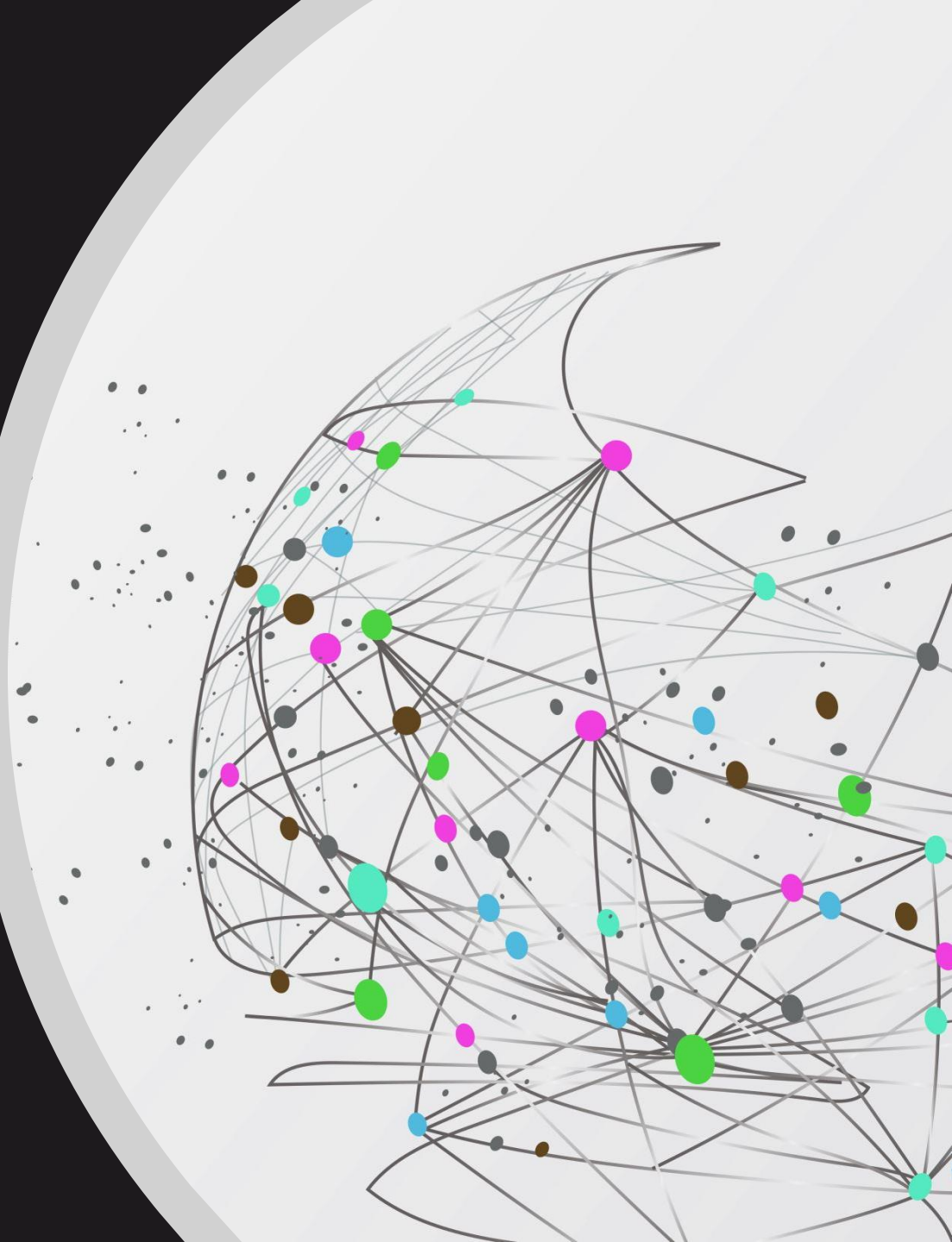
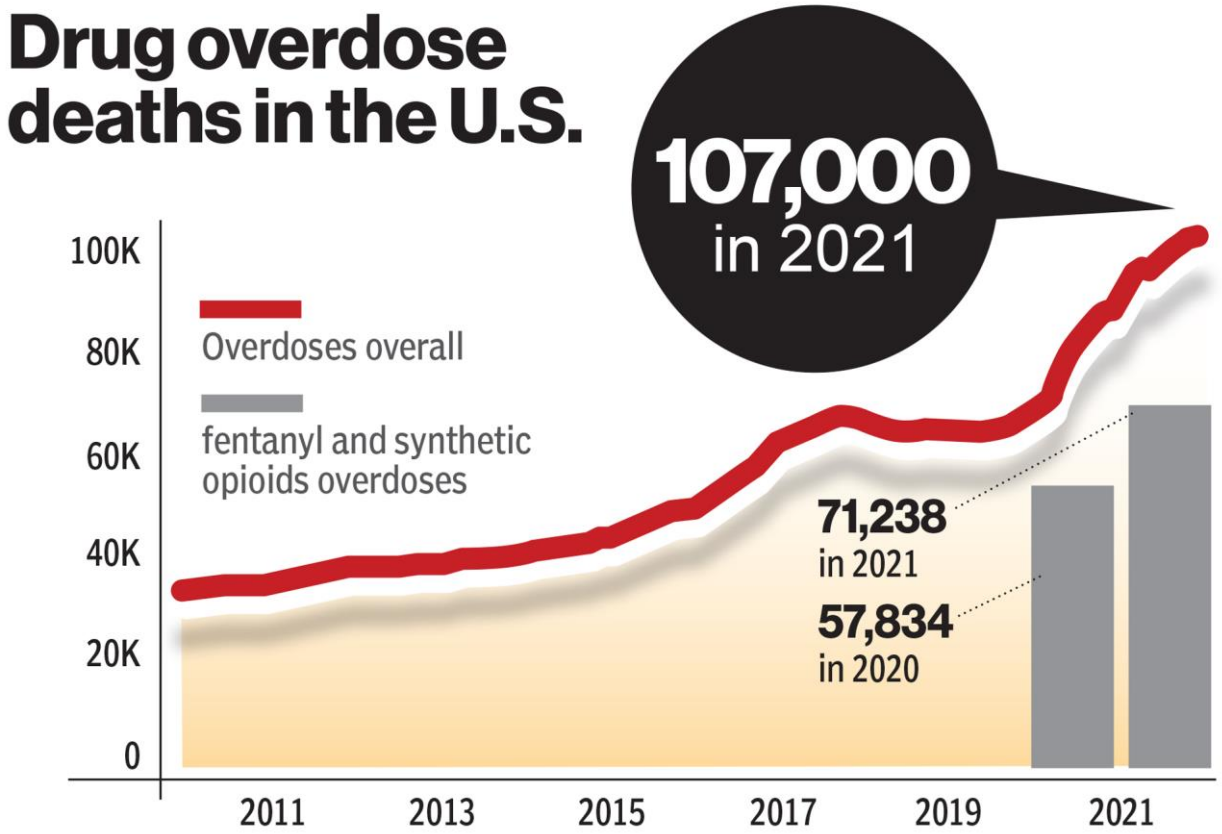
# PSYCHEDELIC DRUGS IN TREATMENT FOR OPIOID ADDICTION

*J. Salinas, MD, ABIM, Associate Professor of Medicine, Pacific Northwest University (ret.), CEO, Internal Medicine Associates of Richland*



# *Contents*

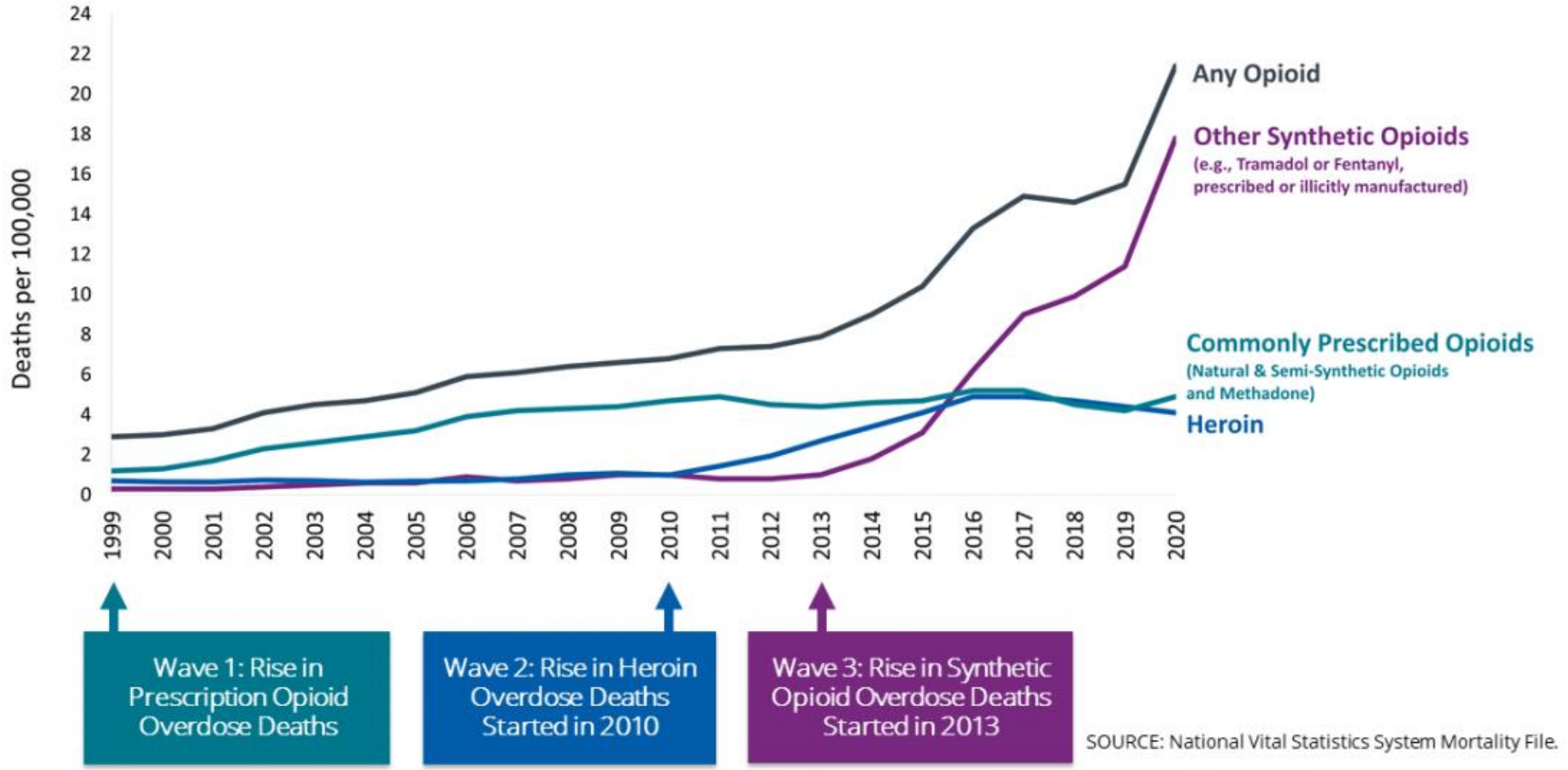
- Overdose “State of the Union”
- Review of current treatment strategies
- State of the science on psychedelic studies
- Novel treatment paradigm
- Traditional use




nypost.com

# *OVERDOSE – RELATED MORTALITY & MORBIDITY RELATED TO SUBSTANCE USE ARE AT AN ALL – TIME HIGH*

# Three Waves of Opioid Overdose Deaths




SOURCE: National Vital Statistics System Mortality File.

# *Current SUD based pharmacologic treatment is limited in efficacy*

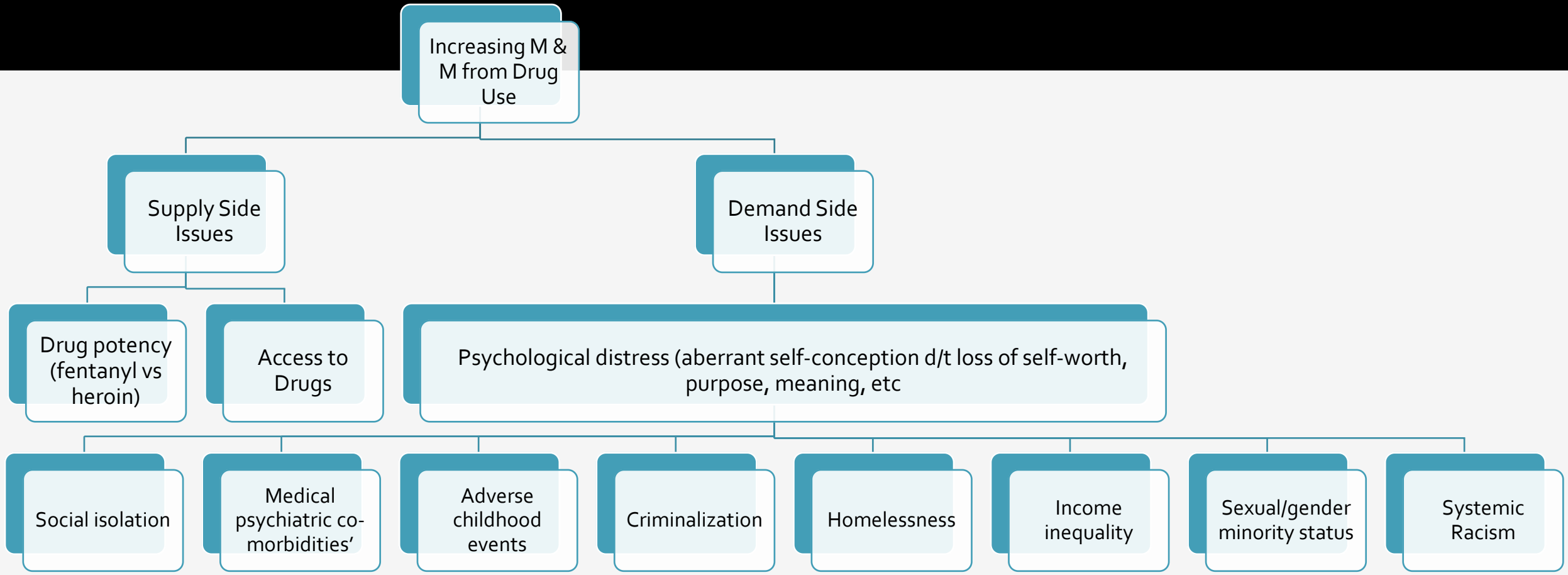
| MEDICATION | OUTCOME | # RCTs | NNT |
|---|---|---|---|
| Buprenorphine | Tx Retention (OUD) | 10 | 4 |
| Methadone | Tx Retention (OUD) | 6 | 2 |
| IM Naltrexone | Tx Retention (OUD) | 8 | 13 |
| Acamprosate | Return to drinking (AUD) | 27 | 12 |
| Naltrexone (PO) | Reduced heavy drinking (AUD) | 53 | 12 |
| IM Naltrexone/PO Bupropion | >3/4 urine samples negative (methamphetamine) | 1 | 9 |
| Mirtazapine | EOSA 2+ weeks (methamphetamine) | 2 | 15 |

Korowynk 2019; Jonas 2014; Trivedi 2021; Coffin 2019; Frank 2021

# *Limitations of current SUD treatment strategies*

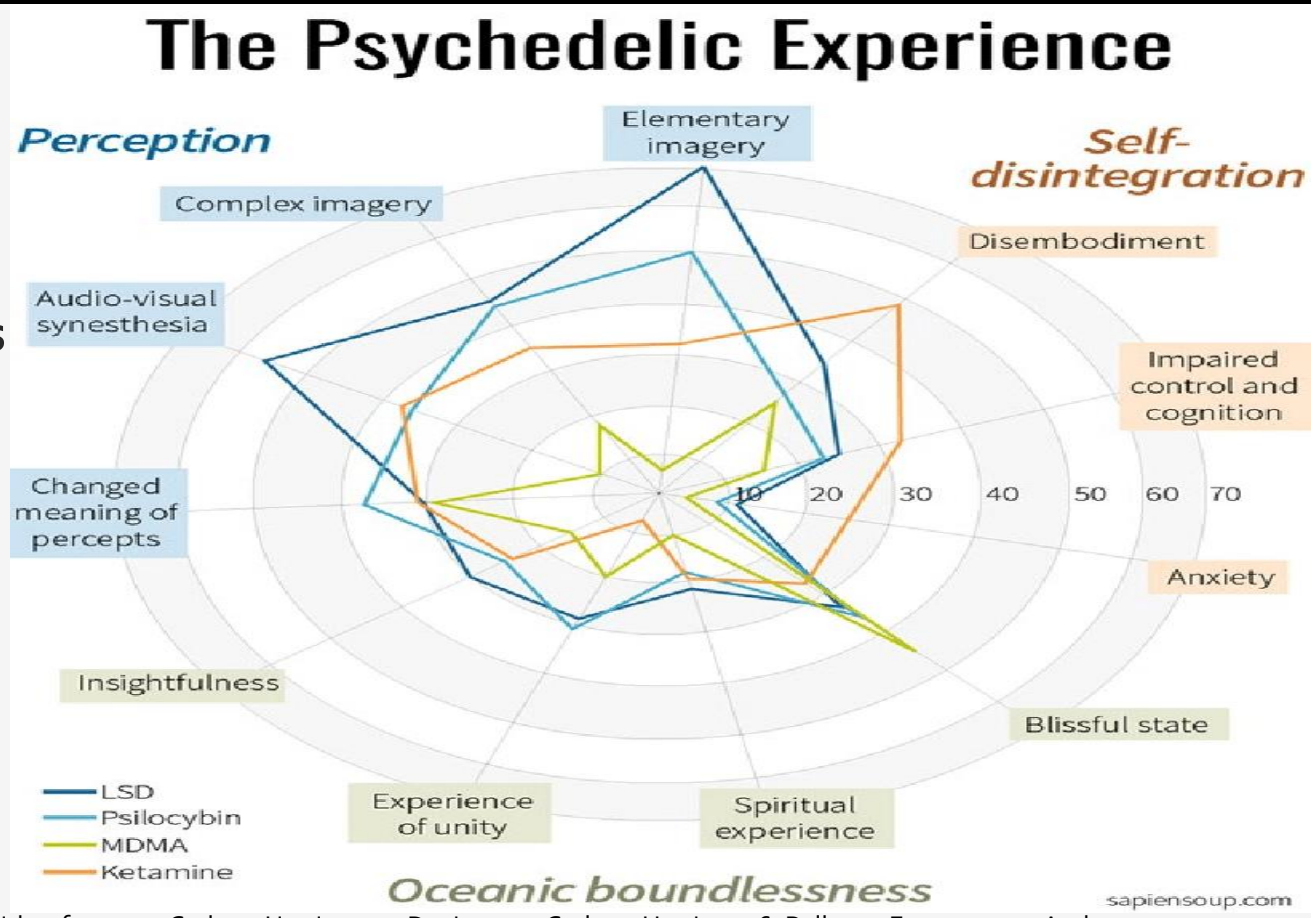
- Limited Scope
  - Biochemically – focused
  - Fail to address underlying psychological motivations for substance use
- Limited efficacy
  - High NNT (to *retain* one patient in treatment, not cure)
  - Not universally acceptable (trading one drug for another)

# *Socio-structural exposures underly trauma & development of addictions*



# *Preliminary evidence supports potential role of psychedelics in addressing psychologic conditions underlying SUDs*

- **High doses may occasion "mystical-type experiences" causing transformative "quantum change" in values and behaviors**
- **Used in ethnomedical contexts across indigenous cultures since pre-historic times**
- **Increasing clinical trial evidence supporting sustained therapeutic effects in PTSD, depression, psychological distress and substance use disorders**
- **All trials combined medications with intensive psychotherapy**



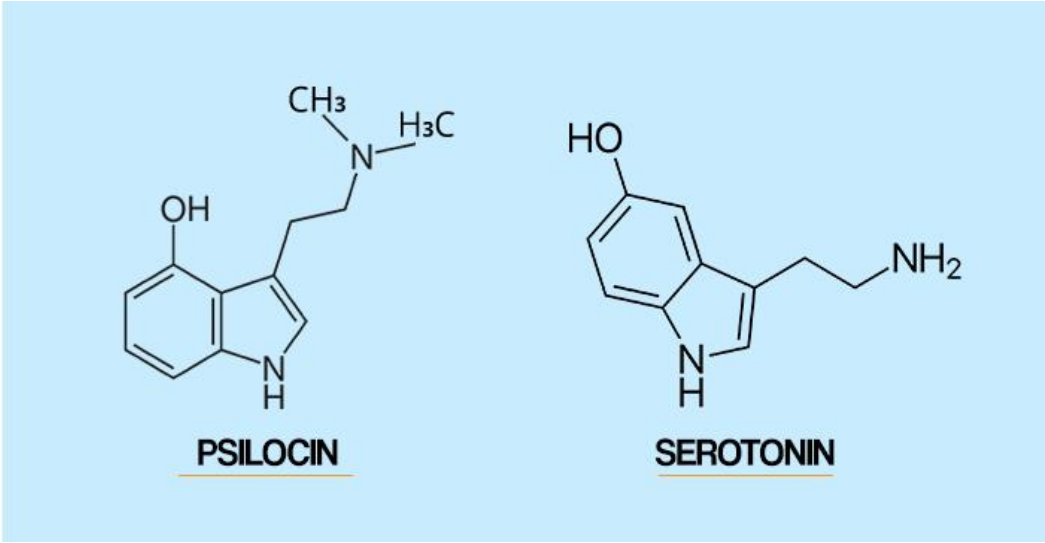

Vollenweider/Kometer 2010; Griffiths 2006; Nichols 2004; Miller 2004; Mitchell 2021; Mithoefer 2019; Carhart-Harris 2021; Davis 2019; Carhart-Harris 2016; Palhano-Fontes 2019; Anderson 2020

# *Evidence for Psychedelics in Addiction Treatment*

- Psilocybin
- Ketamine
- Ibogaine
- MDMA

# *Psilocybin*

- Background
  - Naturally occurring psychedelic prodrug produced by >200 fungi species
  - Ritualistic use among indigenous groups across millennia
  - Acts primarily at 5-HT2A receptor; onset 15-45 min.; duration 2-6 hours



# *Psilocybin PUBLISHED clinical trials for SUD treatment*

## Alcohol use disorder – pilot (n=10)

## Alcohol use disorder – phase 2 double blind (n=95)

- Bogenschutz et al 2022 – alcohol dependence randomized to 12 wks CBT/MET + 2 med sessions
  - Experimental (n=49): Psilocybin 25mg/70kg (at week 4), 25-40mg/70kg (at week 8)
  - Control (n=46): Diphenhydramine 50mg (at week 4), 50-100mg (at week 8)
  - Largest therapeutic psilocybin study to date for SUD and second largest for any clinical indication
  - Psilocybin 41% lower PHDD (% heavy drinking days) and 4X greater odds of NO heavy drinking days (OR 4.0, 95% CI: 1.32-12.1)

## Tobacco use disorder – pilot (n=15)

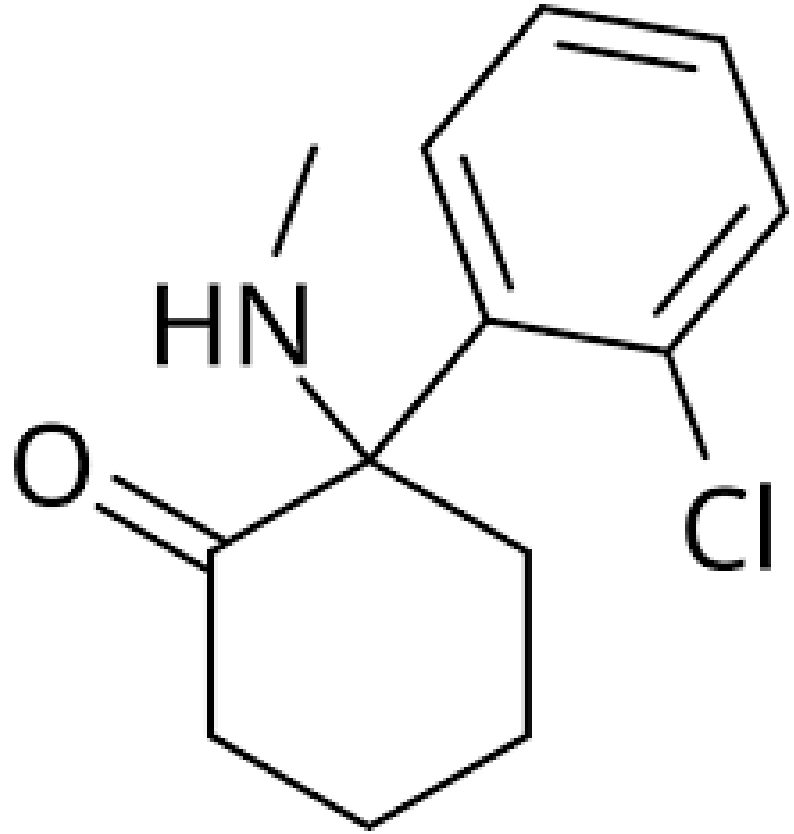
- Johnson et al 2014 – Psilocybin 20mg at week 4,  30mg at week 7 w/ optional at week 13
- 80% seven-day biomarker confirmed abstinence at 6 months
- 67% abstinence at 12 months

# *Psilocybin ongoing clinical trials for addiction*

- M.W. Johnson, A Randomized, Double-Blind Study of Psilocybin for Opioid Use Disorder in Patients on Methadone Maintenance With Ongoing Opioid Use
  - Johns Hopkins University
  - Participants will be randomized to an active group or control group (46 per group). Participants will undergo a total of 2 dosing sessions (whether psilocybin or placebo). The active group will receive 40mg psilocybin first. All participants will receive a second dosing session at three months. The active group will be further randomized, with half receiving 40mg psilocybin, and half receiving placebo at three months.
    - Estimated Study Start Date: December 2023
    - Estimated Primary Completion Date: February 2024
    - Estimated Study Completion Date: December 2024
- Cocaine use disorder – phase 2 (n=40)
- Tobacco use disorder – phase 2, double blind (n=66)
- Methamphetamine use disorder – pilot (n-12); pilot/phase 2 (n=30)

# *Ketamine*

- Neurobiological
  - NMDA receptor antagonist
  - Glutamate modulation
  - Increased neuroplasticity, dampening of certain functional brain connections
- Subjective
  - Trance like (relaxed) state
  - Out of body experience (Dissociation)
  - Temporary release from "Ordinary mind state"
  - Objective view of self in relation to surroundings (from 30,000 feet)
  - Insight from "higher self/inner self"



# *SUD Research on Ketamine*

## Promotes abstinence initiation

## Improves relapse prevention

- Krupitsky studies (2002/2007/2011) on ketamine for heroin dependence found **high dose ketamine to be statistically superior to low dose** in achieving **abstinence** from heroin over 2 years and **50% of 26 patients remaining abstinent at 1 year** after **three ketamine therapy sessions** vs **22% abtincence after only one** ketamine therapy session

## Improves ability to manage cravings

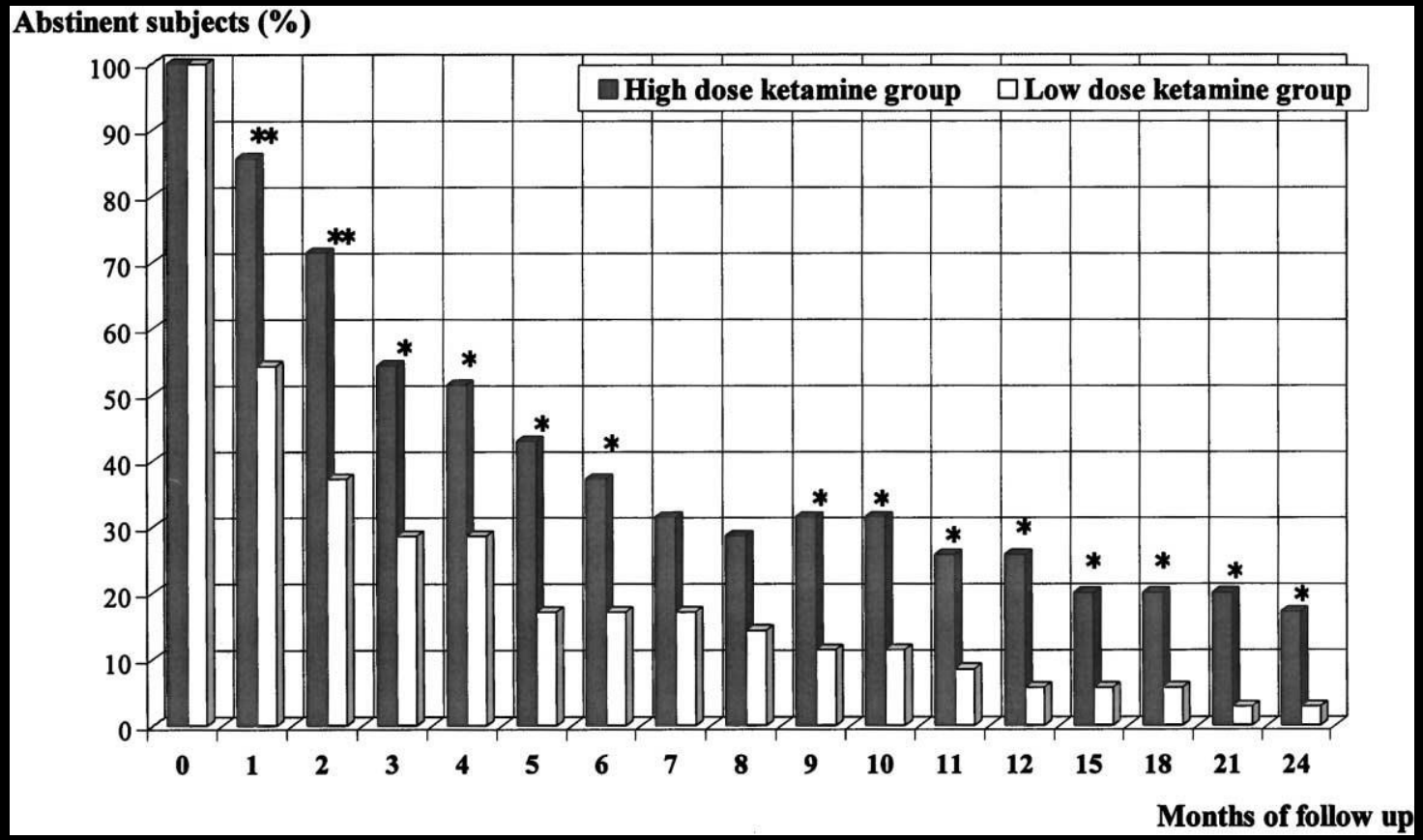
- Dakward study (2019) found **cocaine craving scores were 58%** lower among 27 inpatients who received a ketamine IV session compared to 28 patients receiving a placebo session, coupled with MBSR

## Increases motivation to terminate drug use

## Reduced physiological response during opioid withdrawal

## Changes relationship to drug/alcohol

- KARE study fouind people's relationship to alcohol could change from uncontrolled use to controlled use (alcohol became a less prioritized and there was a shift in the "central focus of life" away from alcohol use




# *Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up*


- *Evgeny Krupitsky, M.D., Ph.D.*, Andrey Burakov, M.D., Tatyana Romanova, M.A., Igor Dunaevsky, M.D., Rick Strassman, M.D., Alexander Grinenko, M.D.*
  *St. Petersburg Research Center of Addictions and Psychopharmacology, Novo-Deviatkino 19/1, Leningrad Region 188661, Russia*


*Received 5 November 2001; received in revised form 29 May 2002; accepted 24 June 2002*

# *Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up*

*Evgeny Krupitsky, M.D., Ph.D.*, Andrey Burakov, M.D., Tatyana Romanova, M.A., Igor Dunaevsky, M.D., Rick Strassman, M.D., Alexander Grinenko, M.D.*

*St. Petersburg Research Center of Addictions and Psychopharmacology, Novo-Deviatkino 19/1, Leningrad Region 188661, Russia* *Received 5 November 2001; received in revised form 29 May 2002; accepted 24 June 2002*

- The results of this double-blind, randomized clinical trial of KPT for heroin addiction showed that high dose (2.0 mg/ kg) ketamine psychedelic psychotherapy elicits a **full psychedelic experience** in heroin addicts. On the other hand, low dose KPT (0.20 mg/kg) elicits a "sub-psychedelic" experience which functions as ketamine-facilitated guided imagery.
- High dose KPT produced a **significantly greater rate of abstinence in heroin addicts within the first 24 months** of follow-up than did low dose KPT.
- High dose KPT brought about a **greater and longer-lasting reduction in craving for heroin**, as well as greater positive change in nonverbal unconscious emotional attitudes.
- Thus, it is possible that the higher rate of abstinence in the high dose group was to some extent due to positive effects of ketamine on craving, similar to other **NMDA** receptor ligands such as **ibogaine and acamprosate**

Prior study found that one ketamine-assisted psychotherapy session was significantly more effective than active placebo in promoting abstinence (Krupitsky et al. 2002)

This study compared the efficacy of single versus repeated sessions of ketamine-assisted psychotherapy in promoting abstinence in people with heroin dependence

- **59 detoxified inpatients** with heroin dependence received a ketamine assisted psychotherapy **(KPT) session prior to their discharge** from an addiction treatment hospital. Then randomized into two treatment groups.
  - Participants in the first group received two addiction counseling sessions followed by **two KPT sessions, with sessions scheduled on a monthly interval (multiple KPT group).**
  - Participants in the second group **received two addiction counseling sessions on a monthly interval,** but **no additional ketamine** therapy sessions (single KPT group).

At one-year follow-up, survival analysis demonstrated a **significantly higher rate of abstinence** in the multiple KPT group. Thirteen out of 26 subjects **(50%) in the multiple KPT group** remained abstinent. compared to 6 out of 27 subjects **(22.2%) in the single KPT group** ($p < 0.05$).

No differences between groups were found in depression, anxiety, craving for heroin, or their understanding of the meaning of their lives. It was concluded that three sessions of ketamine-assisted psychotherapy are more effective than a single session for the treatment of heroin addiction.

***Single Versus Repeated Sessions of Ketamine-Assisted Psychotherapy for People with Heroin Dependence***

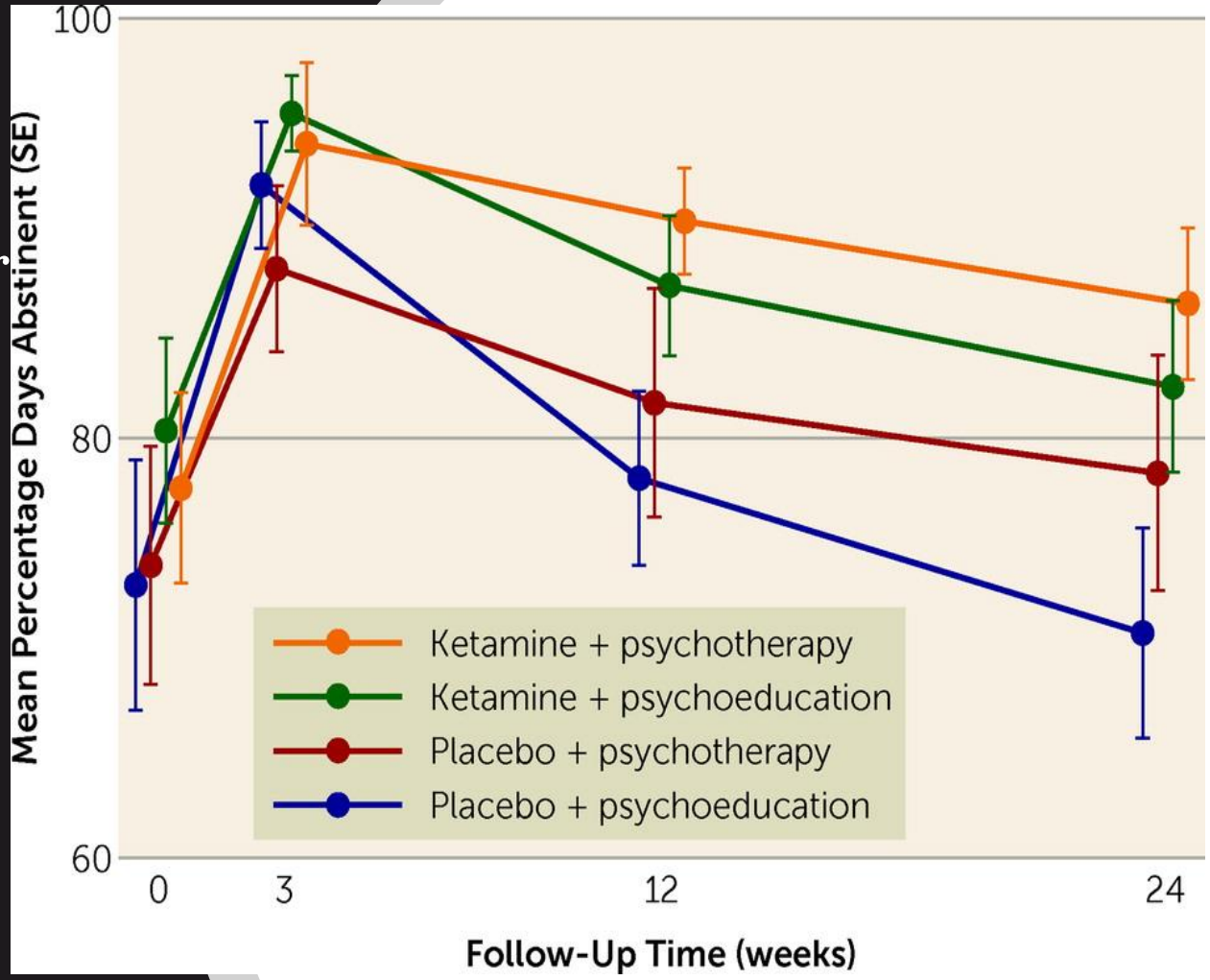
Evgeny M. Krupitsky, Andrei M. Burakov, Igor V. Dunaevsky, Tatyana N. Romanova, Tatyana Y. Slavina & Alexander Y. Grinenko

*Pages 13-19 | Published online: 08 Sep 2011*

# *From: Adjunctive Ketamine With Relapse Prevention–Based Psychological Therapy in the Treatment of Alcohol Use Disorder*

*American Journal of Psychiatry*

- The ketamine plus therapy group shows the greatest percentage days abstinent and the placebo plus psychoeducation group the lowest. Confidence intervals are not overlapping for these two most extreme groups at 12 weeks and 24 weeks. Number of participants at week 3: ketamine plus therapy, N=22; ketamine plus psychoeducation, N=23; placebo plus therapy, N=23; placebo plus psychoeducation, N=25. Number of participants at weeks 12 and 24: ketamine plus therapy, N=21; ketamine plus psychoeducation, N=22; placebo plus therapy, N=22; placebo plus psychoeducation, N=24.




Percentage days abstinent across the four treatment conditions in the study of

# KARE
# Qualitative Follow up Study

## Perspective on Life

"it helped family wise, relationship wise in every, every single avenue of my life. It's changed it… doing the ketamine and seeing this other dimension enforced my belief of another life and I now live every single day to the max. When I go for a walk, I'm very observant of my world around me. I take pleasures in life rather than pleasures of…drink…So…it's still with me and I hope it'll stay with me forever" (P03)

## Relationship with alcohol

"I think before the trial all my life was sort of focused on alcohol. I was either drinking it at home or selling it to students or working in an event where there was alcohol, the alcohol was a focus of it. So, it was sort of everything and then afterwards, it just sort of stopped… enjoy a drink ev3ery now and then, but under much safer ways really…So it just made me realize I don't need to sort of drink to excess because there's nothing else to doe. I can just do other things…and that alcohol isn't everything"

## Ego dissolution

"It was a sense of completeness , of, I suppose ina away finality, a source of finish. But also, a sense of enormous growth and a feeling of oneness with other entitie3s, other living beings in particular, but also the world and univers as a whole." (P07)

## Epiphanies and Enlightenment

"I think the first two like, they sort of left me…like they answered a lot of questions. You know, thinking about my children aned I have a stepdaughter and …it was things about that. And about, you know what I should be doing and how I should be, you know, I don't know it seemed to be like all the things that are really heavy on my mind and that I stress about whatever it was sort of going through those thihgs…just realizing how little importanfe swome things had or were" (P10)

## Transcendence of time

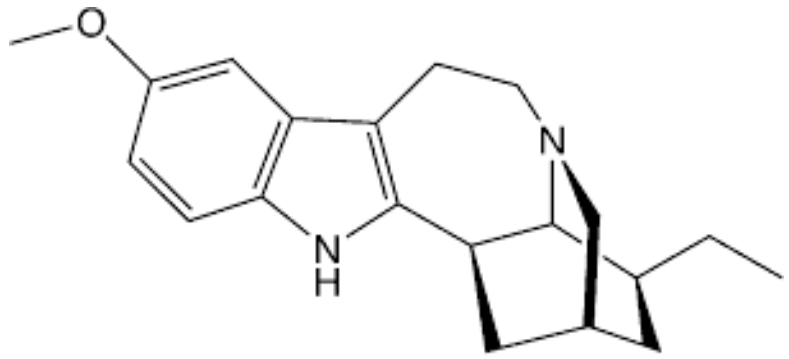
"…while we're on the subject of time. I mean, that just goes bananas and I love it…It's almost like…this afternoon, this evening, the way we think of that – That just blows apart and doesn't exist anymore" (P06)

## Hallucinations or visions

"I was lying there, and there was this like a cacophony coming from the hallway, everyone was going like, he's coming he's coming! And I was like what's going on, you know, like thinking this shouldn't be happening in the hospital. I thought this is a peaceful place and everyone's like rushing out into the hallway to see what's happening. And it's this cartoon very simply drawn constructed of neon light rendering of God, essentially is walking down the corridor…and he came up to me and he was like… you can ask me two questions" (P09)

# *Ibogaine*

- Found in the root bark oof *Tabernanthe iboga*, a shrub native to western equatorial Africa, where it is used as a botanical sacrament in the Bwiti religion
- Naturally occurring ALKALOID (class of naturally occurring psychedelic chemicals
- Has been used in medical and nonmedical settings to treat substance use disorders




Ibogaine

# *Ibogaine*

Background

a monoterpene indole alkaloid used in medical and nonmedical settings for the treatment of opioid use disorder. Its mechanism of action is apparently novel

Use in religious conte4xts in West Africa

Currently an addiction treatment in some countries

Onset – 0.5-3 hours/ Duration – 48-72 hours

**Agonism** at D2, GHT2A, kapa opioid receptor

**Antagonism** at NMDA, alpha3Beta4 nicotinic receptor

## Published case series:

Alper 1999; n=33 OUD: 25 state "no desire to use"

Shenberg 2014; n=75 AUD, CUD: long-term abstinence

Mash 2018; n=191 OUD, CUD: 92% "useful" for SUDs

Ibogaine 8-12mg/kg, 12 day inpatient detoox w/counseling

Referral to community-based 12 step program

- Objectives: To study outcomes following opioid detoxification with ibogaine.
- Methods: In this observational study, 30 subjects with DSM-IV Opioid Dependence (25 males, 5 females) received a mean total dose of 1,540 ± 920 mg ibogaine HCl.
- Subjects used oxycodone (n = 21; 70%) and/or heroin (n = 18; 60%) in respective amounts of 250 ± 180 mg/day and 1.3 ± 0.94 g/day, and averaged 3.1 ± 2.6 previous episodes of treatment for opioid dependence.
- Detoxification and follow-up outcomes at 1, 3, 6, 9, and 12 months were evaluated utilizing the Subjective Opioid Withdrawal Scale (SOWS) and Addiction Severity Index Composite (ASIC) scores, respectively.
- Results: **SOWS scores decreased from 31.0 ± 11.6** pretreatment to **14.0 ± 9.8** at 76.5 ± 30 hours posttreatment ($t = 7.07$, $df = 26$, $p < 0.001$).
- At **1-month posttreatment follow-up, 15 subjects (50%) reported no opioid use during the previous 30 days**.
- ASIC **Drug Use and Legal and Family/Social Status** scores were **improved** relative to pretreatment baseline **at all posttreatment time points ($p < .001$).**
- Improvement in Drug Use scores was maximal at 1 month, and subsequently sustained from 3 to 12 months at levels that did not reach equivalence to the effect at 1 month.
- Conclusion**: Ibogaine was associated with substantive effects on opioid withdrawal symptoms and drug use in subjects for whom other treatments had been unsuccessful** and may provide a useful prototype for discovery and development of innovative pharmacotherapy of addiction.

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

*Thomas Kingsley Brown & Kenneth Alper (2018) The American Journal of Drug and Alcohol Abuse, 44:1, 24-36, DOI: 10.1080/00952990.2017.1320802*

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

*Thomas Kingsley Brown & Kenneth Alper (2018) The American Journal of Drug and Alcohol Abuse, 44:1, 24-36, DOI: 10.1080/00952990.2017.1320802*

- In this study 15 (50%) and 10 (33%) of subjects reported no opioid use during the previous 30 days at 1 and 3 months respectively.
  - By **comparison**, a large recent study reported an **8.6% rate of treatment success**, defined as self-report of **≤4 days of opioid use in the previous 30 days, at 8 weeks** subsequent to tapering and **discontinuing buprenorphine with no subsequent pharmacotherapy** (Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, Gardin J, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2- phase randomized controlled trial. Arch Gen Psychiatry 2011;68:1238–1246)
  - Recent systematic reviews on follow-up of **opioid detoxification without subsequent maintenance** treatment report rates of **abstaining** from illicit opioid use of **18% at 4 week**s following detoxification with **buprenorphine** (Bentzley BS, Barth KS, Back SE, Book SW. Discontinuation of buprenorphine maintenance therapy: perspectives and outcomes. J Subst Abuse Treat 2015;52:48–57), and **26% at 6 weeks** following detoxification with **methadone** (Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev 2013;2).

# *Ibogaine*

**TABLE 8.** Self-reports of ibogaine experience.

| | |
|---|---|
| Connection to higher power, universe | 58.3% |
| Dreamlike state | 45.0% |
| Self as child | 43.3% |
| Able to resist/control experience * | |
| Cocaine-dependent subjects | 40.0% |
| Opiate-dependent subjects | 16.7% |
| As film or movie | 36.7% |
| Passive/outside observer | 28.3% |
| Life review | 16.7% |
| Unaware of reality/immersed in experience | 11.7% |

*Semi-structured elicitation narrative and content coding were used to capture common elements. *Category with observed differences between opioid and cocaine dependence groups. N = 60; Demographics of cocaine and opioid dependent subjects are shown in Supplementary Table S3. *Category with observed differences between groups.*

**TABLE 9.** Frequently reported interpretations of the ibogaine experience.

| | |
|---|---|
| Useful for drug problems | 91.7% |
| Given insight | 86.7% |
| Need to become sober/abstinent now | 68.3% |
| Cleansed/healed/reborn | 50.0% |
| Second chance at life | 40.0% |
| Increased self-confidence | 33.3% |
| Impending self-destruction if drug use continued | 18.3% |
| Willingness to repeat ibogaine experience | 16.7% |

*Semi-structured elicitation narrative and content coding. N = 60; Demographics of cocaine and opioid dependent subjects are shown in Supplementary Table S3.*

# *Ibogaine Safety Issues*


High rates of severe adverse events have limited clinical utility in U.S.

Since 1990's at least 15-30 sudden, unexplained deaths (Alper, et al, 2012)

| | | |
|---|---|---|
| Often with higher doses (>20mg/kg) or "dose stacking" | Few conducted under medical supervision | Patients often had pre-oexisting conditions (CV, prolonged QTc, other drug use) |

Currently active clinical trials in Spain, Brazil and UK

| | | |
|---|---|---|
| Methadone detoxification | OUD | AUD |

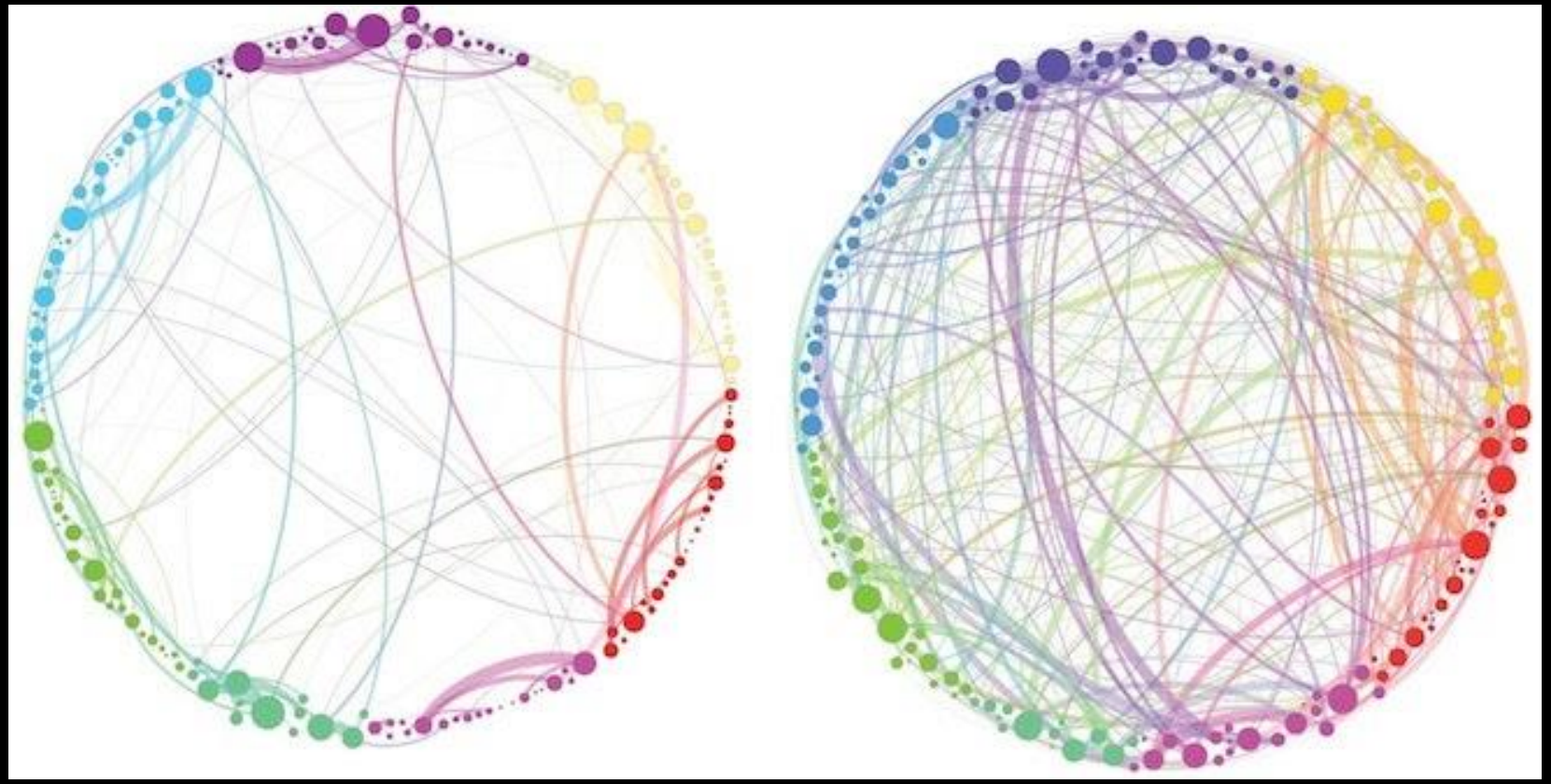
# WHY PSYCHEDELICS?

*Treat PATHOPHYSIOLOGY -Subjective Experience and Underlying assumptions vs SYMPTOMS - Mood regulation, Reactivity, Self-medication*

# *Common Biochemistry of Psychedelics*

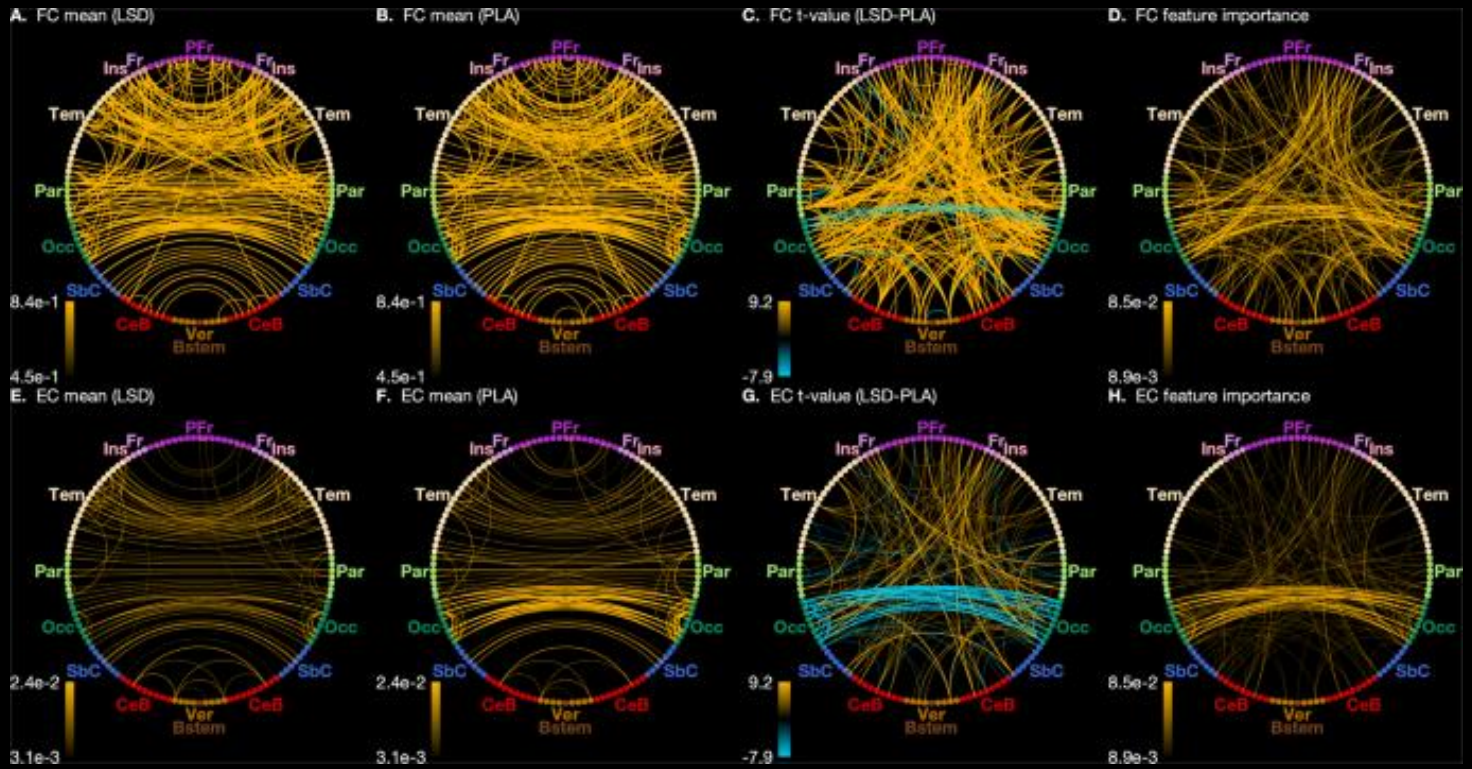
- Alkaloids
- Indole Amines
- Tryptamine
- 5HT2A receptor Agonists
- NMDA Receptor Antagonist (Ketamine)

# *Psychedelic effects on Brain State*



- There is increased integration between cortical regions (Synesthesia)
- There is decreased activity of certain regions (Default Mode Network)

Communication between brain networks of people given a psychedelic (right) vs those given non- psychedelic compound (left), Petri et al, *Homological scaffolds of brain functional networks*, Proceedings of Royal Society of Neuroscience




**Connectogram views of differences in functional (FC) and effective connectivity (EC) between LSD and placebo conditions**

- **A** Across-participant average FC in the LSD condition. **B** Across-participant average FC in the placebo condition. **C** Across-participant *t*-statistic values of difference between FC in LSD and placebo conditions. **D** Feature importance estimates for the FC classification model. See 'Statistical analysis' for a detailed definition of feature importance. **E** Across-participant average EC in the LSD condition. **F** Across-participant average EC in the placebo condition. **G** Across-participant *t*-statistic values of difference between EC in LSD and placebo conditions. **H** Feature importance estimates for the EC classification model. Differences in magnitudes of connectivity are indicated in each connectogram by both line width and opacity. In (**C**) (FC) and (**G**) (EC), orange and blue lines indicate stronger and weaker connectivity, respectively, in connectivity in the LSD condition. Note that for (**E**)–(**H**), both directional EC values between each pair of regions have been averaged for display. To maintain visibility, only the top 250 connections have been displayed. PFr Prefrontal cortex. Fr Frontal cortex. Ins Insular cortex. Tem Temporal cortex. Par Parietal cortex. Occ Occipital cortex. SbC Subcortical regions. CeB Cerebellum. Ver Vermis. Bstem Brainstem.

Aertsen A, Preißl H. Dynamics of activity and connectivity in physiological neuronal networks. In: HG S, editor. *Nonlinear Dynamics and Neuronal Networks.* VCH Publishers; New York: 1999. pp. 281–302

# *Substance Use Disorder as a Learning Disorder*

The symptoms are manifestations of survival or coping mechanisms that were helpful at the time but that have negative consequences

- Fight or flight
- Dissociation (obesity, poor hygiene, etc.)
- Self medication
- Denial
- Self denigration

The symptoms are related to beliefs that were reinforced during periods of vulnerability/high suggestability

- Low self worth
- Hopelessness/unchangeability
- Skewed idea of "normal"

# *Phenomenology of the Psychedelic Experience*

- Synesthesia
- loss of default mode (self)- Ego dissolution
- loosen associations (strongly held beliefs about self and the world)- Pivotal Mental State
- reduced experiential avoidance
- open up memories long suppressed
- turn down amygdala Dissociation of affect to thought (opposed to pathologic dissociation to current events like flash backs or catatonia)- still feel strong emotions but with less immenence (immediacy)
- plasticity (allows for consolidation of new insights)
- Mystical experience

# *Therapeutic Context of the Psychedelic Experience*

- set and setting - this and integration is what differentiates therapeutic from "experience"
  - Preparation
  - Experiential
  - Integration
- Unlike any other medication that we use where the effect of the medication is predictable and reproducible, psychedelics work differently in different people. Their experience is volatile and malleable, which allows for cross efficacy over many varied psychological pathologies. Their therapeutic effects are phenomenological level, not directly biochemical level.

# *Set and Setting*

- Mindset
  - understand what the drug is doing and what to expect and how to manage it
  - Childhood imprinting/ world view
    - Family
    - Community
    - Ethnicity
    - Religion
  - what is your current situation - how will family and friends/employer/environment help/hinder medicine use and integration)
  - What medications/drugs are you currently using that could interfere with the effect of the medicine
  - Past experience with psychedelics

# *Set and Setting*

- Setting
  - safe container
  - no one who has been through a traumatic, frightening, support and motivate to engage with emotionally challenging experience would discount the benefit of "holding space“
  - Enhance brain entropy Carhart Harris
    - Relaxed Beliefs Under Psychedelics (REBUS)

# *Integration*

- review and process insights and plan for integrating them into coming weeks
- follow up to review and edit strategies
- Pivotal Mental States (PMS)
- Prolonged period of neural plasticity allowing for attenuation of previously and production of new neural associations (thoughts, beliefs, tendencies, habits and reactions.