

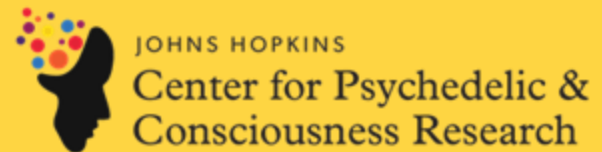


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# Psychedelics Overview: Psilocybin and Ibogaine

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Sandeep Nayak, MD  
Assistant Professor  
Johns Hopkins Center for Psychedelic and Consciousness Research



# Disclosures

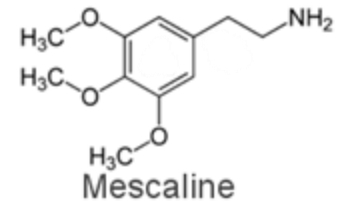
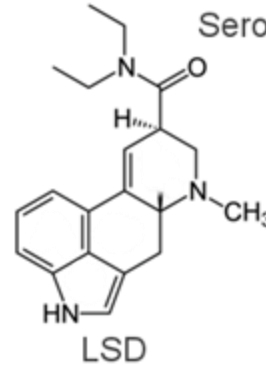
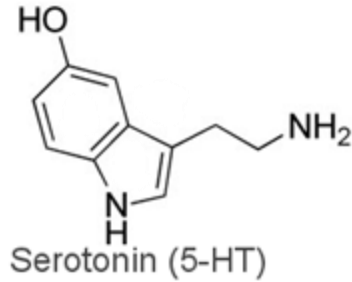
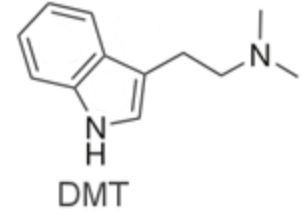
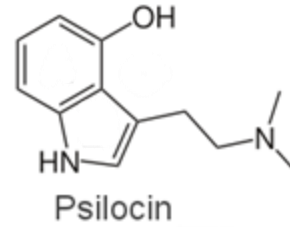
- Consulted for Resilient Pharmaceuticals
- Consulting for MMS Holdings a CRO

## **OVERVIEW**

- 1. Ultrarapid background**
- 2. Results from RCTs**
- 3. Ongoing studies at Hopkins**
- 4. Ibogaine**

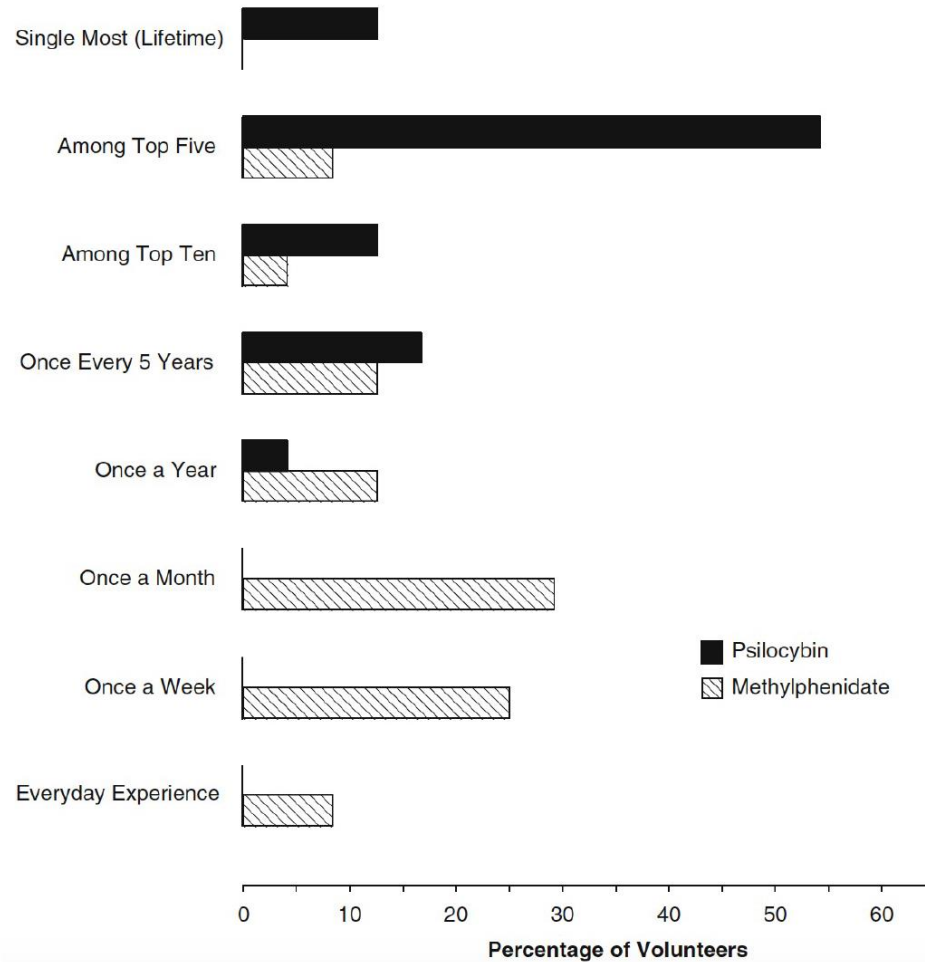
# Background

- What is a psychedelic?
- Trials are drug + psychological support
- Method is surprisingly similar across diverse conditions
- Psilocybin in Phase 3 trials for MDD



# How Personally Meaningful Was the Experience?

(Rated 2 months after session, N=24)

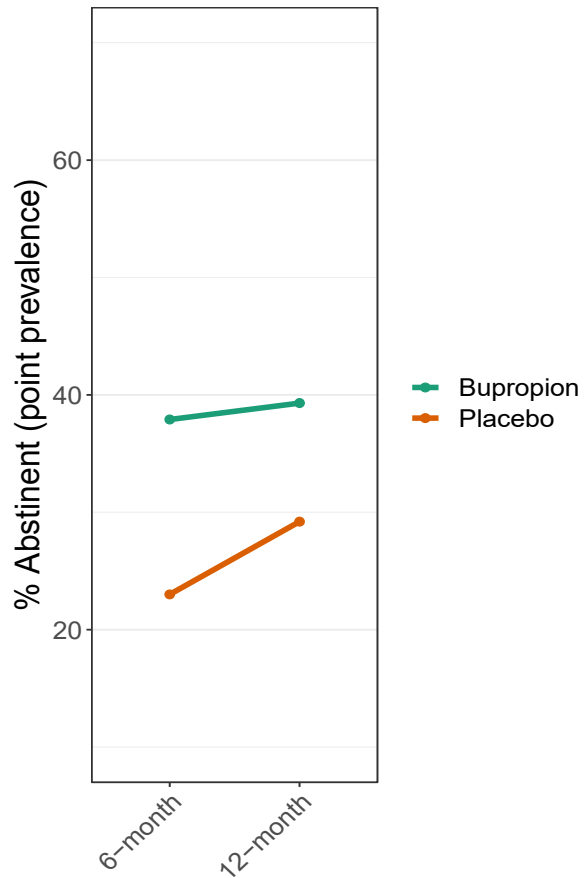


## 2. Completed RCTs

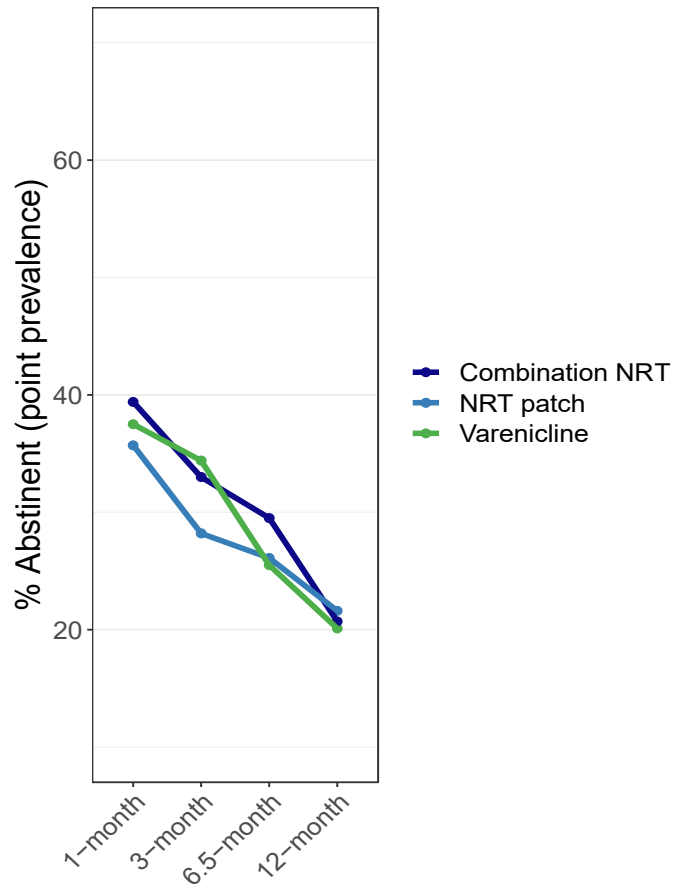
- Tobacco use disorder
- Alcohol use disorder
- Opioid Use disorder

# Tobacco use disorder

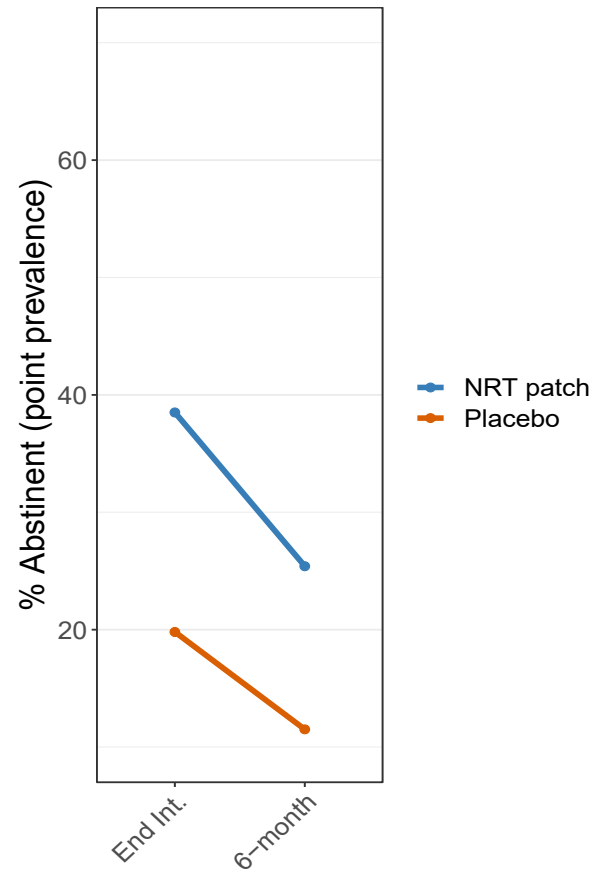
Paszek et al., 2017  
Meta-analysis:  
5 bupropion trials



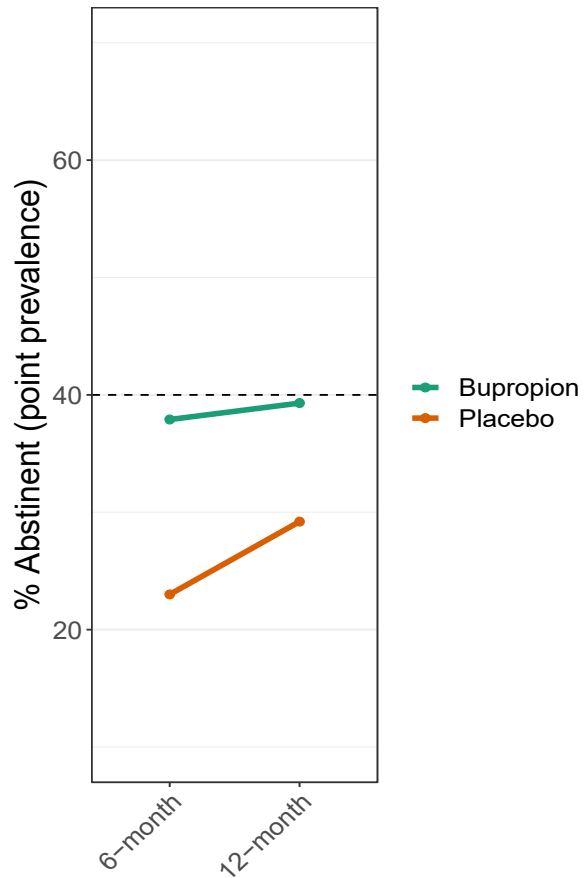
Baker et al., 2016  
Varenicline vs. NRT



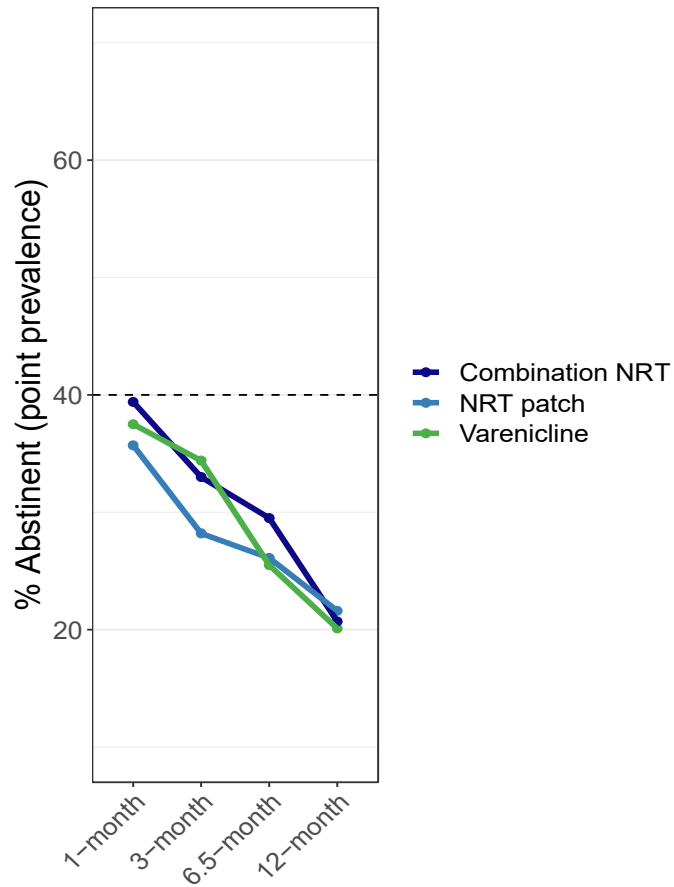
Fiore et al., 1994  
Meta-analysis:  
13 nicotine patch trials



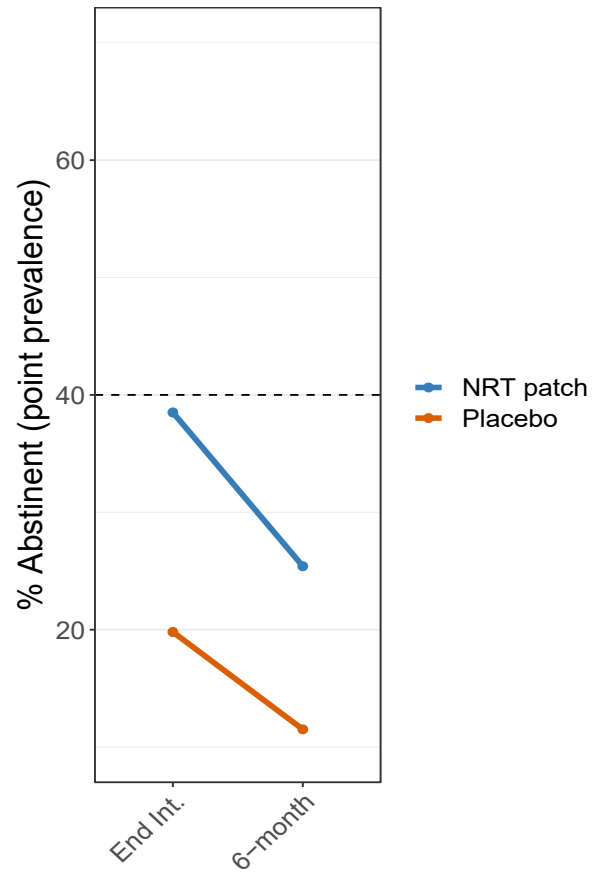
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Baker et al., 2016  
Varenicline vs. NRT



Fiore et al., 1994  
Meta-analysis:  
13 nicotine patch trials



# Ongoing open-label comparative effectiveness trial – tobacco smoking

Active Treatment (weeks 1-13)



# Ongoing open-label comparative effectiveness trial – tobacco smoking

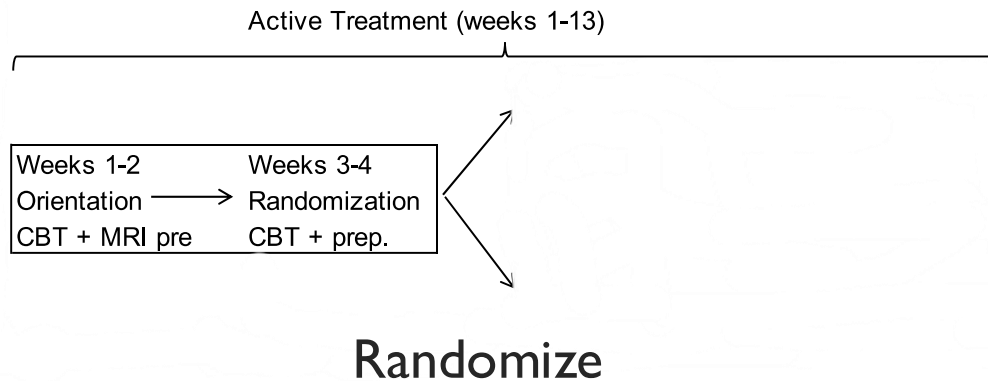
Active Treatment (weeks 1-13)



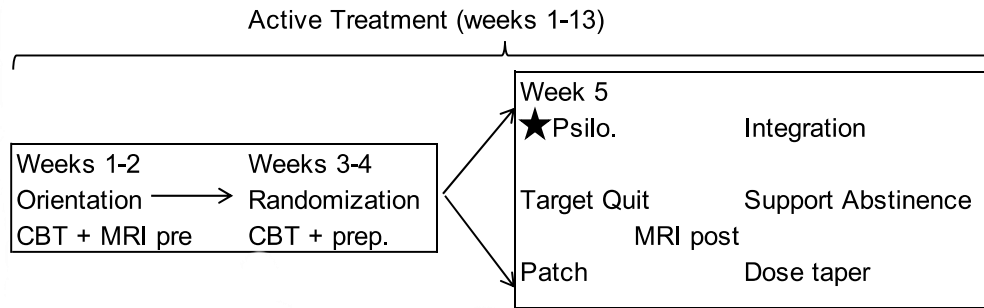
Weeks 1-2 Orientation CBT + MRI pre	→	Weeks 3-4 Randomization CBT + prep.
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4 weeks CBT

# Ongoing open-label comparative effectiveness trial – tobacco smoking

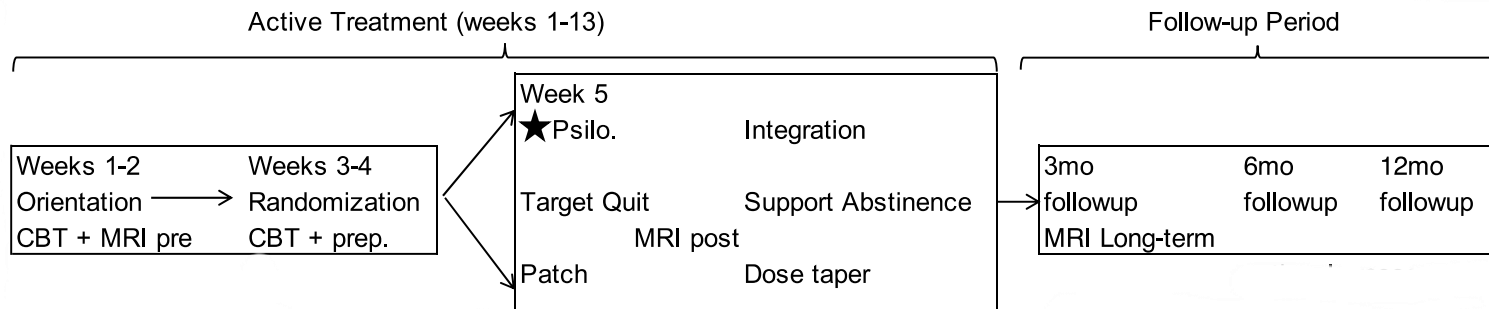


# Ongoing open-label comparative effectiveness trial – tobacco smoking



Psilocybin vs Nicotine patch

# Ongoing open-label comparative effectiveness trial – tobacco smoking

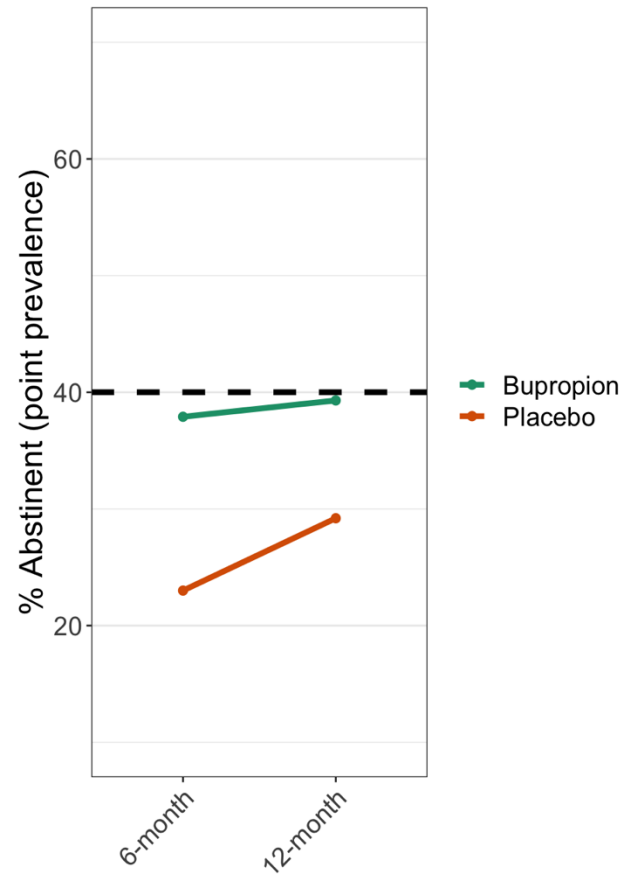


Long-term follow-up

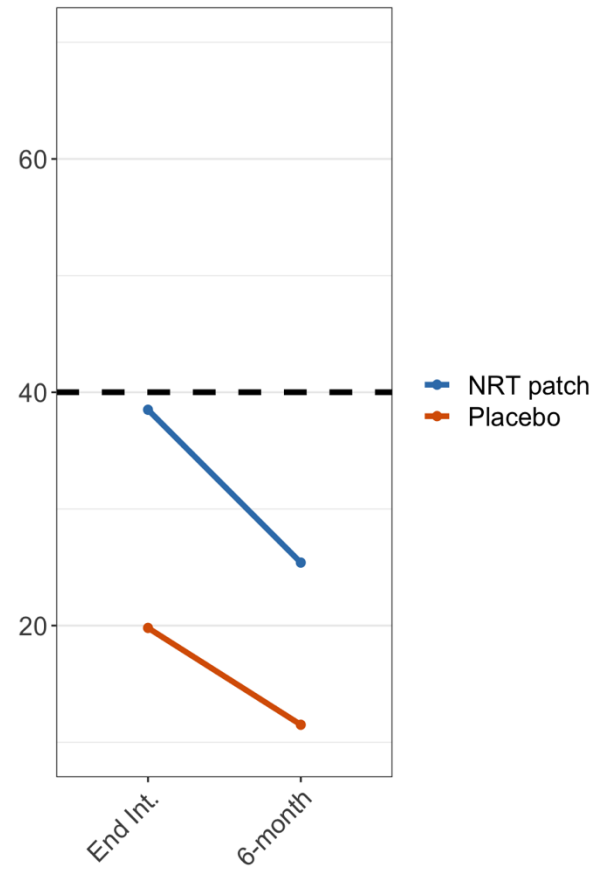
# Baseline smoking characteristics

- About 1 pack a day
- Mean duration 26 years
- Mean 7 quit attempts

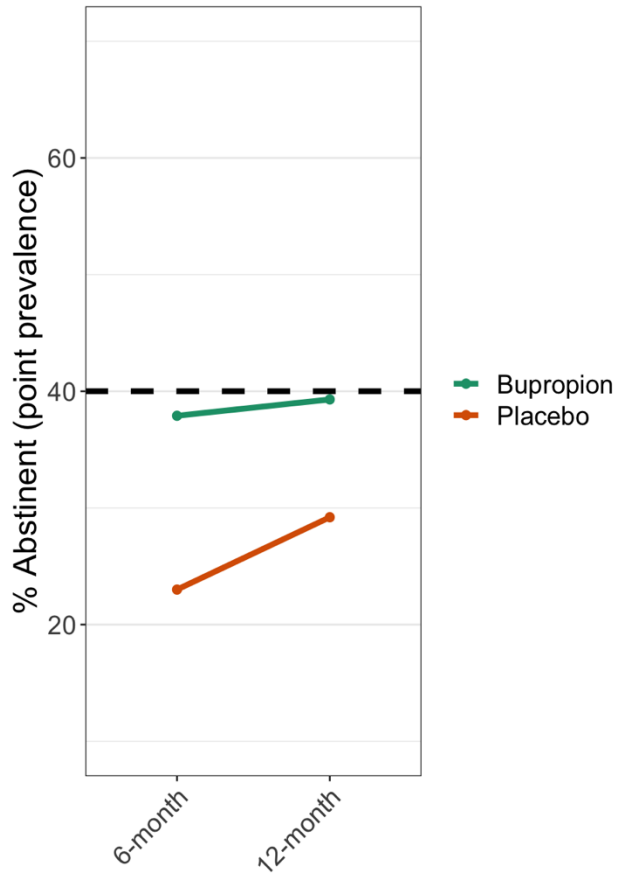
Paszek et al., 2017  
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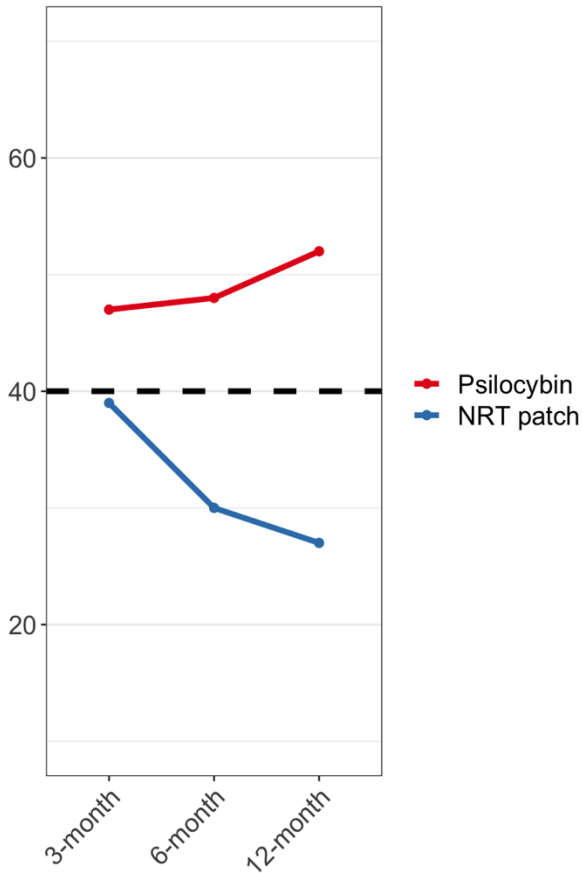
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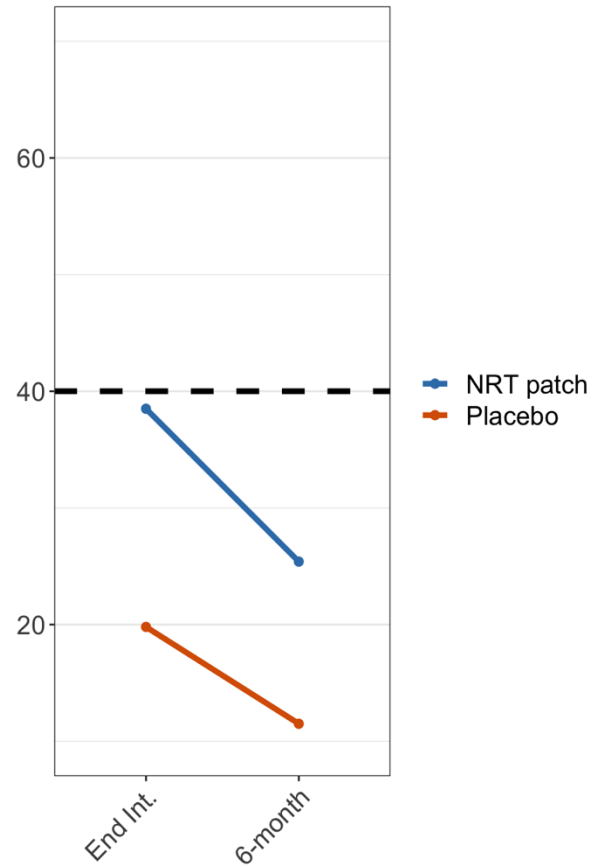
Paszek et al., 2017  
Meta-analysis:  
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Hopkins, ongoing



Fiore et al., 1994  
Meta-analysis:  
13 nicotine patch trials



# **Alcohol use disorder**

# Bogenschutz et al., (2022)

JAMA Psychiatry | [Original Investigation](#)

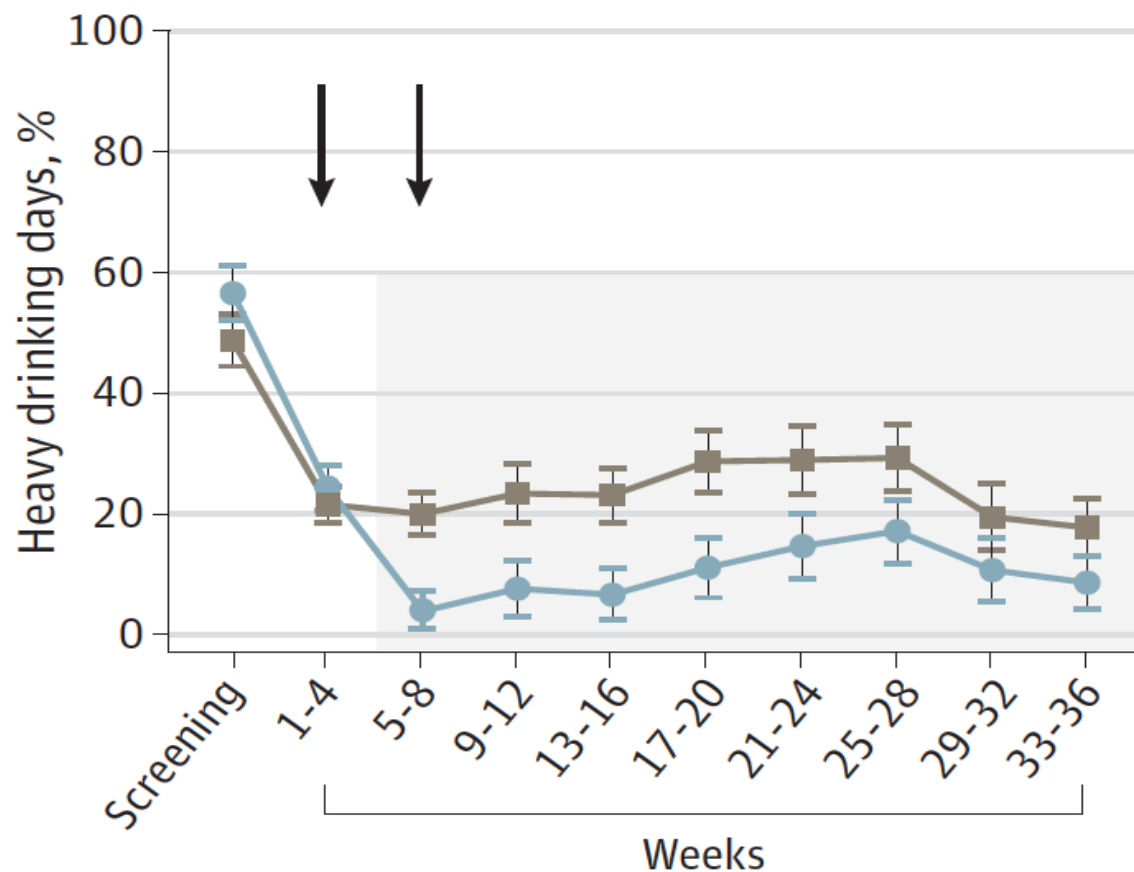
Percentage of Heavy Drinking Days Following  
Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment  
of Adult Patients With Alcohol Use Disorder  
A Randomized Clinical Trial

RCT (N = 95)

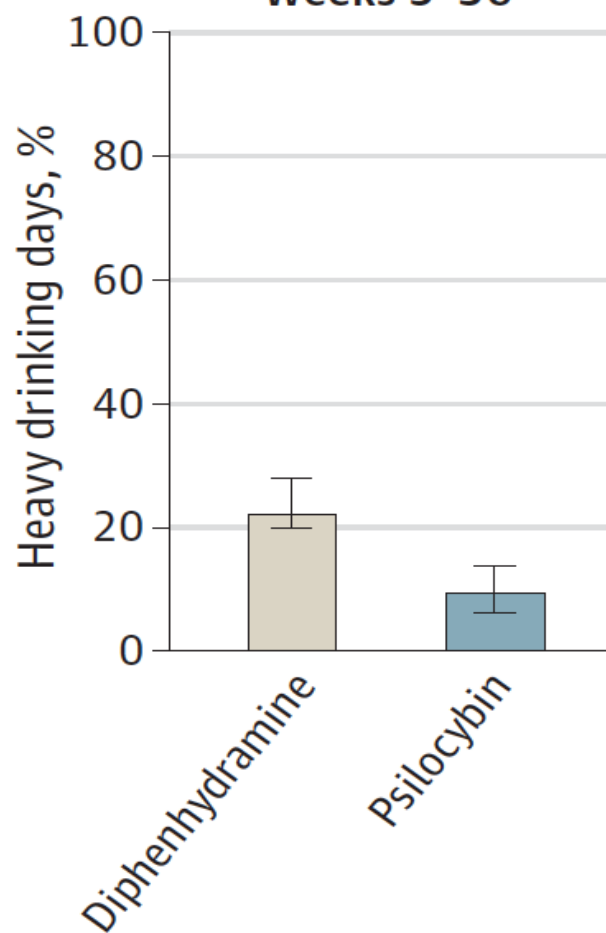
- Psilocybin 25mg/70kg - 40mg/70kg x 2 vs
  - Diphenhydramine 50mg-100mg x 2
  - Psychological support throughout for both
- Primary outcome % heavy drinking days over 32 wk period

Baseline	%
% Drinking days	75%
% Heavy drinking days	53%
Drinks per day	4.8
Drinks per drinking day	7.1
Years dependent	14.2

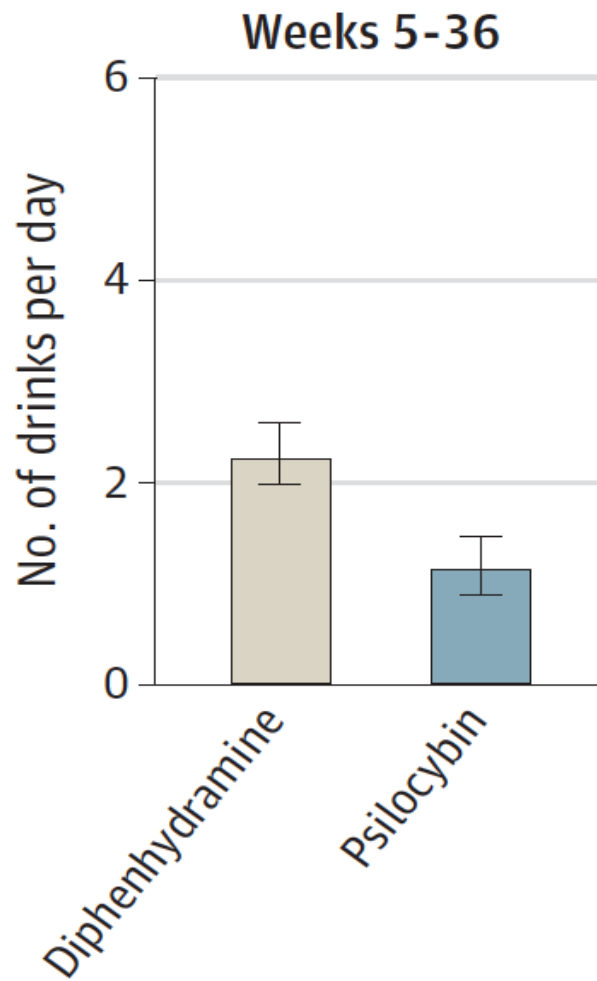
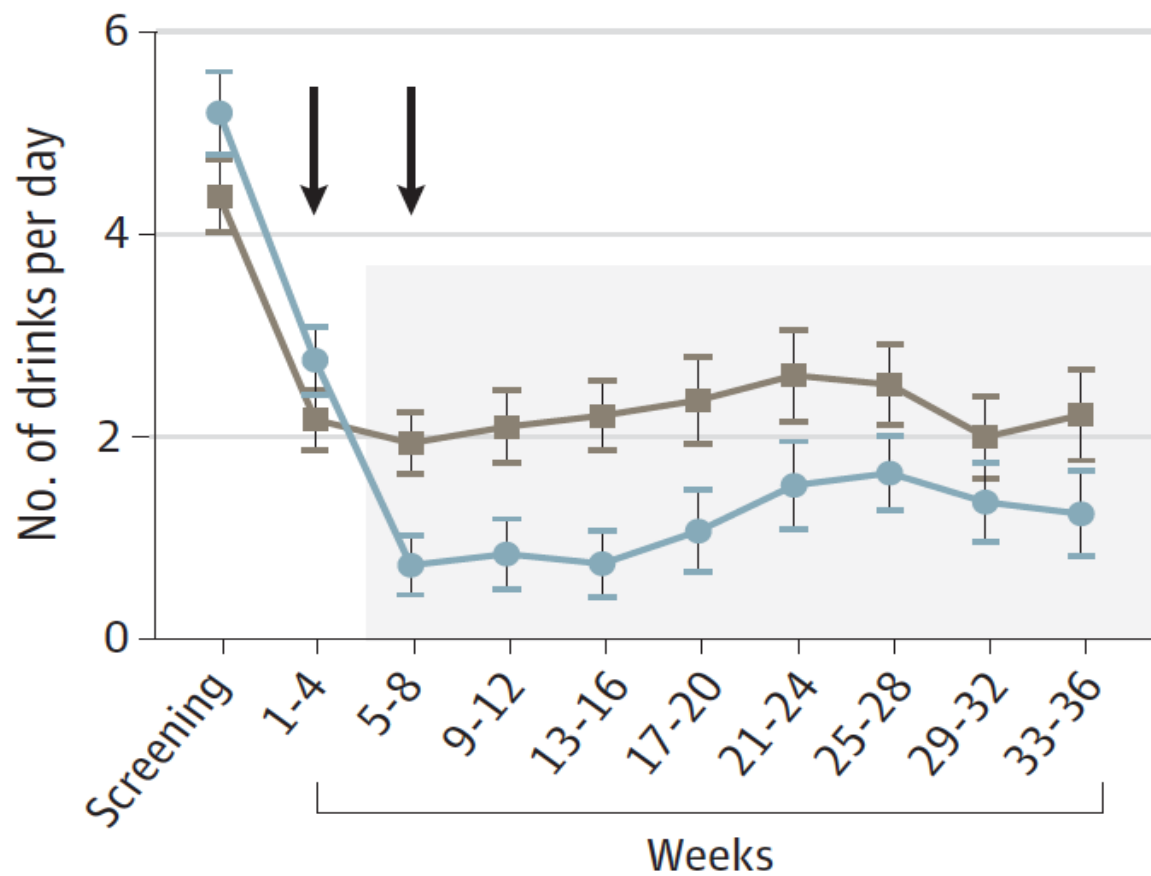
### A Percent heavy drinking days



### Weeks 5-36



**C** Drinks per day




# Bogenschutz et al., (2022)

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


- Abstinence
  - Psilocybin: 48%
  - Control: 24%

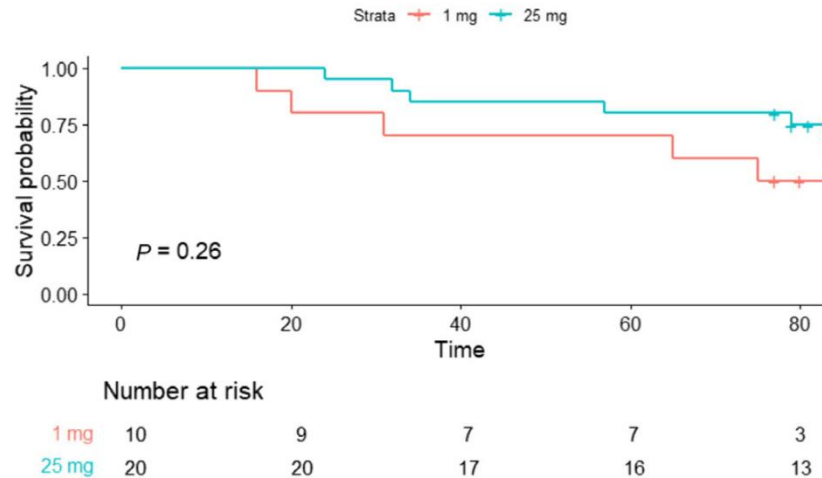
# Psilocybin in alcohol use disorder and comorbid depressive symptoms: Results from a feasibility randomized clinical trial

Amandine Luquiens<sup>1</sup>  | Dahbia Belahda<sup>2</sup> | Carine Graux<sup>2</sup> | Noe Igounenc<sup>1</sup> |  
Chris Serrand<sup>3</sup> | Paul Rochefort<sup>1</sup> | Thibault Mura<sup>3</sup> | Felix Sergent<sup>2</sup>

- N = 30 RCT
- 25mg vs 1 mg; 2 doses
- Feasibility primary outcome

# Psilocybin in alcohol use disorder and comorbid depressive symptoms: Results from a feasibility randomized clinical trial

Amandine Luquiens<sup>1</sup>  | Dahbia Belahda<sup>2</sup> | Carine Graux<sup>2</sup> | Noe Igounenc<sup>1</sup> |  
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**FIGURE 6** Survival curve for the event first heavy drinking day in the two groups.

# Psilocybin-assisted therapy for relapse prevention in alcohol use disorder: a phase 2 randomized clinical trial

*Nathalie M. Rieser,<sup>a,\*</sup> Raoul Bitar,<sup>a</sup> Simon Halm,<sup>a</sup> Christina Rossgoderer,<sup>a</sup> Ladina P. Gubser,<sup>a</sup> Maeva Thévenaz,<sup>a</sup> Yara Kreis,<sup>a</sup> Robin von Rotz,<sup>a</sup> Carlos Nordt,<sup>a</sup> Monika Visentini,<sup>a</sup> Flora Moujaes,<sup>a</sup> Etna J. E. Engeli,<sup>a</sup> Andres Ort,<sup>a</sup> Erich Seifritz,<sup>a</sup> Franz X. Vollenweider,<sup>a</sup> Marcus Herdener,<sup>a,b</sup> and Katrin H. Preller<sup>a,b</sup>*

- N = 37 RCT, mostly severe
  - Intended N of 60
- 25mg vs placebo; single-dose

# Psilocybin-assisted therapy for relapse prevention in alcohol use disorder: a phase 2 randomized clinical trial

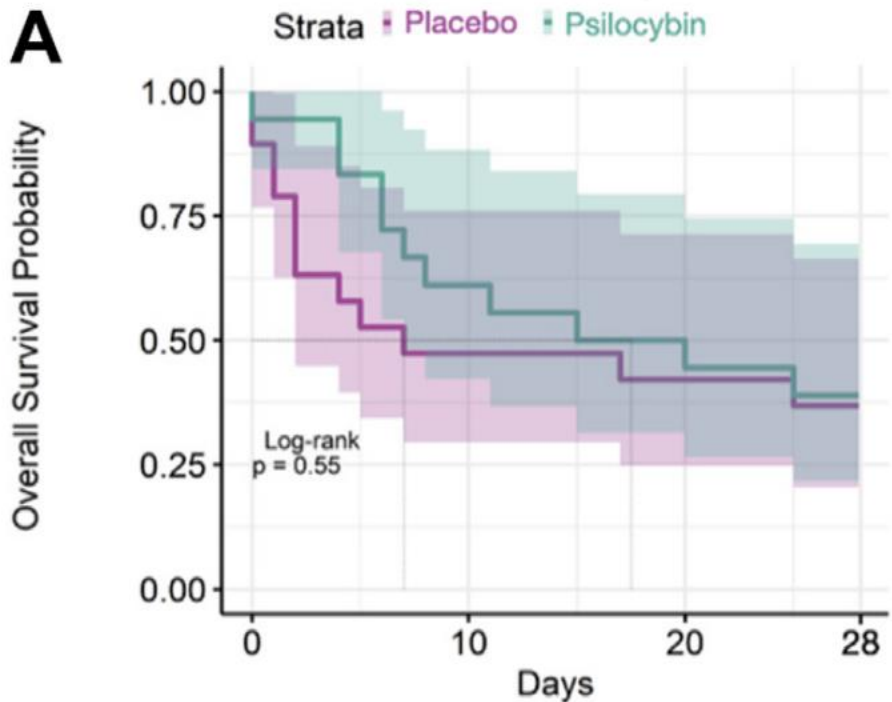


*Nathalie M. Rieser,<sup>a,\*</sup> Raoul Bitar,<sup>a</sup> Simon Halm,<sup>a</sup> Christina Rossgoderer,<sup>a</sup> Ladina P. Gubser,<sup>a</sup> Maeva Thévenaz,<sup>a</sup> Yara Kreis,<sup>a</sup> Robin von Rotz,<sup>a</sup> Carlos Nordt,<sup>a</sup> Monika Visentini,<sup>a</sup> Flora Moujaes,<sup>a</sup> Etna J. E. Engeli,<sup>a</sup> Andres Ort,<sup>a</sup> Erich Seifritz,<sup>a</sup> Franz X. Vollenweider,<sup>a</sup> Marcus Herdener,<sup>a,b</sup> and Katrin H. Preller<sup>a,b</sup>*

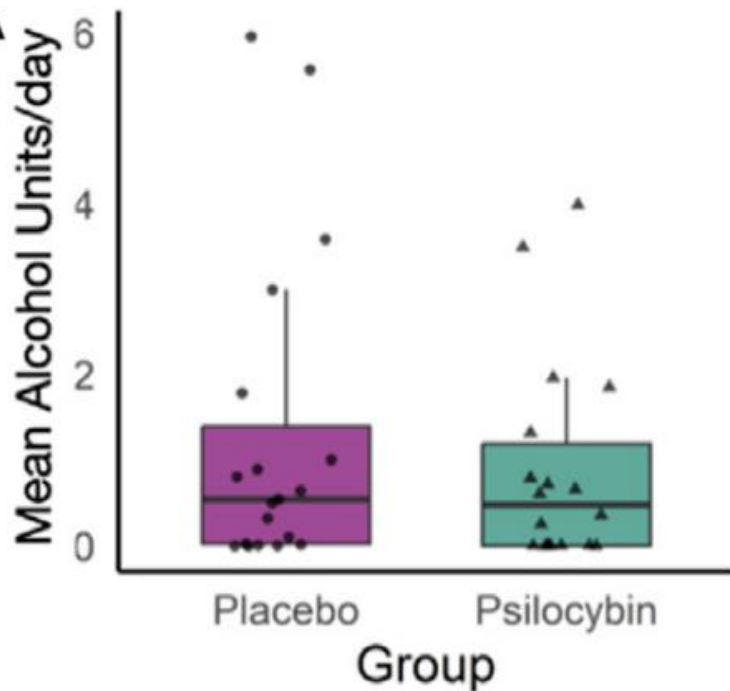
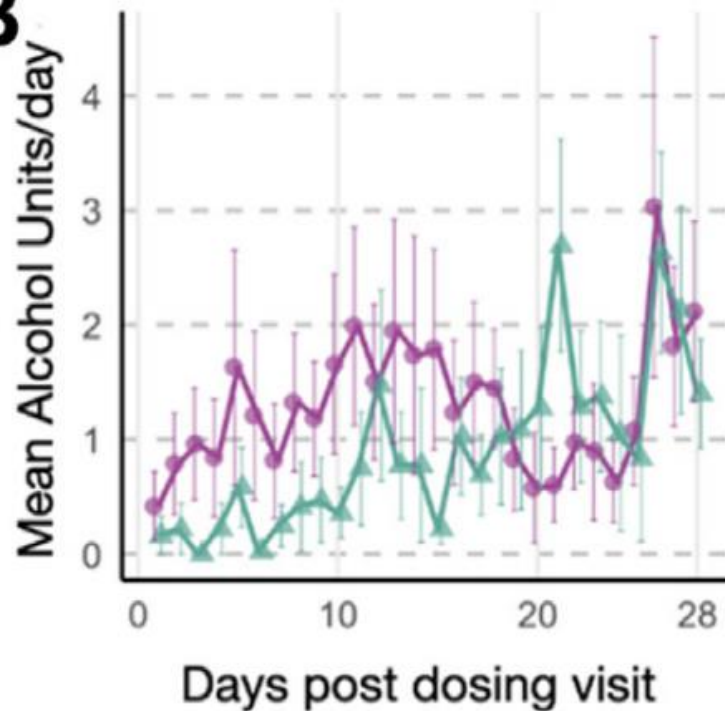
- Primary outcome
  - Abstinence
  - Mean drinks/day at 4 weeks

# Abstinence: 4-week follow-up

## A



## Mean alcohol use: 4-week follow-up

**A**

**B**


# Opioid use disorder

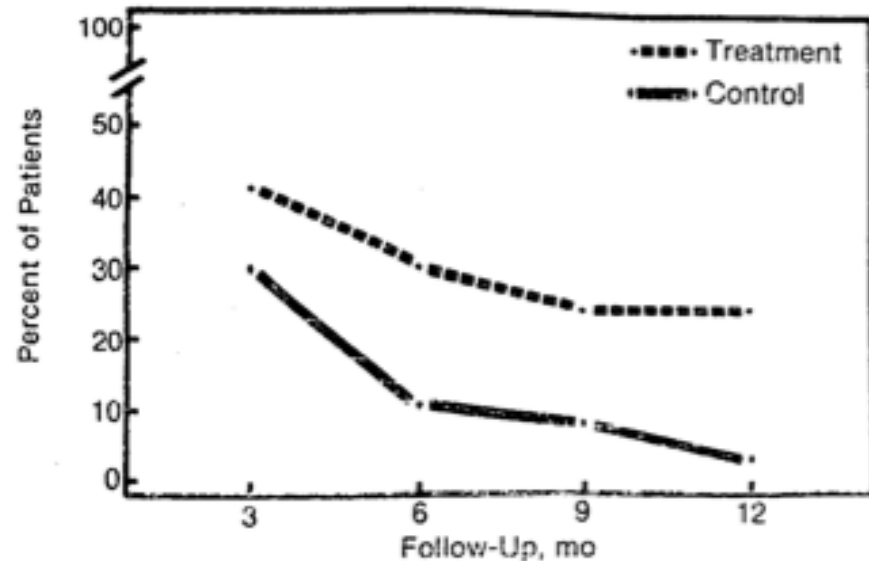
- N = 74
- Pts paroled in an outpt tx program with daily urine tox, weekly group tx
- Single dose LSD plus substantial psychological support prior VS TAU
- Violation of tx program rules leads to reincarceration

## Residential Psychedelic (LSD) Therapy for the Narcotic Addict

A Controlled Study

Charles Savage, MD, O. Lee McCabe, PhD, Baltimore

Fig 1.—Percent of patients maintaining total abstinence at 3-, 6-, 9-, and 12-month follow-up.



### **3. Ongoing RCTs**

- MDD-AUD
- OUD

# Ongoing RCTs – actively recruiting

- MDD-AUD – PI: Barrett
- OUD – PI: Nayak

# MDD-AUD

- DBRCT (N = 90)
- Single dose of psilocybin (25mg) vs placebo with 3-month open-label psilocybin 25mg
- Standard psychological support
- Motivational interviewing intervention

# MDD-AUD

## Inclusion:

- GRID-HAMD  $\geq 16$
- At least 4 non-drinking days per month
- Concurrent antidepressant treatment okay

## Exclusion:

- Suicide attempt
- Bipolar or psychotic disorder

# **BIPOD: Buprenorphine Induction with Psilocybin for Opioid use Disorder**

- Screening
- Buprenorphine induction
- 3-4 preparation sessions
- 1 psilocybin session (30mg or 1mg)
- Follow-up sessions at day 1 and weeks 2, 4, 6, and 8 post-session
- 8-week abstinence primary outcome

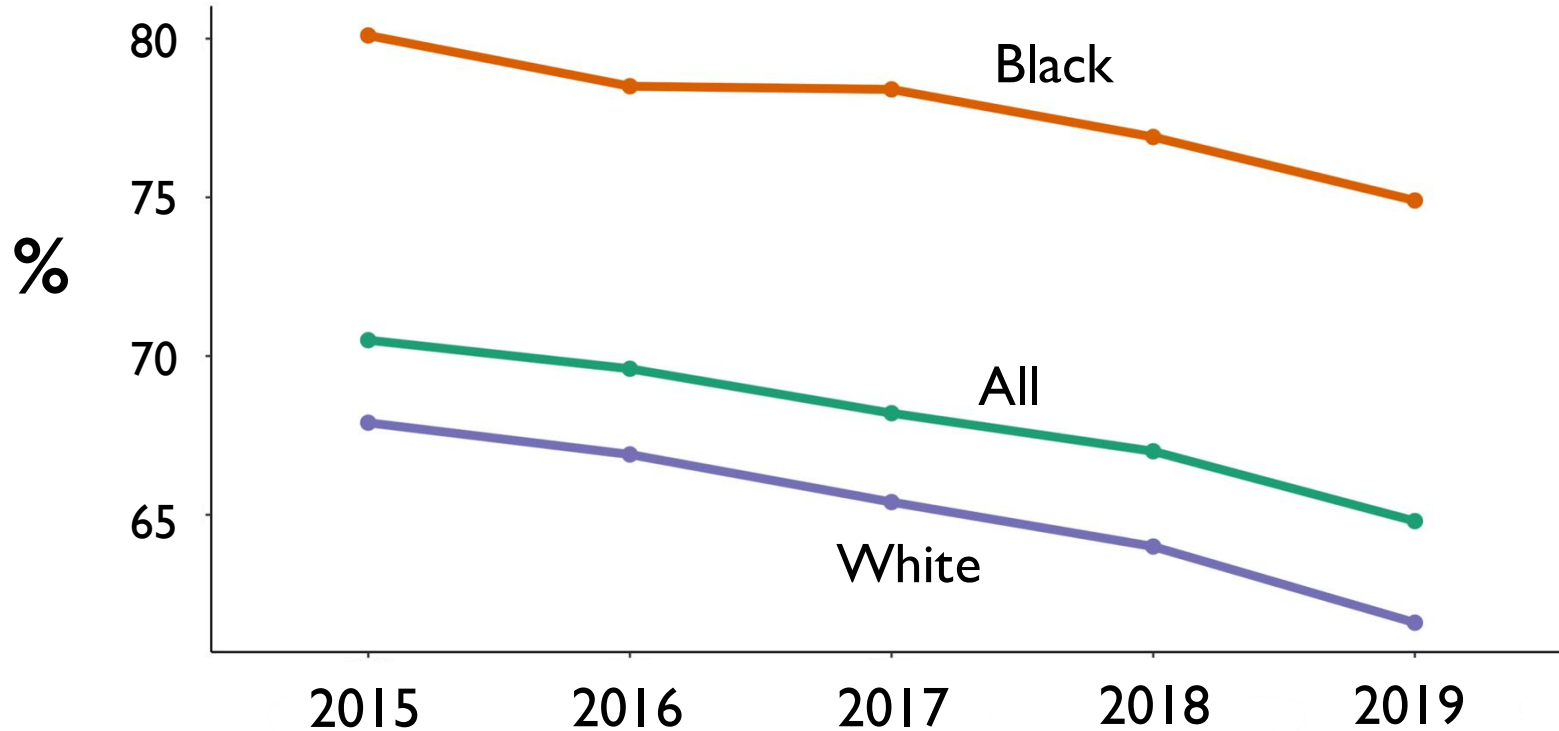
# BIPOD Recruitment

- Enrolled 28
- 12 drop-outs prior to starting prep
- Dosed 14

# BIPOD Demographics

- 40% black
- Half unemployed
- 45% income < \$10k
- 40% prior incarceration
  - Mean (SD) 3.3 (6.7) years incarcerated
- 55% psychedelic experienced
  
- 5 (25%) incarcerated during the study
- 2 serious overdoses (hospitalized)

# Perception of Great Risk of trying LSD once or twice



# Psilocybin OUD future directions

- Large RCTs
- Delivered in variety of treatment settings, in combination with various treatments

# Other indications

- Psilocybin cocaine RCT completed
- Pilots for methamphetamine

# Ibogaine

- Anecdote
- Pharmacology
- Research
- Future

# Ibogaine anecdote

- Atypical ‘psychedelic’
- Suppresses opioid withdrawal/craving
- Resets opioid tolerance
- Long duration of drug action
- Long duration of therapeutic effects
  
- Deaths (cardiac, opioid overdose)
  
- Typically administered as a “flood dose” with substantial subjective effects

# Ibogaine pharmacology

- Ibogaine  $\xrightarrow{\text{CYP2D6}}$  Noribogaine
- Dirty drug
  - SERT reuptake inhibition
  - $\kappa$ -opioid partial agonist (like salvinorin A)
  - $\mu$ -opioid agonist (though noribogaine possibly an antagonist; Maillet 2015).
  - NMDA antagonist (like ketamine)
  - $\alpha 3\beta 4$  nicotinic acetylcholine antagonist
  - hERG ( $K^+$  channel) blockade  $\rightarrow$  QT prolongation  $\rightarrow$  death

# Ibogaine pharmacology

- Ibogaine  $\xrightarrow{\text{CYP2D6}}$  Noribogaine
- Half-life:
  - Ibogaine ~7 hours
  - Noribogaine 28-49 hours (Glue et al., 2015)

# Ibogaine research

- Phase I study in the US stopped after pt in Netherlands trial died
- No published RCTs

# Ibogaine subjective effects (“flood dose”)

- **Acute Phase (0–8 hrs)**
  - Begins within 1–3 hours of ingestion, lasting 4–8 hours
  - Characterized by intense visionary or dream-like states
  - Often involves vivid visual imagery, especially with eyes closed
- **Evaluative Phase (4–20 hrs)**
  - Reflective, emotionally neutral tone
  - Patients introspectively process earlier visions
  - Decreased external engagement; focus on internal experiences
- **Residual Stimulation Phase (12–36 hrs)**
  - Diminishing psychoactive effects
  - Mild residual stimulation and insomnia may persist for days
  - Patients reengage with their surroundings

# Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study

Geoffrey E. Noller, Chris M. Frampton & Berra Yazar-Klosinski

- 12-month observational study in New Zealand (N = 14)
- Single-dose ibogaine HCl (25–55 mg/kg) for opioid dependence
- Outcomes measured: withdrawal, opioid use, depression
  
- 10/14 were on methadone

# Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study

Geoffrey E. Noller, Chris M. Frampton & Berra Yazar-Klosinski

- One fatality!
- Urine (% negative/positive/missing):
  - 3 months: 7 negative / 1 positive / 6 missing
    - 50% negative
  - 6 months: 6 negative / 1 positive / 7 missing
    - 43% negative
  - 12 months: 6 negative / 2 positive / 6 missing
    - 43% negative

## Treatment of opioid use disorder with ibogaine: detoxification and drug use outcomes

Thomas Kingsley Brown, PhD<sup>a</sup> and Kenneth Alper, MD<sup>b</sup>

- N = 30 DSM-IV opioid dependence
- Observational, Mexican ibogaine clinic
- Overnight opi abstinence → test dose (3mg/kg)
- “Flood” dose 2-12 hrs post test dose (~4x test dose)
- 3-5mg/kg booster following flood at 1-16hr
- 1-month post-tx 50% reported no opi use

## Treatment of opioid use disorder with ibogaine: detoxification and drug use outcomes

Thomas Kingsley Brown, PhD<sup>a</sup> and Kenneth Alper, MD<sup>b</sup>

<b>Timepoint</b>	<b>% abstinent (of N = 30)</b>
<b>Baseline</b>	0%
<b>1 Month</b>	50%
<b>3 Months</b>	20%
<b>6 Months</b>	37%
<b>12 Months</b>	23%

# **Ibogaine Detoxification Transitions Opioid and Cocaine Abusers Between Dependence and Abstinence: Clinical Observations and Treatment Outcomes**

*Deborah C. Mash<sup>1,2\*</sup>, Linda Duque<sup>1</sup>, Bryan Page<sup>3</sup> and Kathleen Allen-Ferdinand<sup>4</sup>*

- N = 102 opioid dependent patients, St Kitts Ibogaine clinic
- Given morphine to treat w/d
- Single dose ibogaine 8-12 mg/kg
  - 12 hours after last morphine dose
  
- Dramatic improvement in w/d at 24 hours post-ibogaine
- Large decreases in craving

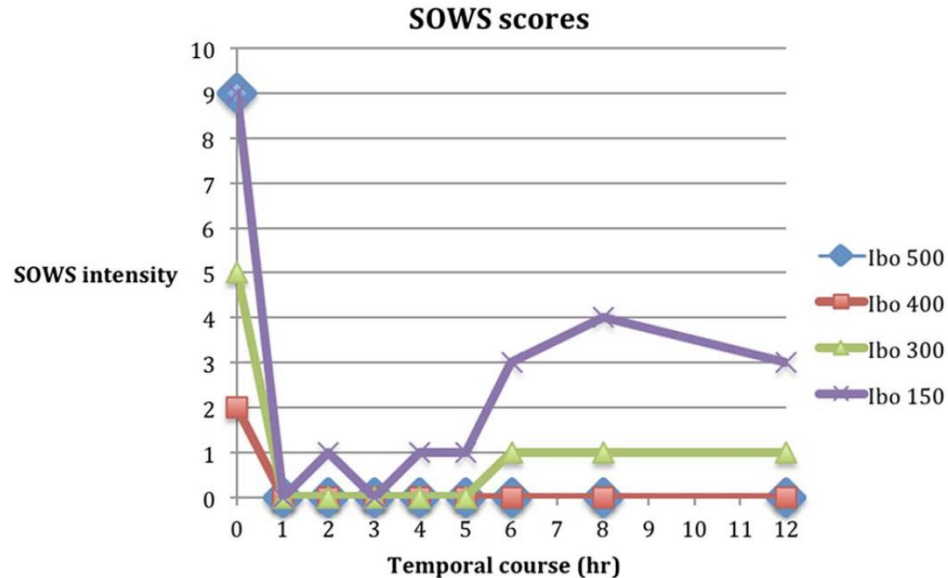
## **Detoxification from methadone using low, repeated, and increasing doses of ibogaine: A case report**

CLARE WILKINS<sup>1</sup>, RAFAEL G. DOS SANTOS<sup>2,3,4</sup>, JORDI SOLÁ<sup>2</sup>, MARC AIXALÁ<sup>2</sup>, PEP CURA<sup>2</sup>, ESTEFANÍA MORENO<sup>2</sup>, MIGUEL ÁNGEL ALCÁZAR-CÓRCOLES<sup>5</sup>, JAIME E. C. HALLAK<sup>3,4</sup> and JOSÉ CARLOS BOUSO<sup>2\*</sup>

- **N = 1 case study on methadone 37mg x 17 years**
  - Previously unable to stop methadone
- **Multiple low-ish doses of ibogaine over 6 weeks**
  - 5 doses (150, 300, 400, 500, 600mg ibogaine)
    - Interspersed by 3-7 days
  - Progressively decreasing methadone doses (cut in half)

## Detoxification from methadone using low, repeated, and increasing doses of ibogaine: A case report

CLARE WILKINS<sup>1</sup>, RAFAEL G. DOS SANTOS<sup>2,3,4</sup>, JORDI SOLÁ<sup>2</sup>, MARC AIXALÁ<sup>2</sup>, PEP CURA<sup>2</sup>, ESTEFANÍA MORENO<sup>2</sup>, MIGUEL ÁNGEL ALCÁZAR-CÓRCOLES<sup>5</sup>, JAIME E. C. HALLAK<sup>3,4</sup> and JOSÉ CARLOS BOUSO<sup>2\*</sup>



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- **Mild effects**
  - No “visionary content” but “psychological insights... with emotional non-distressing reactions”
  - Insomnia
  - Fatigue
  - Memory impairment
  - Restlessness
- **20-point increase in QTc**

## **Detoxification from methadone using low, repeated, and increasing doses of ibogaine: A case report**

CLARE WILKINS<sup>1</sup>, RAFAEL G. DOS SANTOS<sup>2,3,4</sup>, JORDI SOLÁ<sup>2</sup>, MARC AIXALÁ<sup>2</sup>, PEP CURA<sup>2</sup>, ESTEFANÍA MORENO<sup>2</sup>, MIGUEL ÁNGEL ALCÁZAR-CÓRCOLES<sup>5</sup>, JAIME E. C. HALLAK<sup>3,4</sup> and JOSÉ CARLOS BOUSO<sup>2\*</sup>

- Stopped methadone
- Dosed with ibogaine with onset of w/d sx (SOWS 9)
- One-hour post-ibogaine, w/d resolved

**Subjective effectiveness of ibogaine treatment for problematic opioid consumption: Short- and long-term outcomes and current psychological functioning**

ALAN K. DAVIS<sup>1\*</sup>, JOSEPH P. BARSUGLIA<sup>2</sup>, AUSTIN-MARLEY WINDHAM-HERMAN<sup>3</sup>, MARTA LYNCH<sup>2</sup> and MARTIN POLANCO<sup>2</sup>

- Online survey of **88 patients** treated with ibogaine at a single private clinic in Mexico
- Only **~30% of contacted patients** completed survey → strong self-selection bias

## **Subjective effectiveness of ibogaine treatment for problematic opioid consumption: Short- and long-term outcomes and current psychological functioning**

ALAN K. DAVIS<sup>1\*</sup>, JOSEPH P. BARSUGLIA<sup>2</sup>, AUSTIN-MARLEY WINDHAM-HERMAN<sup>3</sup>, MARTA LYNCH<sup>2</sup> and MARTIN POLANCO<sup>2</sup>

- **70% daily use**
- **30% abstinent**
  - Half of these for  $\geq 1$  year
- **70% relapsed**

# Ibogaine future directions

- Continued gray market use
- Integration with existing treatments?
- Future studies
- Non-cardiotoxic analogues

# Thank you!



**Frederick Barrett, PhD**  
 Associate Professor  
 Center Director



**Roland Griffiths, PhD**  
 Professor  
 Founding Director



**Sandeep Nayak, MD**  
 Assistant Professor  
 Center Medical Director



**Albert Garcia-Romeu, PhD**  
 Assistant Professor



**David Yaden, PhD**  
 Assistant Professor



**Bit Yaden, MD**  
 Assistant Professor



**Brandon Weiss**  
 Research Associate



**Alan Davis, PhD**  
 Adjunct Assistant Professor



**Justin Strickland, PhD**  
 Assistant Professor



**Mary Cosimano, LMSW**  
 Director of Guide/Facilitator  
 Services



**Ceyda Sayali, PhD**  
 Postdoctoral Research  
 Fellow



**Adam Safron, PhD**  
 Postdoctoral Research  
 Fellow



**Praachi Tiwari, PhD**  
 Postdoctoral Research  
 Fellow



**Sean Goldy, PhD**  
 Postdoctoral Research  
 Fellow



**Andrew Gaddis, MD MHS**  
 Postdoctoral Research  
 Fellow



**Rebecca Ehrenkrantz, PhD**  
 Postdoctoral Research  
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**Terence Penn, PhD**  
 Postdoctoral Research  
 Fellow



**David Rosen, PhD**  
 Postdoctoral Research  
 Fellow



**Jérémie Richard, PhD**  
 Postdoctoral Research  
 Fellow



**Nathan Sepeda**  
 Director of Data & Analytics



**Jess Dyal**  
 Sr. Compliance Monitoring  
 Specialist



**Andraya Dolbee**  
 Executive Assistant



**Ian Geithner**  
 Research Coordinator



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# Hopkins tobacco trial – qualitative responses

- Themes:
  - Altered sense of self
  - Interconnectedness
  - Rapport with study team

# Theme: Altered sense of self

- It felt like I'd died as a smoker and was resurrected as a nonsmoker. 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'.
- ...smoking just seemed like this miniscule flick of the – pshh, like that, it was nothing compared to everything that I was feeling and thinking, and it was all coming together in this holistic picture of everything, past, present and future. And smoking – whatever! – like just so pointless, it's just nothing to do with anything. Like a little pebble in your shoe – just brush it off and then you... you know, the world is so much bigger!

# Theme: Interconnectedness

- 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.

# Theme: Rapport with study team

- I think if you didn't have that [the rapport] I'm not sure if it would work. I don't know. And then the trust with the people, the folks in this clearly – when you know that people want you to do well...want this to work for you...and then you don't want to let them down. Because there's so much invested.