

Mystical Experience Questionnaire (30 items)

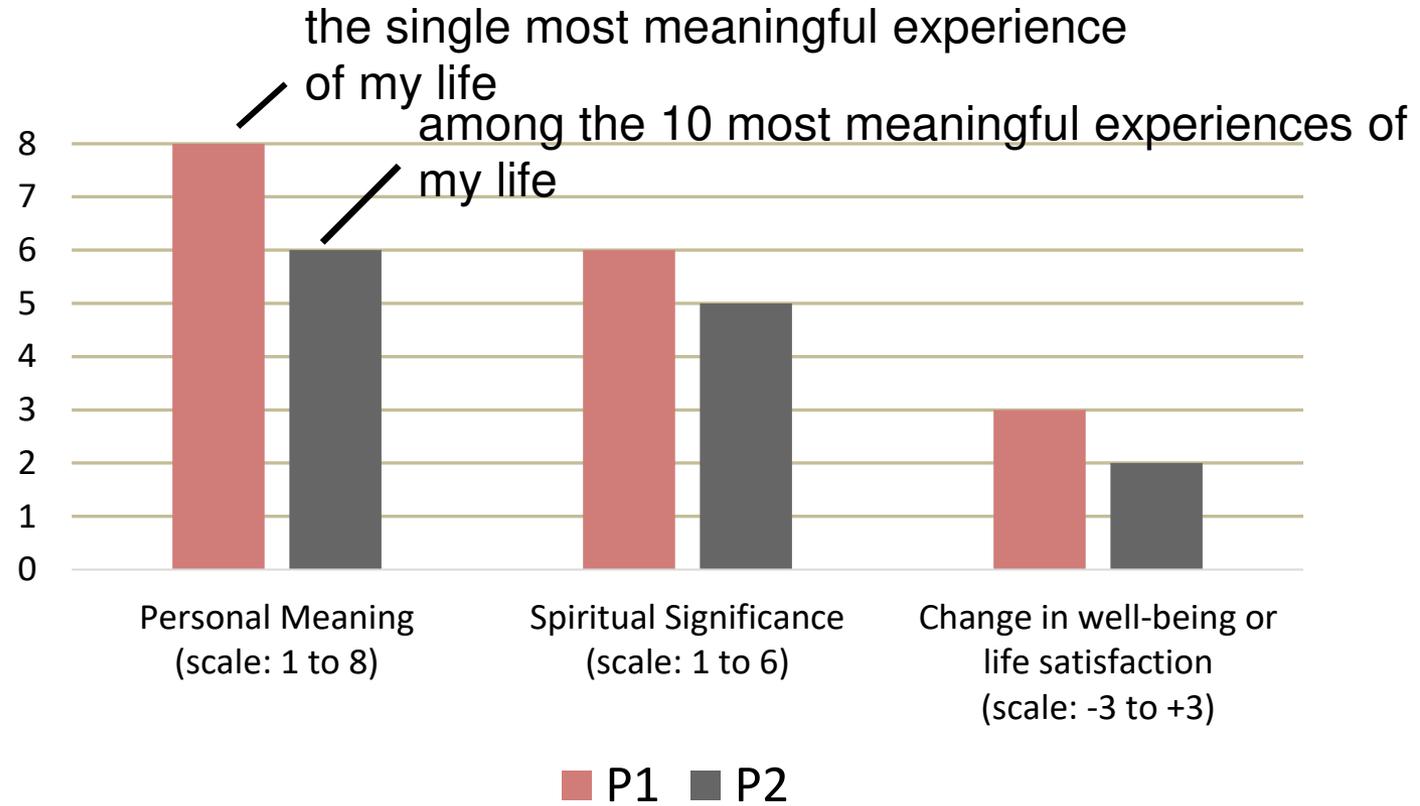


* **Mystical Experience: $\geq 60\%$ of possible score across four subscales**

Nicholas et al., 2018, Journal of Psychopharmacology

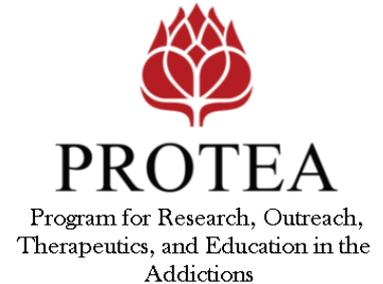
Persisting Effects

(~4 weeks post Dose 2)



Recruitment and Study Changes

- **Study start on 10/2019**
 - Covid delays
 - Staffing shortage
 - Identifying individuals stabilized on MOUD (buprenorphine)
 - Resource based barriers (e.g. transportation)
 - **Criteria and sample were modified (Fall 2022):**
 - Criteria was updated to reflect current conventions and standards
 - Removed ADHD and THC use restriction
 - Modified psychiatric inclusion criteria
 - Funding for transportation
 - Changed sample to include individuals with active opioid use disorder who are willing to transition to MOUD
- **Completed two participants prior to above modifications:**
 - P1: Female, 30's, Enrolled 1/2021, buprenorphine: 8 mg
 - P2: Male, 50's, Enrolled 8/2021, buprenorphine: 1/3 of 8 mg/day

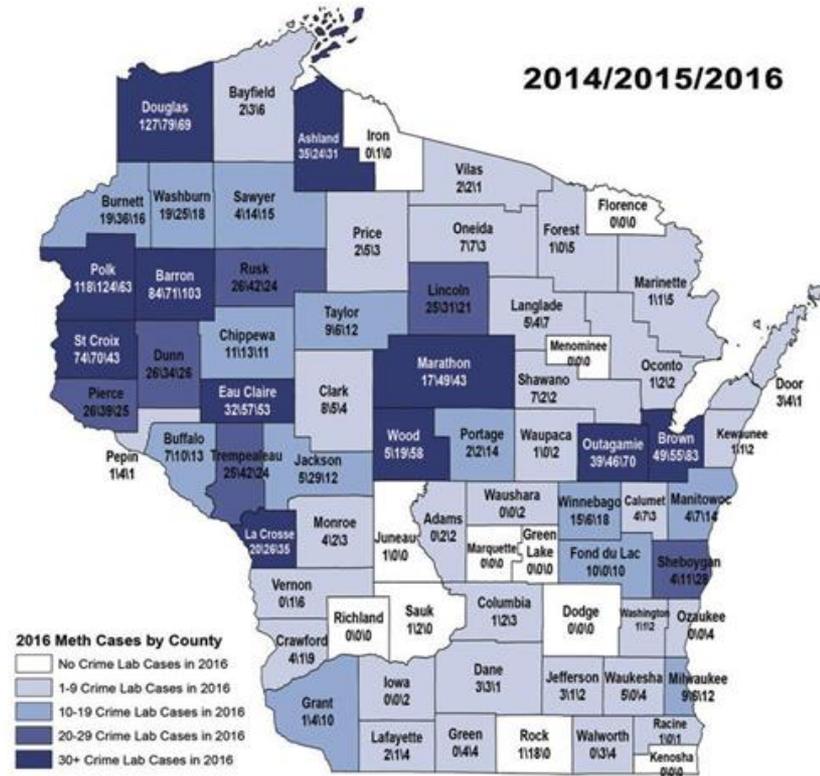
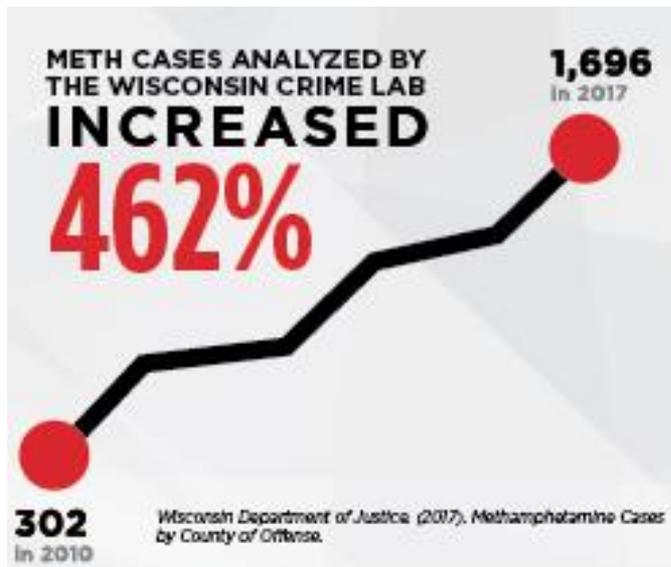




PSILOCYBIN IN THE TREATMENT OF METHAMPHETAMINE USE DISORDER



About 1 in every 5 drug cases at the Wisconsin State Crime Labs involved meth



Significance

- Annual WI economic burden \$424 to \$875 million (WI DOJ & FBI, 2016)
 - Premature death, crime, child endangerment/abandonment, lost productivity, drug treatment, and health care (WI DOJ & FBI, 2016)
- High risk sexual behaviors and risk for blood-borne virus (HIV, hepatitis C) transmission (Degenhardt & Hall, 2012)
- No pharmacological treatment has been approved
- Behavioral treatments are only moderately effective (Shearer, 2007) and may be cost prohibitive in WI (WI DOJ & FBI, 2016)



Rationale

- Limited treatment options for meth use for WI residents (WI DOJ & FBI, 2016)
- Impressive preliminary evidence for psilocybin as a safe and non-addictive treatment option for addiction (Johnson, 2014; Bogenschutz, 2015; Hendricks, 2018)
- Potentially time-limited/cost-effective intervention which may be optimal for meth (Shearer, 2007)



Aims/Method

Primary Aims:

- Will be well tolerated, with no serious adverse events
 - Adverse events categorized according to NCI Common Toxicity Criteria version 4.0. and assigned attribution (probably, possibly, and not related).
- The study will demonstrate that at least 70% of eligible participants completing screening will remain in the study through 1-2 doses of psilocybin and that at least 50% of participants will complete a 2-month follow-up



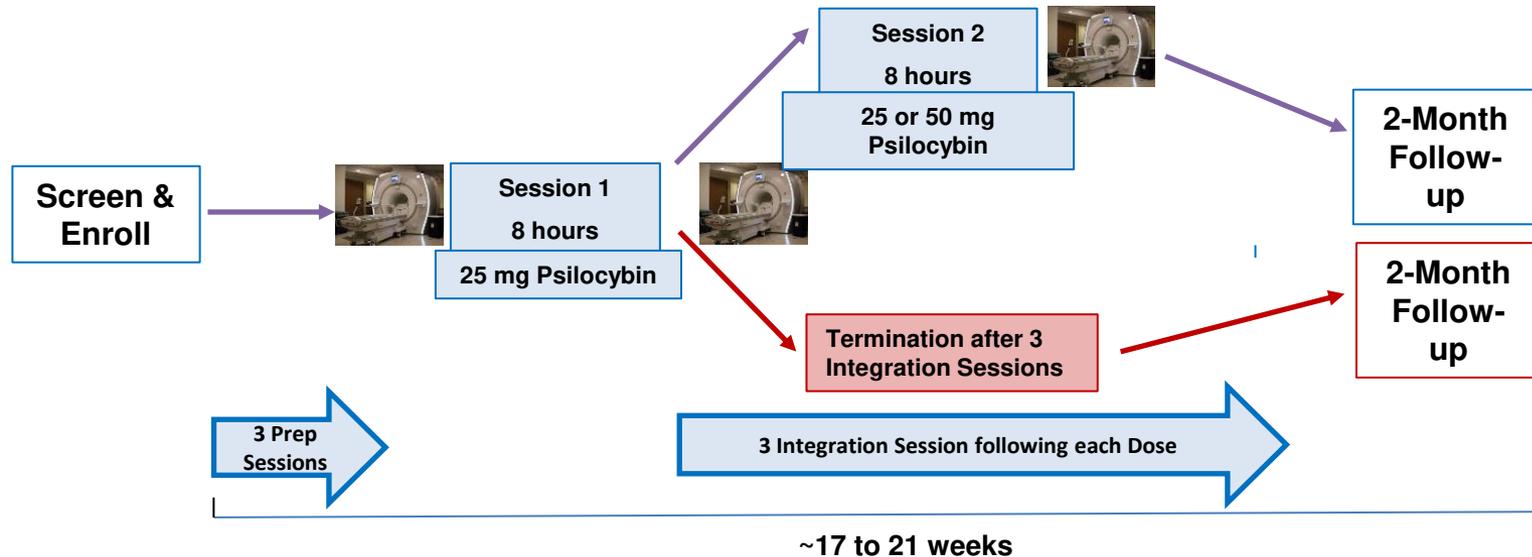
Aims/Method

Secondary Aims:

- Will result in a relative decrease in methamphetamine use at 1- and 2-month follow-up
 - Meth use assessed with timeline follow-back (TLFB) interview and confirmed by drug screen at each in-person visit
 - Questionnaires on craving, self-efficacy, motivation, affect, sexual activities
- Is feasibly evaluated with neuroimaging as a measure of pre-post psilocybin induced changes in addiction-related brain circuitry
 - Resting-state connectivity analysis: Addiction related brain networks involving salience detection, cognitive control, affective functioning, self-reflection



Open-label Safety Feasibility Study of Psilocybin for Methamphetamine Use Disorder



- PI: Christopher Nicholas, PhD
- N=12, adults with mild to moderate Meth Use Disorder
- Placebo + psychotherapy (Harm Reduction, MI, Mindfulness, CBT, Emotion/Somatic-Focused)
- Strategies to optimize retention



Thank You!!!



**The UW
SETTING**



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