Wisconsin Public Psychiatry Network Teleconference (WPPNT)

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WPPNT Reminders

How to join the Zoom webinar

- **Online:** https://dhswi.zoomgov.com/j/1606358142
- **Phone:** 669-254-5252
- Enter the Webinar ID: 160 635 8142#.
  - Press # again to join. (There is no participant ID)

Reminders for participants

- Join online or by phone by 11 a.m. Central and wait for the host to start the webinar. Your camera and audio/microphone are disabled.
- Download or view the presentation materials. The evaluation survey opens at 11:59 a.m. the day of the presentation.
- Ask questions to the presenter(s) in the Zoom Q&A window. Each presenter will decide when to address questions. People who join by phone cannot ask questions.
- Use Zoom chat to communicate with the WPPNT coordinator or to share information related to the presentation.

- Participate live or view the recording to earn continuing education hours (CEHs). Complete the evaluation survey within two weeks of the live presentation and confirmation of your CEH will be returned by email.
- A link to the video recording of the presentation is posted within four business days of the presentation.
- Presentation materials, evaluations, and video recordings are on the WPPNT webpage: https://www.dhs.wisconsin.gov/wppnt/2022.htm.

RESEARCH INTO PSYCHEDELIC COMPOUNDS FOR SUBSTANCE USE DISORDERS

Randall Brown MD, PhD, DFASAM
WPPNT Learning Community
August 25, 2022

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

School of Medicine
and Public Health
UNIVERSITY OF WISCONSIN-MADISON

Disclosures

- Research activity supported in part by Usona Institute, Heffter Research Institute, Multidisciplinary Association for Psychedelic Studies

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Thank you!!

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Usona Institute

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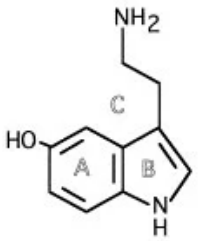
Significance

- Substance use disorders (SUDs) are common
  - 15-20% lifetime prevalence in general U.S.
  - 30+% in primary care/hospital samples
- Cost estimates range $200-700 billion
- < 10% access needed treatment
- Challenges in current treatments
  - Relapse 40-90% (3 mo-2 yr)
  - Treatment retention (~40-50%)

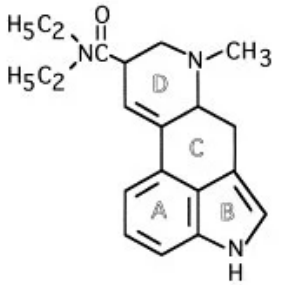
National Survey on Drug Use & Health 2019
NIDA Drug Addiction Treatment Outcomes Study (e.g. Schoenthaler et al 2015. J Reward Deficienc)
Andersson et al 2019. Addict Beh.

Classic Psychedelics

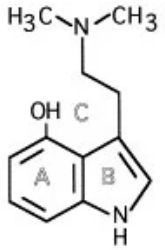
- Common site of action at $5HT_{2A}$ receptors
  - Subj effects blocked by ketanserin
- "Mystical" or "transformative" experience
  - Ineffability
  - Noetic quality/"special knowledge"
  - Conscious unity/ego dissolution
  - Time/space transcendence
  - Deeply felt positive mood
  - Sense of sacredness



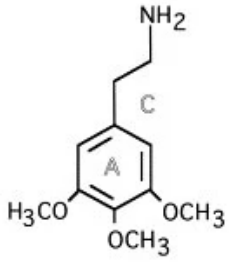
5-HT



LSD



psilocin



mescaline

Aghajanian G 1999. Neuropsychopharm

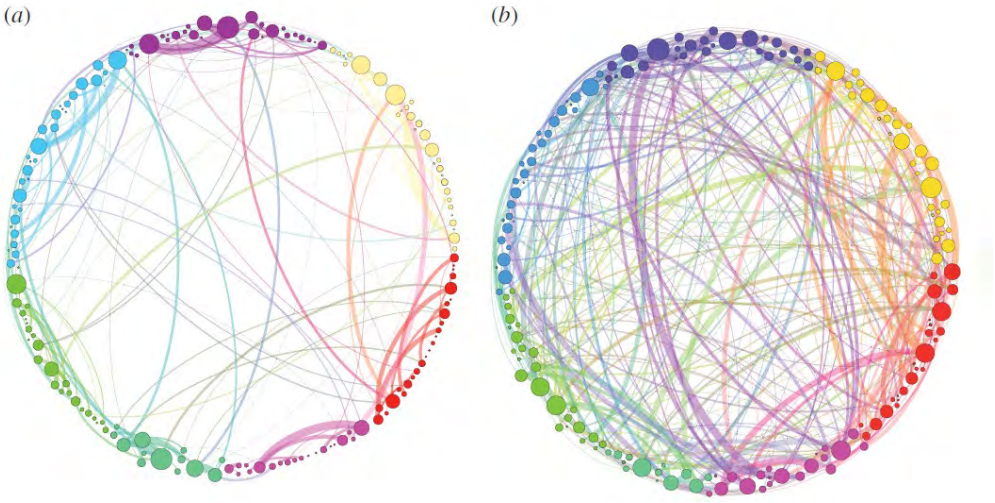
Richards WA. 2018. *Sacred Knowledge: Psychedelics & Religious Experience*

Theoretical Basis for Consideration of Psychedelics

- Cathartic emotional experience
- Mystical/spiritual experience
  - "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
- Awe
- 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 psychologic distress, past year suicidal thinking, past-year suicidal planning, or past-year suicide attempt
  - Decreased rate of supervision failure among criminal justice-involved

Krebs & Johanssen 2013. PLoS One
Hendricks et al 2015. J Psychopharm
Hendricks et al 2014. J Psychopharm

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

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<u>Set</u>: person's psychological state

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

<u>Setting</u>: environment & context

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

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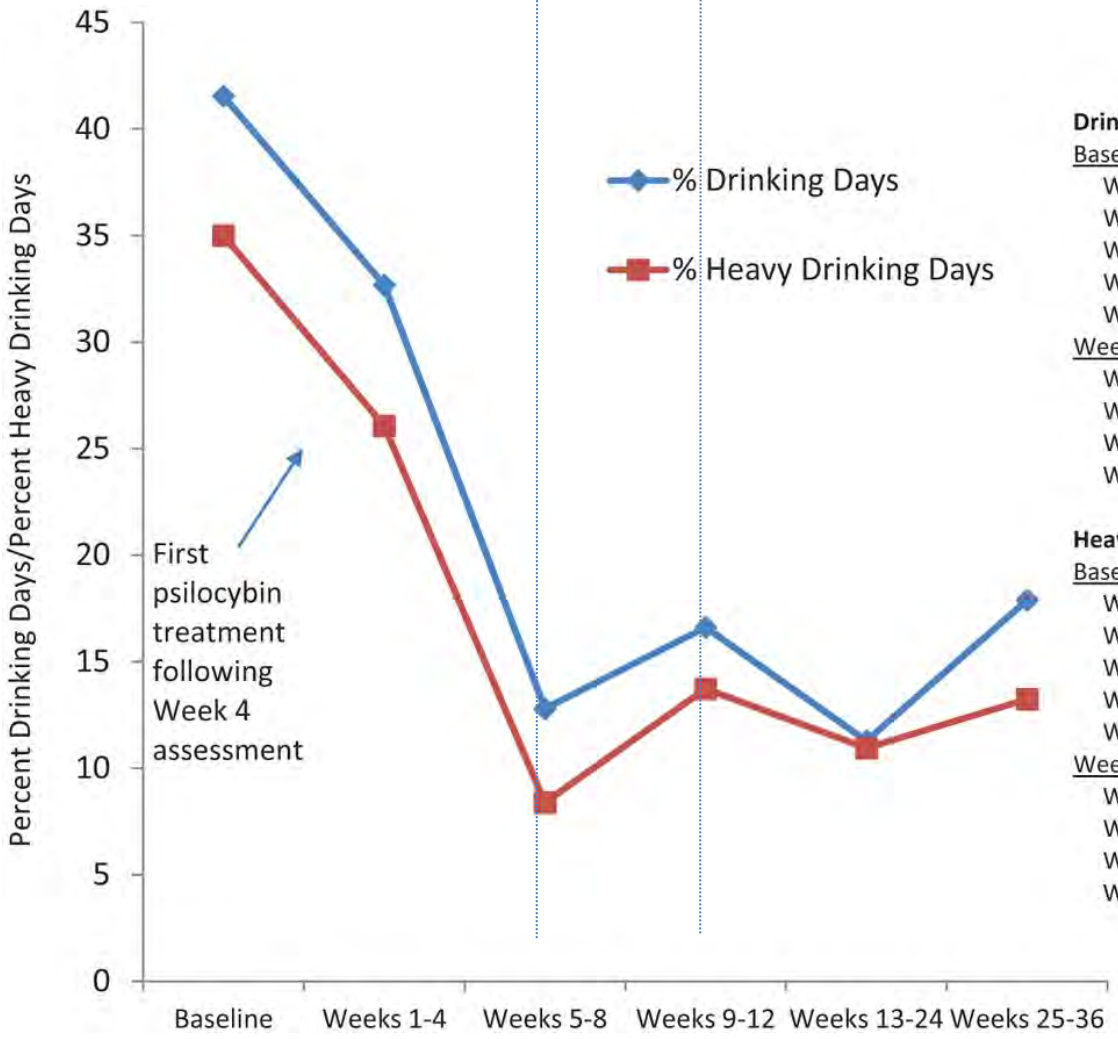
Psilocybin Session

- 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 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	$p = .164$	$d = 0.490$
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	$p = .018$	$d = 1.040$

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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 OPIOID USE DISORDER INVESTIGATION (HOUDI)

Current OUD Treatment

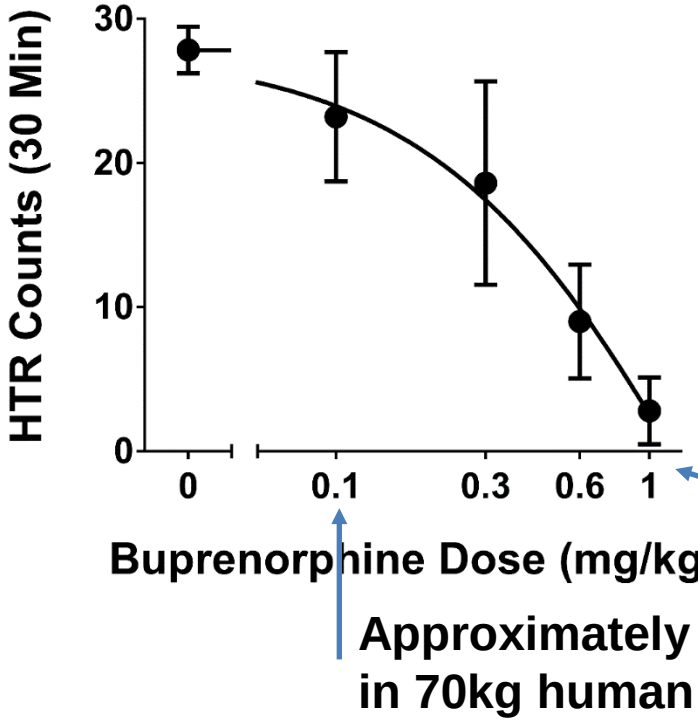
- Medication (MOUD) = first line
  - Methadone
  - Buprenorphine
  - Naltrexone (less so)

- Challenges with MAT
  - Geographic access (methadone)
  - Capacity (methadone, buprenorphine)
  - Treatment retention and ongoing substance use

HOUDI: Rationale

- Treatment retention and ongoing use during treatment is a major issue
- Without medication for OUD (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

Data from Mouse Model



Halberstadt, A. 2018. Unpublished data.

HOUDI: Proposed Study Aims

Primary

- In patients with OUD in early or sustained remission, characterize effects of adding psilocybin to a stable 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

HOUDI: Methods

- Single arm, open label n = 10
- Recruitment via local MOUD prescribers
- Key Inclusion Criteria
  - age 21-55 years
  - OUD in early or sustained recovery
  - ≤ 20mg daily buprenorphine

608-228-5325 (Amelia Baltes, Julia Malicki)

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HOUDI: Methods

- Key Exclusion Criteria
  - creatinine clearance < 30ml/min
  - personal history of primary psychotic disorder (SCID)
  - 1st or 2nd degree relative with primary psychotic disorder
  - urine drug testing
  - cardiac conduction abnormality/ischemic heart disease
  - uncontrolled hypertension
  - physical exam findings of concern

Methods

- 2 dosing sessions separated by 4 weeks--(1) 25 mg, (2) 25 or 50mg
  - Serial ECGs
  - Respiratory monitoring
  - Clinical Opioid Withdrawal Scale
- Overnight on UW Clinical Research Unit
- Weekly study follow-up visits (exploratory measures, AEs)
- Other secondary/exploratory measures (e.g. opioid craving, use, QoL) baseline, pre-dosing, and week 9

Future Related Work

- Randomized, active placebo-controlled trial
- n = 20
  - Active opioid use disorder
  - Buprenorphine initiation/stabilization as part of study
  - Set/setting
  - 2 dosing sessions (25mg, 40mg) 4 weeks apart
- Primary outcomes
  - Retention
  - Opioid use (weekly urine testing, self-report)

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Revive Therapeutics

PSILOCYBIN IN THE TREATMENT OF METHAMPHETAMINE USE DISORDER

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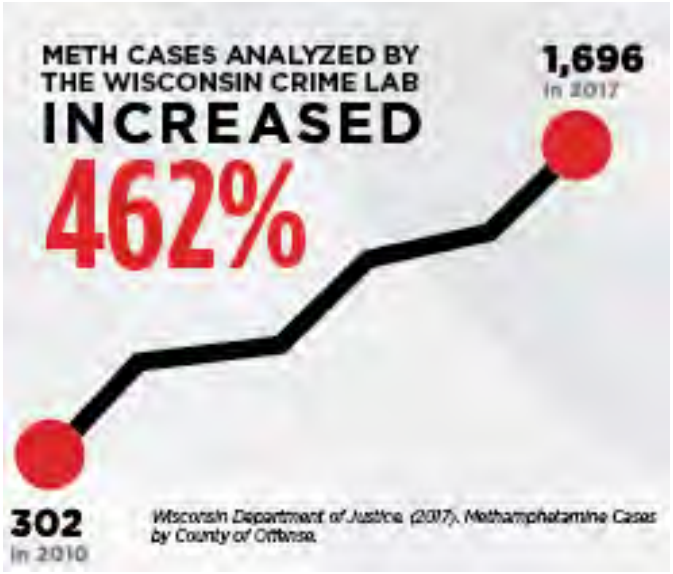
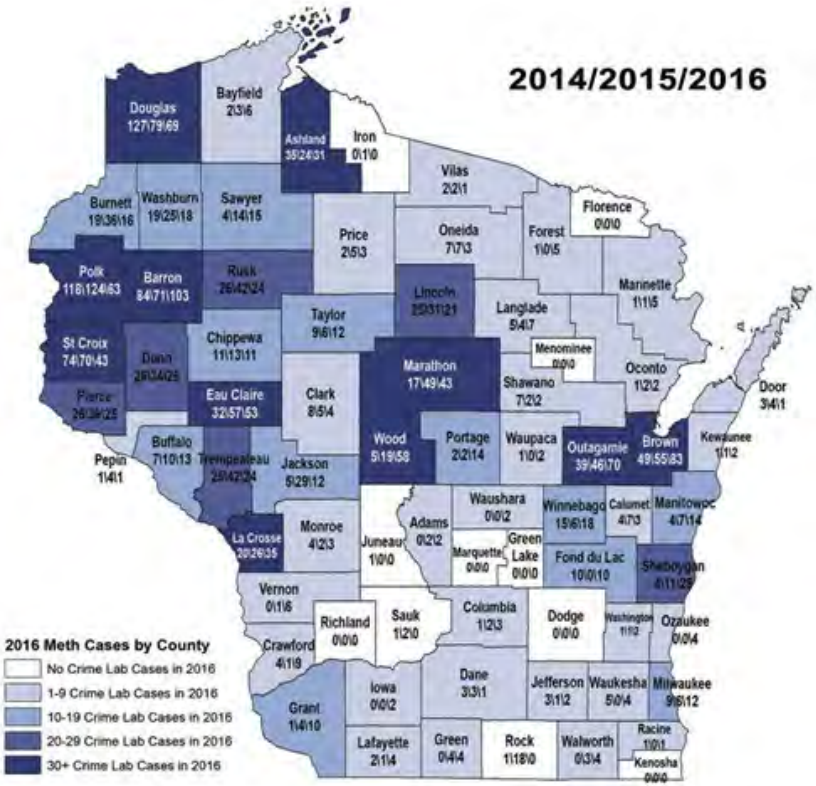
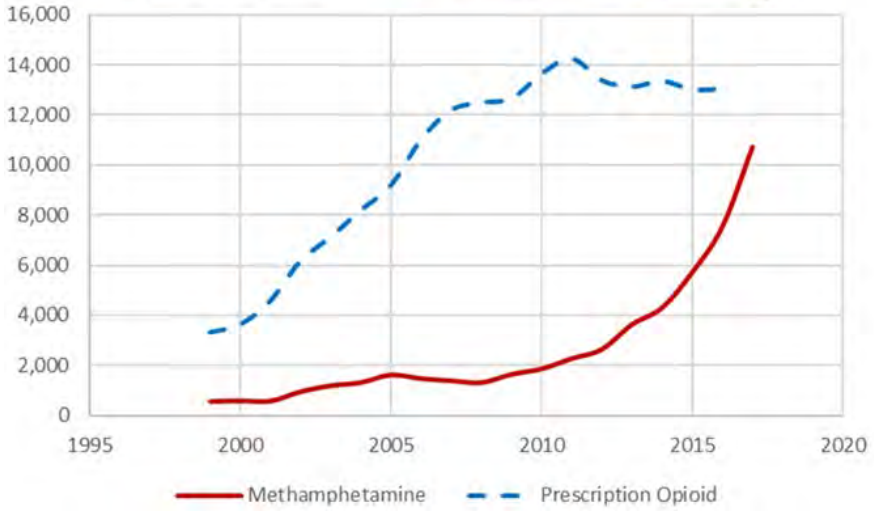
About [1 in every 5](#) drug cases at the Wisconsin State Crime Labs involved meth







CDC. https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

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)

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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)

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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

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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

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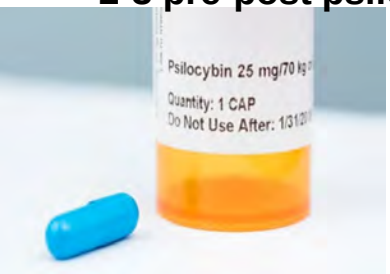
Design

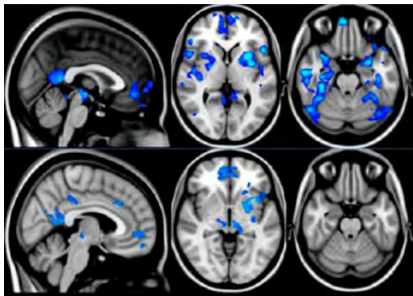
1 or 2 oral doses of psilocybin

Prep	fMRI # 1	Psilocybin 25 mg.	CRU	Next Morning Integration	fMRI # 2	Weekly Therapy

Psilocybin 25 v 40 mg	CRU	Next Morning Integration	fMRI # 3	Weekly therapy	1 month	2 month
Proceed to 1- and 2- month follow-up						

- N= 12
- Diagnosis of mild or moderate methamphetamine use disorder with meth use on less than 16 days in the past month.
- Therapy informed by motivational interviewing, mindfulness, emotion-focused/somatic based approaches.
- 25 mg and/or 40 mg of psilocybin
- Determination of dose progression based combination of team assessment and participant
- 2-3 pre-post psilocybin fMRI scans





Thank You!!!

The UW SETTing

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