PSYCHEDELICS FOR TREATMENT OF USE DISORDERS

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OBJECTIVES

- What are the “Psychedelics”
- History of psychedelics in mental health
- Neurochemistry of psychedelics and how they may work in addictions
- Components of psychedelic therapy
- Evidence to date of safety and efficiency
- Future

Case

- 32 yo male with long history of methamphetamine use. Has been in multiple treatment programs including several residential treatment, outpatient CBT, 12 steps. Only able to obtain recovery for short periods of time, ie 2-4 months, before returning to use. Several hospitalizations for stimulant use disorder. Has severe underlying depression when not using
- Has heard (has been looking extensively on You Tube and other internet sites) about psychedelic therapy for use disorders and feels strongly it might help as everything else has failed
- He is exploring going on line for ketamine treatment out of frustration with lack of success
- What do you tell him

Terminology

- Multiple terms for this class of drugs
  - psychedelics (Greek words mind/soul and to show or reveal)
  - hallucinogens (DSM V uses hallucinogens terminology)
  - psychotomimetics (mimicking psychosis)
  - empathometics (MDMA)
  - entheogens (divine within)
  - enactogens (touching within)
  - dissociatives
  - psychoplastogens/neuroplastogens

What are Psychedelics

- Broad group of agents that have differing mechanisms of action, dose responses, effects

- **CLASSIC (agonist at the 5-HT2aR receptor)**
- Psilocybin (magic mushrooms)
- DMT dimethyltryptamine (Ayauyasca)
- Mescaline (found in Peyota)
- LSD (Lysergic acid diethylamide) and 2 C-B
- **NONCLASSIC**
- Ketamine (dissociative)
- Ectasy (MDMA)- empathometic
- Ibogaine

- In 2022, The Intercept published a letter from an official at the US Department of Health and Human Services saying that it anticipated that the FDA would approve MDMA by 2024. And **in 2017, the FDA granted 'breakthrough' status to both MDMA and psilocybin**, putting the drugs on a regulatory fast track to approval.
- Phase 3 trials underway
- Ketamine is approved for use in treatment resistant depression and anxiety

Klarity Ketamine Clinic
4.5 ★★★★½ (21) · Mental health clinic
Greenwood, IN · (317) 777-1034
Open · Closes 4:30 PM
Medicare/Medicaid accepted
"I strongly recommend this clinic and Dr Reed"

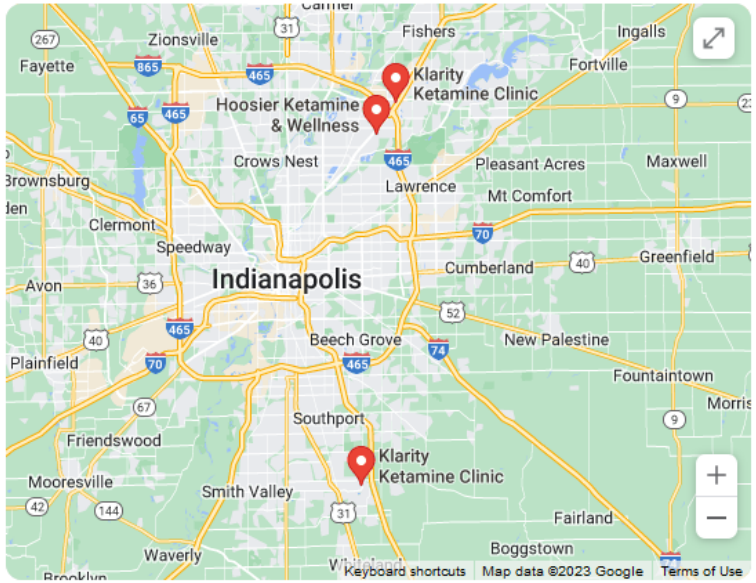
Website Directions

Hoosier Ketamine & Wellness
4.8 ★★★★★ (21) · Mental health clinic
6801 Lake Plaza Dr Suite B-209 · (463) 466-7437
Open · Closes 3:30 PM
"Highly recommend Hoosier Ketamine and wellness!"

Website Directions

Klarity Ketamine Clinic
No reviews · Medical office
8123 Castleton Rd · (317) 777-1034
Open · Closes 4:30 PM
Medicare/Medicaid accepted

Website Directions



Welcome to Indiana Center for Recovery

We understand how challenging it can be to manage these conditions and how they impact your quality of life. That's why we offer cutting-edge ketamine treatment to help you alleviate your symptoms and improve your mental health.

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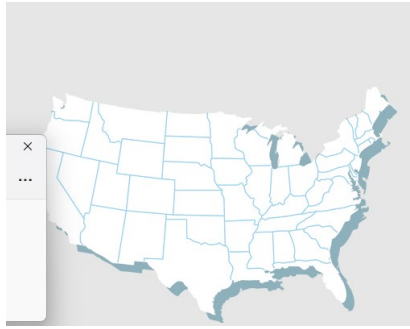

We make it easy to access expert care

With locations stateside, Indiana Center for Recovery the expert care you need to overcome addiction. Our facilities are conveniently located and staffed with caring professionals dedicated to helping you achieve lasting recovery.

Find Detox near you

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Ketamine Clinics

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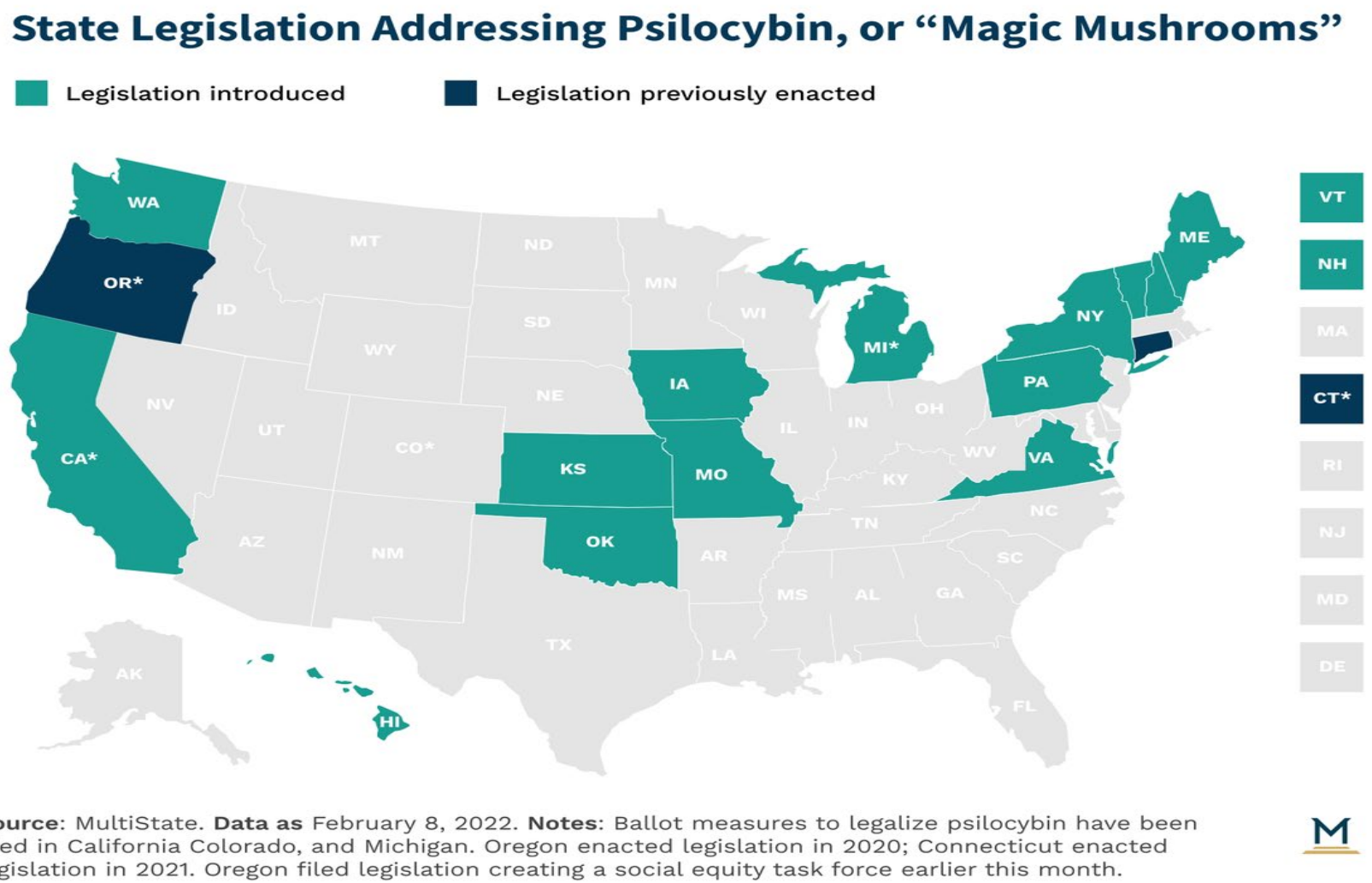
THE FUTURE IS NOW



Source: MultiState. **Data as** February 8, 2022. **Notes**: Ballot measures to legalize psilocybin have been filed in California Colorado, and Michigan. Oregon enacted legislation in 2020; Connecticut enacted legislation in 2021. Oregon filed legislation creating a social equity task force earlier this month.

HISTORY OF PSYCHEDELCS

A few of the estimated two hundred mushroom stones that escaped destruction, despite the concerted efforts of misdirected Catholic missionaries. The smaller mushroom stones are the ones found with metates, which were presumably used for grinding the sacraments prior to use (Borhegi 1961).

History of Psychedelics in Mental Health

- Ancient natural approaches to spiritual awakening and experience
- Bill Wilson story (next slide)
- 1950s there was extensive research on the use of psychedelics for various mental illness (over 1000 articles), predominately LSD
- LSD introduced as part of psychotherapy to facilitate self awareness
- Most of this research was case studies, observational, and naturalistic in design
- “Escapes” lab setting, Timothy Leary, threat felt by government officials
- Early 1970s LSD reclassified as schedule I drug, ended research
- 1990s renewed interest in use of psychedelics in addictions / mental illness but now this research is evidence based: randomized controlled trials
- Expanding our understanding of the potential mechanisms of actions, understanding the neurochemistry from bench to human imaging (fMRI, neurotransmitters levels..)

Bill Wilson

Cofounder of AA with Dr. Bob in Akron OH

One of first documented accounts when Bill Wilson embarked on 4th attempt at recovery

Tried mixture of henbane and belladonna plants that contain alkaloids that have psychedelic lie effects

Under this influence he reported a “bright white light and a feeling of great peace” which he interpreted as spiritual and self transcendent awakening”

Later he tried LSD “If therefore under LSD we can have a temporary reduction so that we better see what we are and where we are going, ..the goal might become clearer. So I consider LSD to be of some value to some people and practically no damage to anyone”

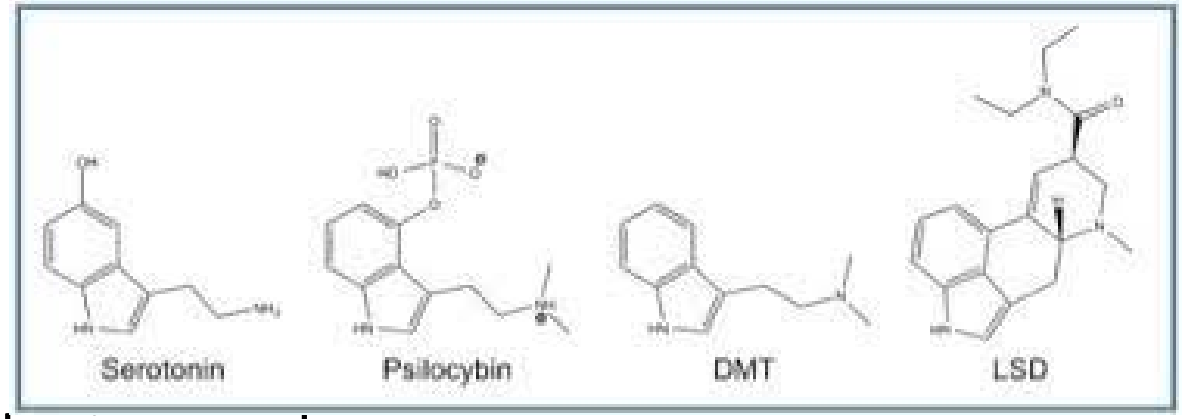
Hartigan F. Bill W.: A biography of alcohol anonymous cofounder Bill Wilson. St. Martin Press 2000

How do they work in treatment of use disorders

- Cellular level
- Neuronal pathways and connections
- Pharmacological
- Psychological Effects- cognitive/emotional/memory.. effects (how do they effect what the person experiences, feels.
- Clinical outcomes

Mechanism of Action of Psychedelics

(CLASSIC) Serotonergic Psychedelics



-psilocybin
-LSD
-mescaline

- Agonist or partial agonist at specific serotonin receptors (5HT2Ar)5-hydroxytryptamine 2A receptors,) located in prefrontal cortex
- **NONCLASSIC**

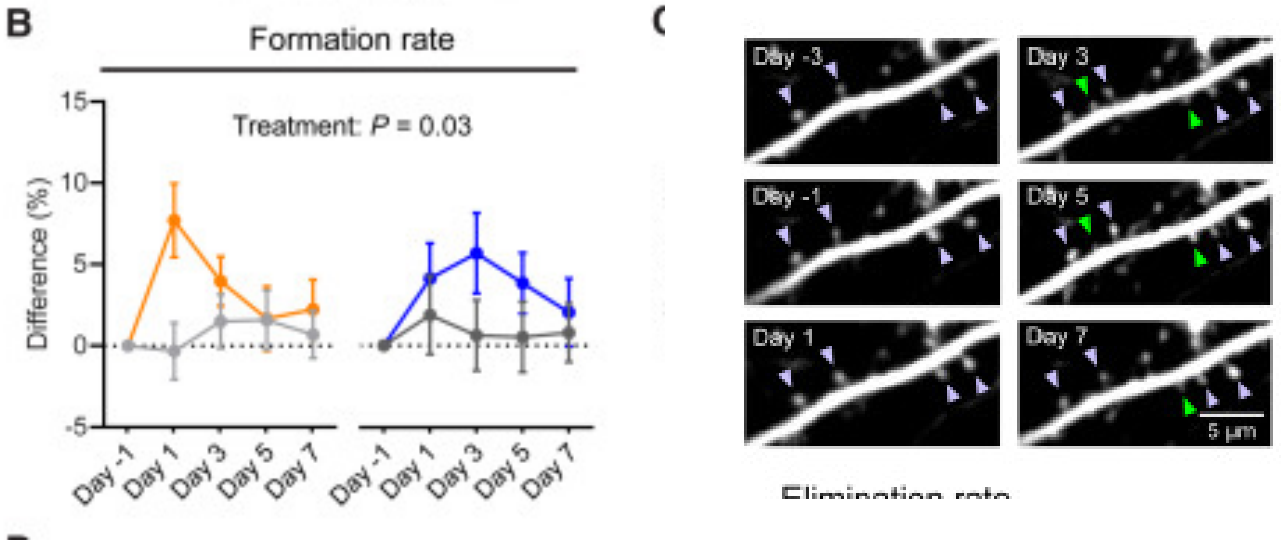
  ketamine
- NDMA receptor antagonist
- Increased in brain derived neurotrophic factor

MDMA

- Increase dopamine, serotonin, norepinephrine, oxytocin

Effect of psilocbin on neurons

Psilocybin has been observed to provoke rapid and sustained dendritic spine growth (spinogenesis) and increase neural connectivity via the formation of new synapses (synaptogenesis).



Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex *in vivo*

•Ling-Xiao Shao t. al., Neuron 2021

NEURONAL PATHWAYS AND CONNECTIONS

- Promote neurogenesis and synaptogenesis in key regions of the brain , ie frontal cortex
- Modulate the DMN (default mode network) allowing new connections (video)
- Ability to unlearn or relearn
- All psychedelics have neuroplasticity

Psychedelics
can change
the brain

WHAT IS THE MECHANISM OF ACTION OF THE PSYCHEDELICS PSYCHOLOGICALLY

- PSYCHOLOGICAL EFFECTS
  - facilitate cognitive “reframing”
  - change of perspective on one self, (self awareness),others and the world
  - changes reward and the connection with the prefrontal cortex
  - changes emotional response to internal and external stimuli
  - inner exploration

- It is not the hallucinogenic effects that are critical

MECHANISM OF ACTION CONCEPTUAL FRAMEWORK FOR ADDICTION

- Described addiction as a narrowed state of consciousness where individual with use disorder crave a certain experience that results in a contraction and fixation of consciousness. “15% window”
- Perhaps addiction results is reduced neuroplasticity
- Reduced activity in the Prefrontal cortex and orbitofrontal cortex, both areas that involved in the weighing the cost/benefit (hub failures)
- Pharmacologic interference with memory reconsolidation may allow overwriting of maladaptive use memories
- In a state of transcendence there is heightened awareness that can reset perspective and awareness , resulting in taking in new information or acquire new salient information
- Addiction results in brain impairments in cognitive, emotional and memory systems

WHAT DOES THE PROCESS LOOK LIKE

- It is not just taking a psychedelic and emerging as a new person
- Development of new networks must be directed **Therapy assisted treatment**
- Set and setting are import
  -Set- internal environment
  -Setting- external environment
- Psychedelic psychotherapist

Roles of the therapist

- Preparing the participant for the therapy
- Guiding the patient during the treatment
- Facilitating integration of the experience into change
- 2 therapists during medication treatment
- Training

TABLE 2. Credentials of therapists in psilocybin clinical trials

Study	Psychiatrist	Psychologist	Master's-level social worker or counselor	Other licensed professional	Bachelor's-level staff
Anderson et al., 2020 (9)	5	5	2	2	1
Bogenschutz et al., 2015 (10)	2	1			
Carhart-Harris et al., 2016 (3)	2				
Davis et al., 2021 (11)	2	3	1		4
Griffiths et al., 2016 (12)		1	2	1	1
Griffiths et al., 2018 (13)		2	2	1	
Grob et al., 2011 (14)	2			1	
Johnson et al., 2014 (15)		2	2		2
Moreno et al., 2006 (16)					
Nicholas et al., 2018 (17)		2		4	
Ross et al., 2016 (4)	6	2	6	1	

Systematized Review of Psychotherapeutic Components of Psilocybin-Assisted Psychotherapy D M. Horton, et. al., The Amer, J of Psychotjerapy, 2021

- First session (preparatory) 1-3 sessions
  - educational
  - build therapeutic alliance
  - discussion of the participant's life experiences, experiences with the presenting problem, and/or setting goals for the treatment.
- Treatment sessions
  - Setting (pts lay down, wear eye shades, music, nonmedical room
  - interactions typically occur during last hour
  - nondirective and supportive, assist pt in focusing their attention to the experience
- Post treatment sessions
  - integration sessions
  - ongoing between session
- TYPES OF THERAPIES
  - motivational enhancement therapy
  - cognitive behavioral therapy
  - supportive expressive group therapy
  - psychoanalytical therapy

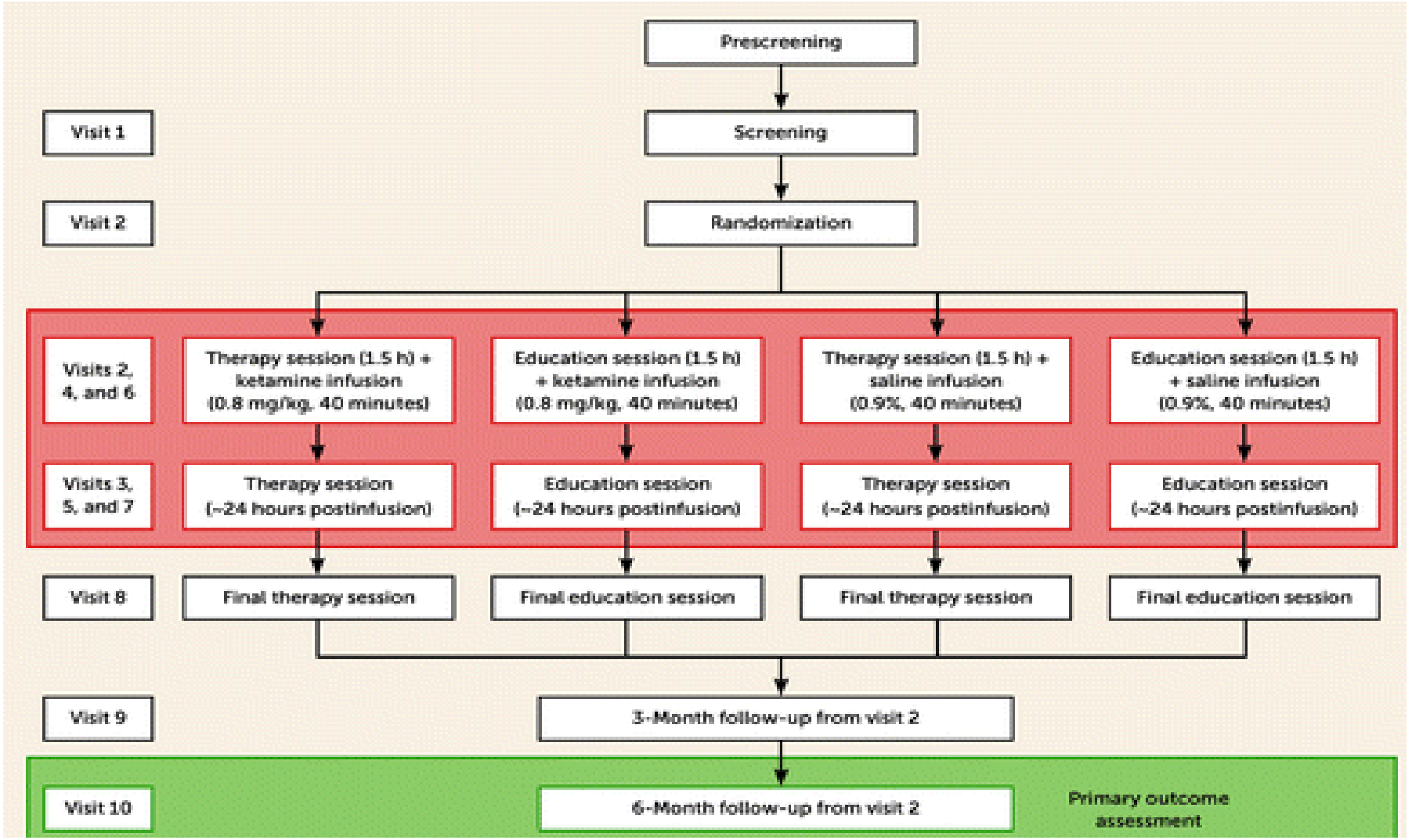
Ketamine and MOA for alcohol use disorder

- Alcohol stimulates the GABA receptor (-) and inhibits the excitatory NMDAr (glutamate excitatory), Also increases release of opioid peptides and dopamine contributing to craving
- But chronic alcohol downregulates GABA and upregulates glutamate receptor sensitivity
- Chronic alcohol ingestion required to maintain homeostasis
- Ketamine noncompetitive inhibitor of NMDAr, normalizing cortical glutamate homeostasis and induce neuroplasticity thus facilitating learning of new coping mechanisms and behaviors
- Glutamate may be important in the memory reconsolidation , accelerating post retrieval extinction of traumatic memories

Ketamine

- First studies in the 1990s, (Kruppisky and Kolp)
- 3 major review articles now
- 11 randomized studies on ketamine and alcohol use disorder (3 in management of alcohol withdrawal)
- More recent randomized controlled studies
  - Dakwar E et a (2000)
  - Rothber et al, 2021
  - Grabski et al 2022

Adjunctive Ketamine With Relapse Prevention–Based Psychological Therapy in the Treatment of Alcohol Use Disorder. Grabski M., et al., Am J of Psychiatry, 11 Jan 2022



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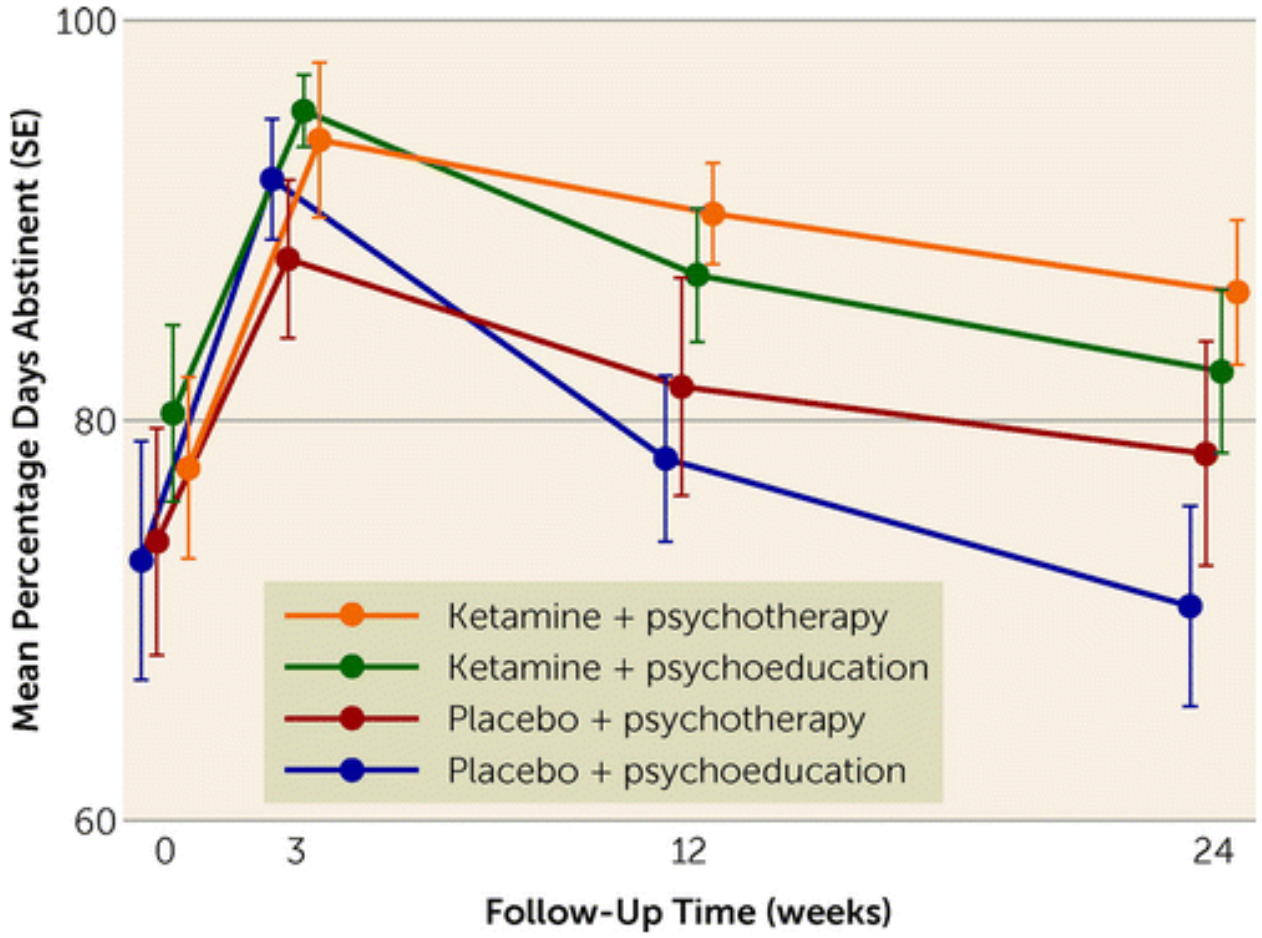

Ketamine and alcohol withdrawal

- 3 studies, retrospective
- Patients in severe withdrawal (DTs or CIWA), ICU,
- Ketamine was an adjuvant to usual treatment, ie benzos , phenobarb
- Ketamine infusions

- Overall the studies show a decrease in amt of benzos required
- Shorter ICU stay
- Good safety profile

Psilocybin

- Main psychoactive compound in “magic mushrooms”
- Synthesized in 1958
- Several studies in the use of alcohol use disorder
- Pilot study 2015
  - 10 volunteers with alcohol dependence
  - 7 sessions of MET + 2 doses of psilocybin
  - reduction of drinking days and # of heavy drinking days at 36 weeks
  - associated with positive mystical experience (mystical experience questionnaire)

Bogen Schutz MP. Et. Al., Psilocybin-assisted treatment for alcohol dependence: a proof of concept study J Psychopharmacol (2015)

Psilocybin

- 2nd larger study, randomized 93 participants
- % heavy drinking days 10% in the psilocybin group vs 24% control group at 32 weeks
- Mean daily alcohol consumption significantly lower in the treatment group
- Ongoing phase III studies multisite

Bogenschutz MP. Et. Al., 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 . JAMA Psychiat. (2022) 79: 953-62

Psilocybin for tobacco use

- John Hopkins
- Single arm open label
- 15 pts with tobacco use disorder (2 packs) who failed > 6 treatments
- 15 weeks with 2-3 psilocybin treatments
- 12/15 were abstinent at 15 weeks
- 11/12 quit after their first administration
- Higher MET scores correlated with success
- Larger phase II trial underway (1st government funded psilocybin study)

Johnson MW, et. Al., Pilot study of the 5-HT@AR agonist psilocybin in the treatment of tobacco use disorder. J Psychopharmacol. (2014) 28:983-92

MDMA for Use Disorders

- Safety and tolerability study (phase 1)
- 14 patients who completed detox, 2 sessions with MDMA
- at nine months post detox, the average units of alcohol consumption by participants was 18.7 units per week compared to 130.6 units per week before the detox.
- No adverse outcomes

First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder Ben S, et. Al., Journal of Psychopharamcology (35)4; 2021

Lysergic acid diethylamine (LSD) and alcohol use disorder

- First synthesized in 1938, psychological properties discovered in 1943
- Binds to 5HT2aR
- Hundreds of times more powerful then natural hallucinogens
- Extensively studied in the 50-60s for alcohol use disorder
- Meta-analysis in 2012: 6 randomized trials of 536 patients
  one dose for alcohol use disorder
  positive result OR 1.96
  59% of LSD group improved vs 38% in the placebo initially but lost significance at 12 months
- No recent randomized clinical trial outcomes

Lysergic acid diethylamine (LSD) and opioid use disorder

- Early studies in the 70s
- 78 inmates
- 2 groups, 37 completers in both groups
- LSD+ 6 weeks inpatient care vs weekly psychotherapy
- 12 month fu
  - abstinence LSD group-33%
  - abstinence control group- 5%

Savage C, McCabeL., Residential psychedelic (LSD) therapy for narcotic addiction. Arch Gen Psychiatry (1973) 28:808-14

IBOGAINE

- Psychoactive alkaloid from roots of a plant native to central Africa called Tabernanthe iboga
- Mechanism of action not clear, is not a primary 5-HT2AR but seems to bind to opioid receptor
- Prolonged hallucinogenic effect and often unpleasant
- Few studies on it
- Approved in New Zealand for opioid use disorder
- NIDA study for opioid withdrawal halted in 1990s due to safety concerns, prolonged QT
- 3 “observational” studies indicate reduced opioid withdrawal. no significant evidence to support long term benefit

Safety and toxicity

- Is addiction to these agents a concern.
- Flashbacks, “bad experiences:
- Acute panic attacks
- Long term effects

Case

- 32 yo male with long history of methamphetamine use. Has been in multiple treatment programs including several residential treatment, outpatient CBT, 12 steps. Only able to obtain recovery for short periods of time, ie 2-4 months, before returning to use. Several hospitalizations for stimulant use disorder. Has severe underlying depression when not using
- Has heard (has been looking extensively on You Tube and other internet sites) about psychedelic therapy for use disorders and feels strongly it might help as everything else has failed
- He is exploring going on line for ketamine treatment out of frustration with lack of success
- How do you respond

Conclusions

- Entering a new era of medications that focus on the rewiring instead of adjusting levels of neurotransmitters. New paradigm of care

- Psychedelics/therapy will become another option in the treatment of addictions (any many mental health disease) as the science evolves

- State regulations and commercial industry will precede the science

- It will need to be linked to psychological support (are there enough therapist trained in this treatment modality?) to be effective

- Patient selection will be key (personality disorders, hx psychosis, significant medical conditions, others…)

- Will see greater experimentation, misuse and consequences such as hallucinogen persisting perception disorder

Review articles

- Efficacy of ketamine intervention to decrease alcohol use, cravings and withdrawal symptoms in adults with problematic alcohol use or alcohol use disorder: A systematic review and comprehensive analysis of mechanisms of action. Garel, N., et.al., Drug and Alcohol Dependence 239 (2022)
  - 8 studies (3 AW, 5 AUD)
- The therapeutic use and efficacy of ketamine in alcohol use disorder and alcohol withdrawal syndrome: a scoping review. Goldfine C., et al, Frontiers Psychiatry, 27 April 2023
  - 10 studies (3 AW, 7 AUD)

Review articles

- Therapeutic potential if ketamine for alcohol use disorder, Neuroscience Biobehav rev, Worrell SD., Et. Al., 126:573-89 2021
- Ketamine Treatment for Alcohol Use Disorder: A Systematic Review Kelson M., et. Al., Cureus, 2023