PSYCHEDELIC MEDICINE 101

"Psychedelics, used responsibly and with proper caution, would be for psychiatry what the microscope is for biology or the telescope is for astronomy." – Stanislav Grof

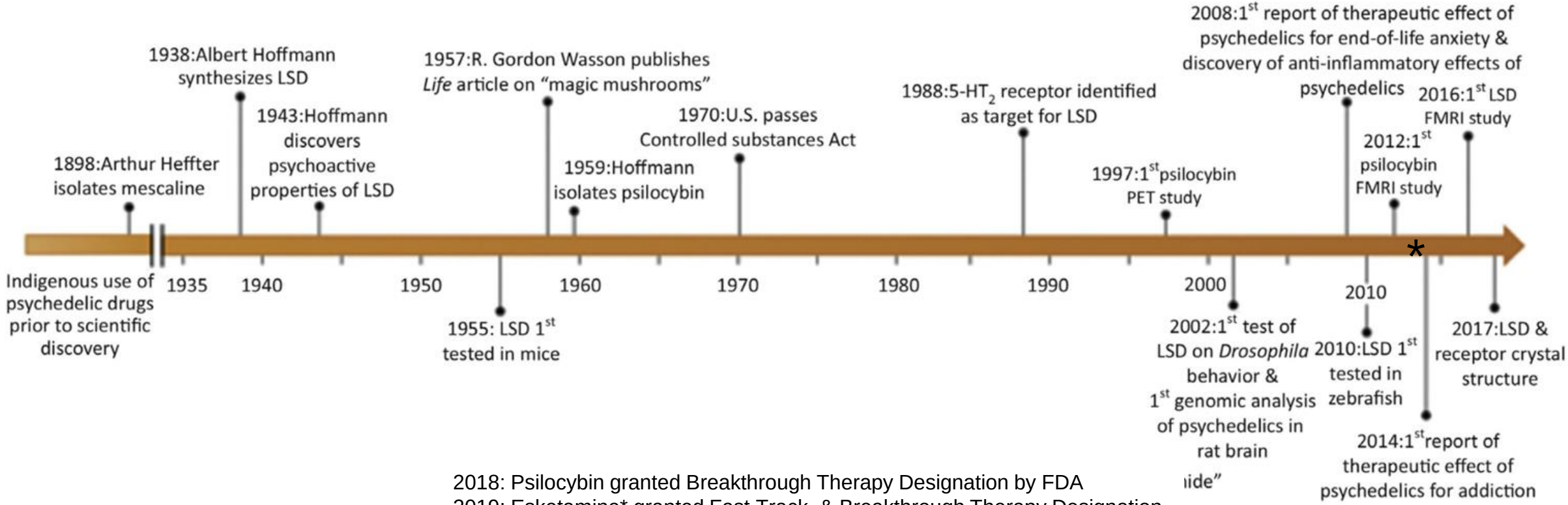
Presented by: Julia Mirer MD
February 16, 2024

Session Overview

- **Timeline of Psychedelic Research**: Overview of the evolution of psychedelic research.
- **Significance in Mental Health Context**: Understanding the relevance of psychedelic medicines amidst the current mental health crisis and opioid crisis.
- **Medication Insights:** Brief on biochemistry, clinical applications, benefits and risks associated with ketamine, MDMA, Psilocybin, LSD, Ibogaine, and DMT.
- **Legal Status Overview**: General insight into the legal status of psychedelic medications.
- **Focus on Ketamine**: Deeper exploration of the clinical applications of ketamine, a dissociative anesthetic being used to elicit psychedelic like experiences legally in the US.
- **The Future of Psychedelic Medicine**: Ethical considerations for providers, need for ongoing research, changes to current mental health care delivery that are needed for adoption.

Attendees will depart with a comprehensive understanding of the historical context, current legal framework, clinical applications, and the challenges and opportunities in the realm of psychedelic medicine research.

History of Psychedelics

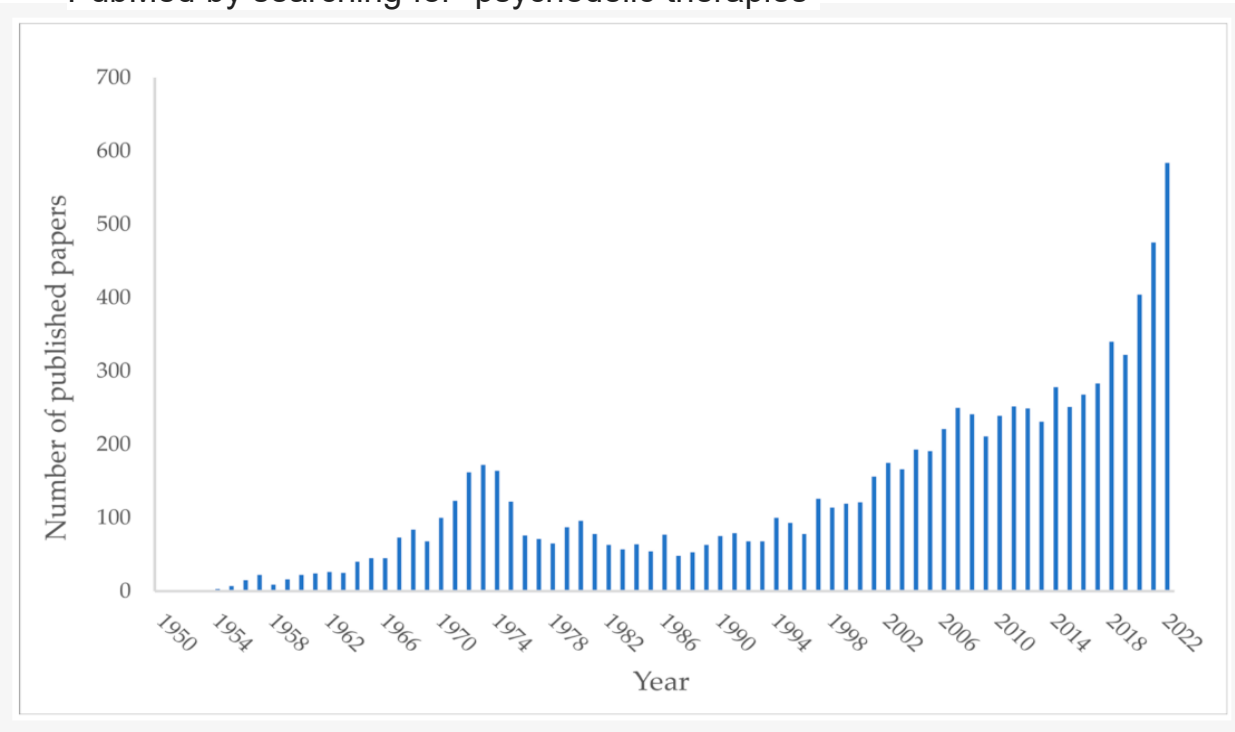


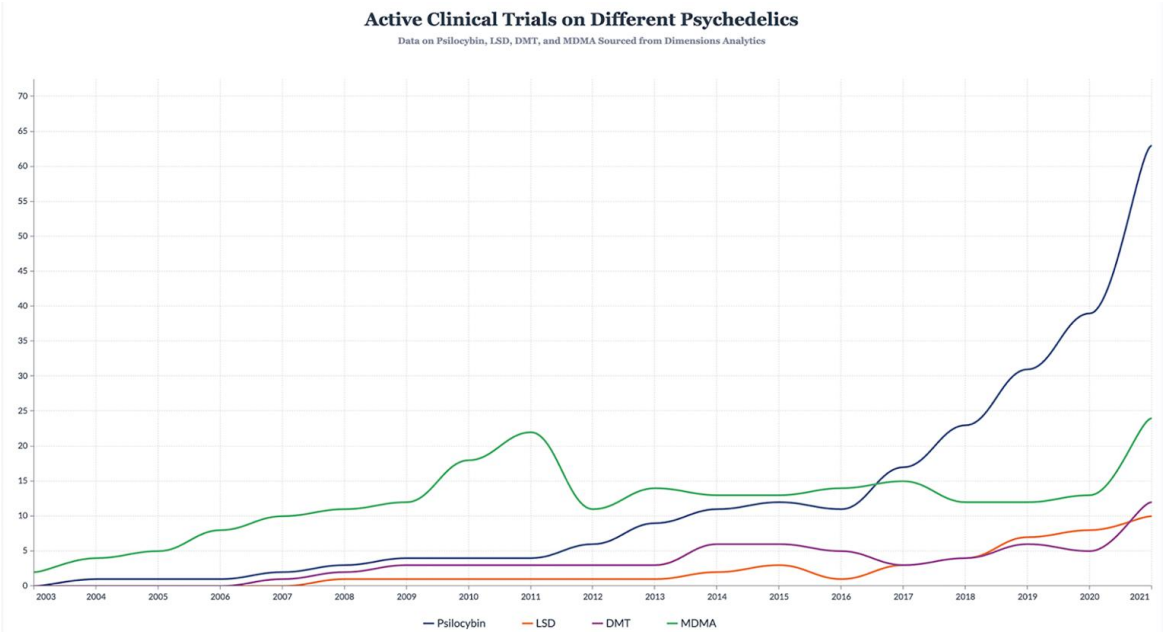
2018: Psilocybin granted Breakthrough Therapy Designation by FDA
2019: Esketamine* granted Fast Track & Breakthrough Therapy Designation by FDA
2020: MAPS publishes long term outcomes from phase II study of MDMA for PTSD
2021: Imperial College London publishes SSRI vs Psilocybin study results

Kyzar EJ, Nichols CD, Gainetdinov RR, Nichols DE, Kalueff AV. Psychedelic Drugs in Biomedicine. Trends Pharmacol Sci. 2017 Nov; 38(11):992-1005. doi: 10.1016/j.tips.2017.08.003. Epub 2017 Sep 22. Review. PubMed PMID: 28947075

Timeline of Psychedelic Research

Number of papers published per year from 1952 to 2022 reported on PubMed by searching for “psychedelic therapies”





Source: Psychedelic Alpha

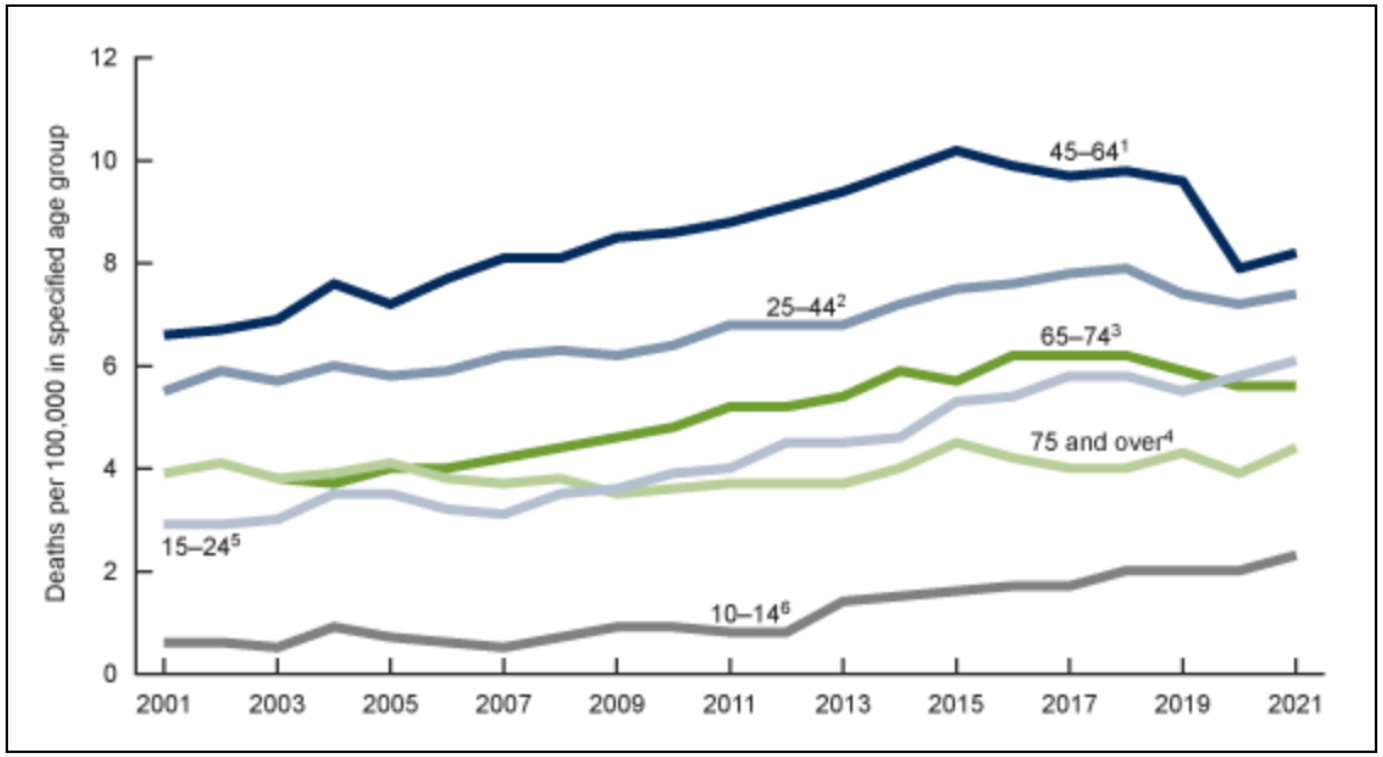
Source: Mastinu, A.; Anyanwu, M.; Carone, M.; et al. The Bright Side of Psychedelics: Latest Advances and Challenges in Neuropharmacology. Int. J. Mol. Sci. ***2023****, 24, 1329*

Current Mental ~~Health~~ Sick Care

- 2021: The total US Medicaid expenditure on antidepressants increased about 10% from 2017 to about **$1.12 billion dollars**.
- 2022: Umbrella review showed "**no consistent evidence of an association between serotonin and depression, and no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations.**"
- Up to 15% of benzodiazepine users become addicted, and adults on antidepressants are 2.5 times as likely to attempt suicide
- Once diagnosed, many patients end up staying on some combination of mental health medications for the remainder of their lives

Current Mental Health Crisis

Suicide rates for **females**, by age group: United States, 2001–2021



Source: CDC

- The suicide rate for males was 3-4.5x the rate for females during the 2001–2021 period.
- U.S. Surgeon General Vivek Murthy issued a call to action in 2021 for a national strategy for suicide prevention as well as a youth mental health advisory
- In 2022, the National Suicide Prevention Lifeline is launched “988”
- Although rates for females were lowest for those aged 10–14, this group experienced the largest percentage increase over this period, from 0.6 in 2001 to 2.3 in 2021.

Psychedelic Assisted Therapy - The Next Frontier

	Depression	End of Life DIstress	PTSD	Eating Disorders	OCD	Anxiety	TBI	Substance Abuse
KETAMINE	✓	✓	✓	✓	✓	✓	✓	✓
MDMA	✓		✓	✓	✓	✓		✓
PSILOCYBIN	✓	✓	✓	✓	✓	✓	✓	✓
LSD	✓	✓	✓	✓	✓	✓		✓
DMT	✓	✓	✓		✓	✓		✓
IBOGAINE	✓		✓	✓	✓		✓	✓

Psychedelic Therapy Works Differently

"The impact of successful psychedelic therapy is often one of revelation or epiphany. People speak of witnessing 'the bigger picture,' placing things in perspective, accessing deep insight about themselves and the world, releasing pent-up mental pain... This is very different from people's descriptions of the effects of SSRIs, where a contrasting feeling of being emotionally muted is not uncommon."

- Robin Carhart-Harris

"The thing about awe and wonder is they're both exquisitely opened states where you are absolutely in parasympathetic, you may be in flow, but you're also primed for new information so you're open to learning. Awe is a really great medicine. "

— Dr. Julie Holland

Psychedelic-Assisted Therapy

- Set (mindset) and Setting (environment)
  - Often referred to as “nonspecific amplifiers” of internal state

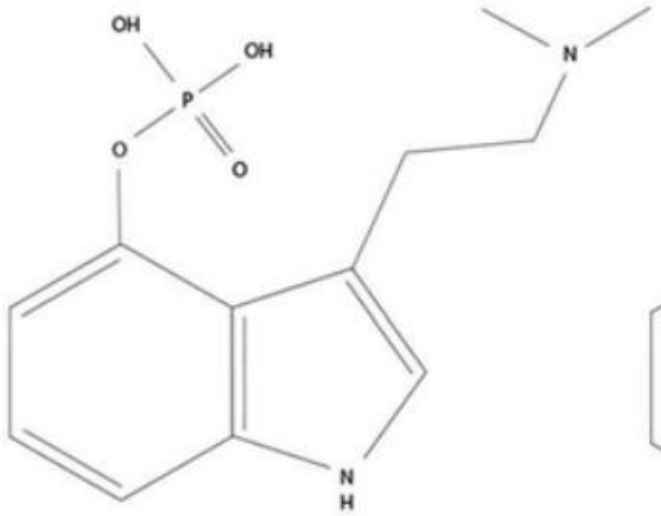
- Preparation and Integration
  - Amplify benefits of pharmacological effect of medicines

Classic Psychedelics - 5HT2A Receptor Agonists

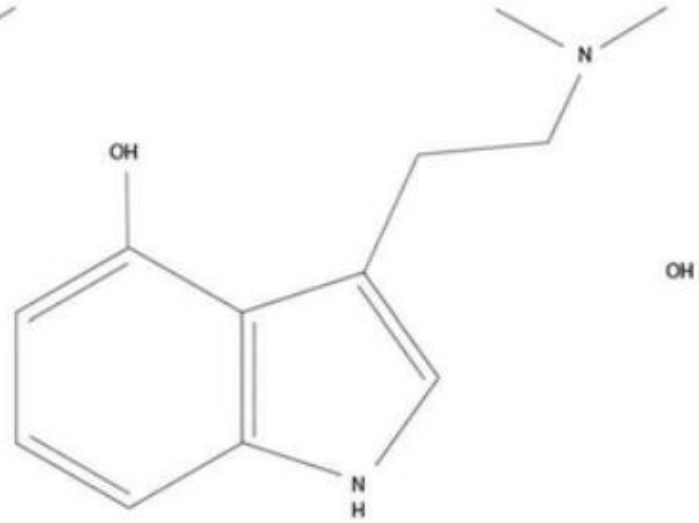
1. C-H (2018) The entropic brain - revisited; 2. C-H (2018) Serotonin, Psychedelics & Psychiatry. World Psychiatry.

PSILOCYBIN - “Magic Mushrooms”

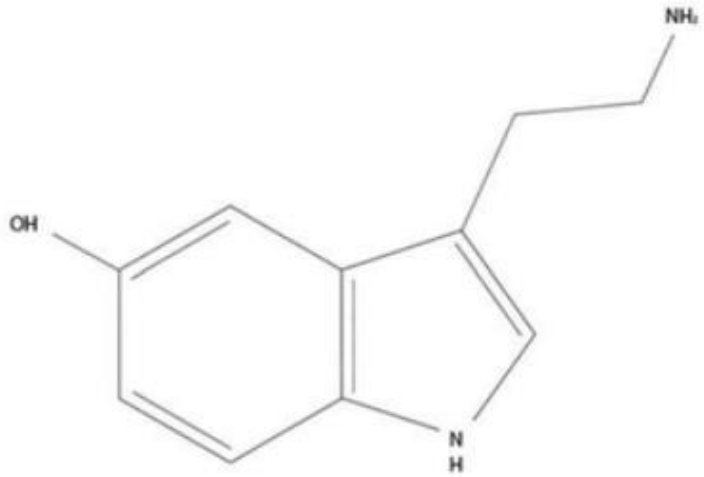
- Psilocin that is the main pharmacologically active substance, psilocybin is considered the prodrug



Psilocybin



Psilocin



Serotonin

de Veen, Bas & Schellekens, Arnt & Verheij, Michel & Homberg, Judith. (2016). Psilocybin for treating substance use disorders?. Expert Review of Neurotherapeutics. 17. 10.1080/14737175.2016.1220834

PSILOCYBIN

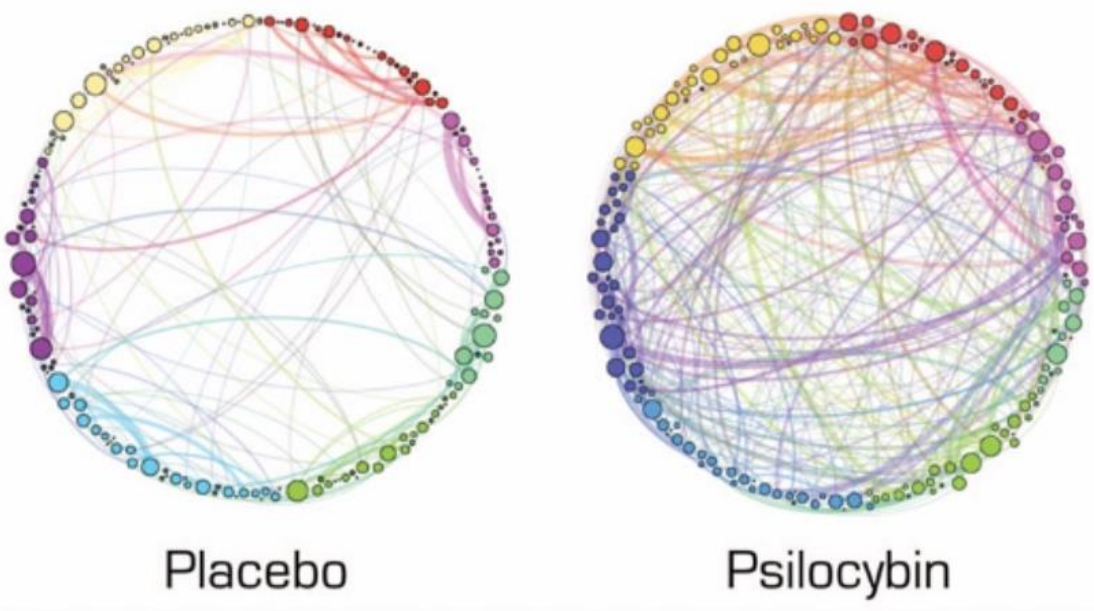


Image:PETRI ET AL./PROCEEDINGS OF THE ROYAL SOCIETY INTERFACE

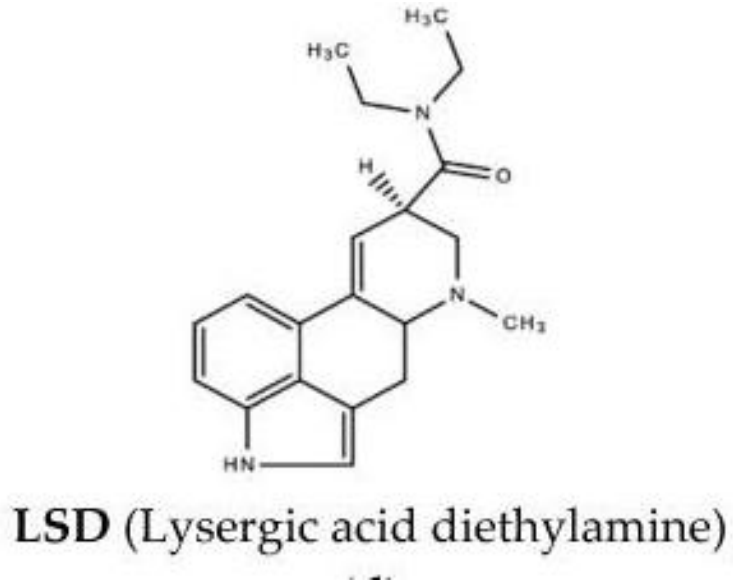
- Found in the *Psilocybe* genus of mushrooms
- "Seeking the Magic Mushroom" article published in 1957 in Life magazine by Gordon Wasson after visiting Maria Sabina in Oaxaca Mexico
- First isolated and synthesized in 1959 by Albert Hoffman
- For standardization purposes, clinical trials utilize synthetic psilocybin that does not include other alkaloids present in the natural form
- Psilocybin is reported to have the most favorable safety profile of all psychedelics

Psilocybin-Assisted Therapy

Dose	25mg (Synthetic) ~ 3.5g-5g dried mushrooms
Onset	30-40 min
Peak	75-120 min
Duration	6-8 hours

- Notable Studies:
  - Johns Hopkins - End of life anxiety
  - NYU - Alcohol Use Disorder
  - USONA - Major Depression
  - Imperial College London - Psilocybin vs SSRI

LSD (Lysergic Acid Diethylamide) - “Acid”



LSD (Lysergic acid diethylamine)

- Affects serotonin, dopamine, and glutamate systems
- Effects are due to agonist action on 5HT2A receptors
- Longest acting “classic” psychedelic
- Discovered in 1938, used for MKUltra in 1953

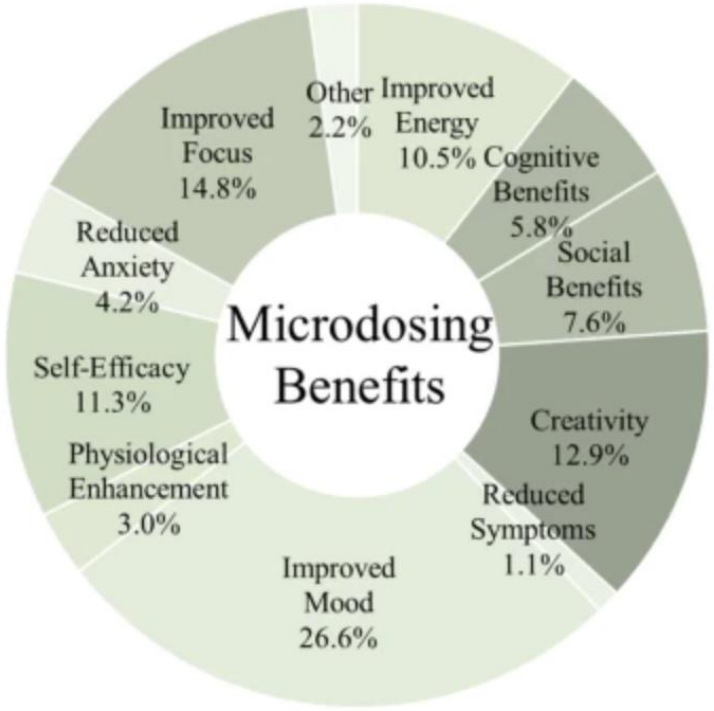
Image: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8156539/

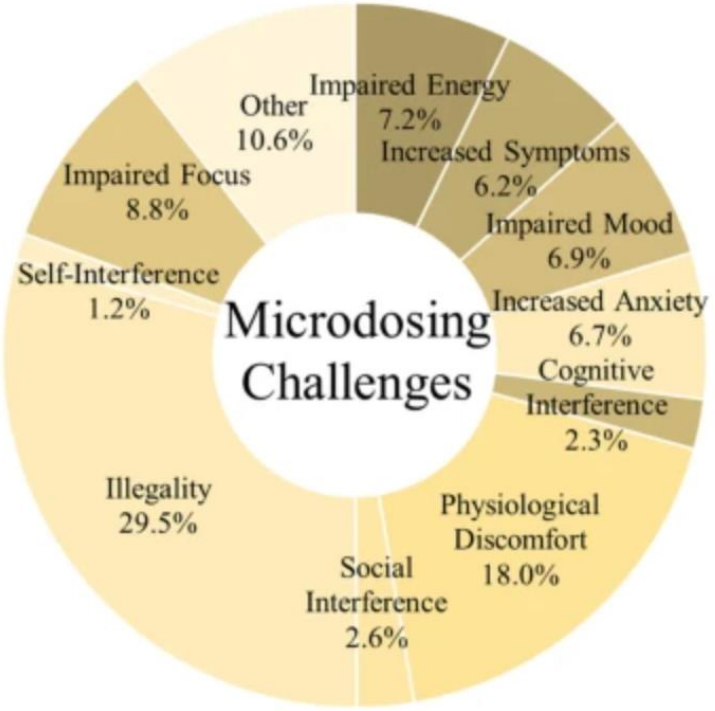
LSD-Assisted Therapy

Dose	200 *micro*grams
Onset	20-30 min
Peak	3-4 hours
Duration	8-12 hours

- Notable Studies:
  - End of life anxiety
  - Alcohol Use
  - Generalized Anxiety

A few words about “Microdosing”

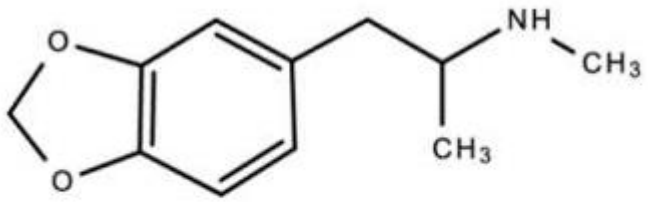




- LSD vs Psilocybin
- Dosing
- Limitations of studies and controversy

Image: Anderson, T., Petranker, R., Christopher, A. *et al.* Psychedelic microdosing benefits and challenges: an empirical codebook. *Harm Reduct J* 16, 43 (2019). https://doi.org/10.1186/s12954-019-0308-4

MDMA (3,4-methylenedioxymethamphetamine) - "Ecstasy"



MDMA (methylenedioxymethamphetamine)

- "entactogen" that induces serotonin release, also releases dopamine and norepinephrine
- effectively modulates fear memory reconsolidation, enhances fear extinction and promotes openness and prosocial behavior
- 1980's popularized party drug
- 1985 MDMA becomes schedule I after studies suggest neurotoxicity (study since debunked)
- 1986 MAPS formed to begin research on MDMA

Image: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8156539/

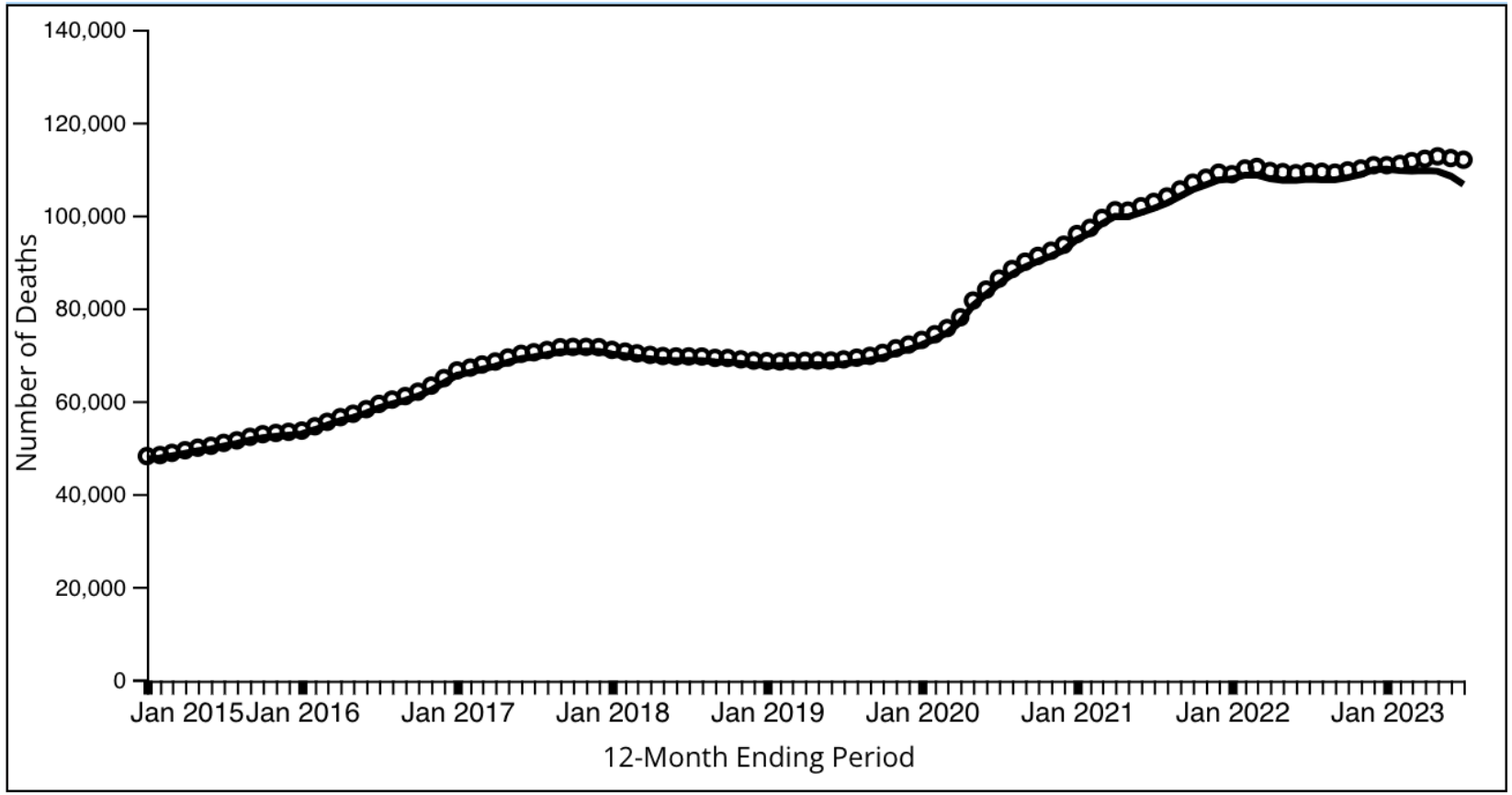
MDMA Assisted Therapy

Dose	75 - 120mg; ~2 mg/kg
Onset	30-60 min
Peak	75-120 min
Duration	3-6 hours

Results of MAPS phase 3 MDMA for PTSD

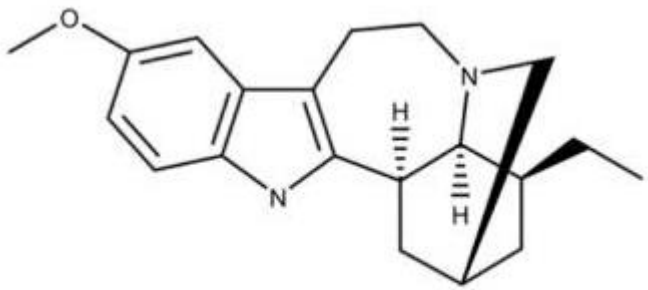
- 86.5% participants treated with MDMA-AT achieved a clinically meaningful benefit
- 71.2% participants no longer met criteria for PTSD by study end

Current Opioid Crisis



- Almost 21 million Americans have at least one addiction (more than the number of people who have all cancers combined) per the U.S. Surgeon General.
- Opioid-related overdoses doubled from 2010-2016, and have continued to rise, especially after the pandemic
- Treatment is often followed by relapse

IBOGAINE



Ibogaine

- Found in Iboga plant (*Tabernanthe iboga*) a shrub indigenous to central west Africa, especially Gabon, Cameroon and Congo
- Ibogaine is an atypical psychedelic, affecting NMDA, kappa-opioid, sigma, 5HT2A, dopamine, nicotinic acetylcholine, and affects GDNF levels
- Metabolized into noribogaine, main metabolite
- noribogaine acts as a potent serotonin reuptake inhibitor, a moderate kappa-opioid receptor agonist, and a weak or a partial mu-opioid receptor agonist
- Most notable effects for: TBI, opioid addiction, Parkinson's

Image: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8156539/

IBOGAINE for OPIOID ADDICTION

Typical Dose	“Flood dose” 15-20 mg/kg “Booster dose” 1-5 mg/kg
Onset	30-45 min
Peak	1-2 hours
Duration	Visual phase 1-4 hours, introspective phase up to several days

- lack of standardized clinical practices in the experimental environments in which ibogaine therapy is generally practiced increases risk
- Often requires monitoring in clinic for cardiac events
- doses above 12 mg/kg have higher risk of cardiac abnormalities
- Ibogaine may work in reversing the effects of opiates on gene expression, with resulting impacts on neuroreceptors, returning them to a pre-addiction condition
- Treatment centers in Canada, Mexico, Netherlands, South Africa, New Zealand

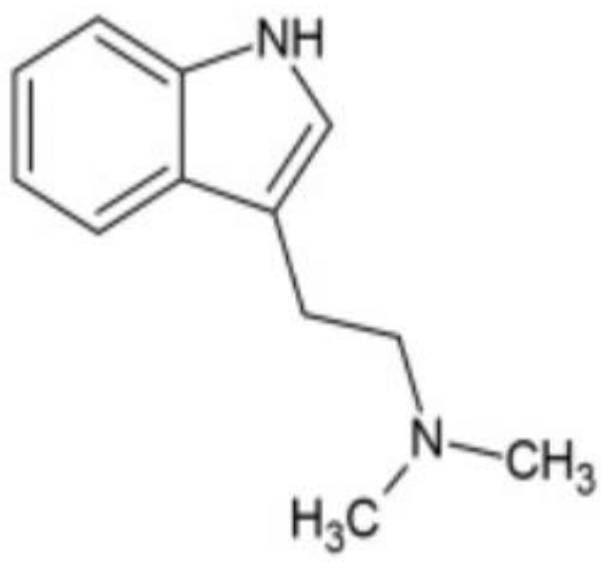
IBOGAINE and VETERANS

Veterans have to leave the country for this treatment because it is illegal

Recent study highlights benefits for TBI:

- NOT a randomized controlled study but possibly the first study to report evidence for a single treatment with a drug that can improve chronic disability related to repeated TBI from combat/blast exposures
- at baseline, study participants experienced clinically meaningful levels of disability, PTSD, depression and anxiety.
- After MISTIC, participants showed a remarkable reduction in these symptoms, disability measures continued to improve and psychiatric symptom remission and response rates 1 month post-MISTIC remained high

DMT (Dimethyltryptamine)



DMT

Encyclopedia of Forensic Sciences, Third Edition

- first synthesized in 1931 and demonstrated to be a hallucinogen in 1956
- Found naturally in **ayahuasca** (*Psychotria viridis,* boiled with an MAOI, *Banisteriopsis caapi*)
- 5-MEO-DMT: found naturally in the **bufotoxin** from the Colorado River Toad
    - When smoked, most powerful and fast acting of the tryptamine class of hallucinogens

DMT as an INTERVENTION

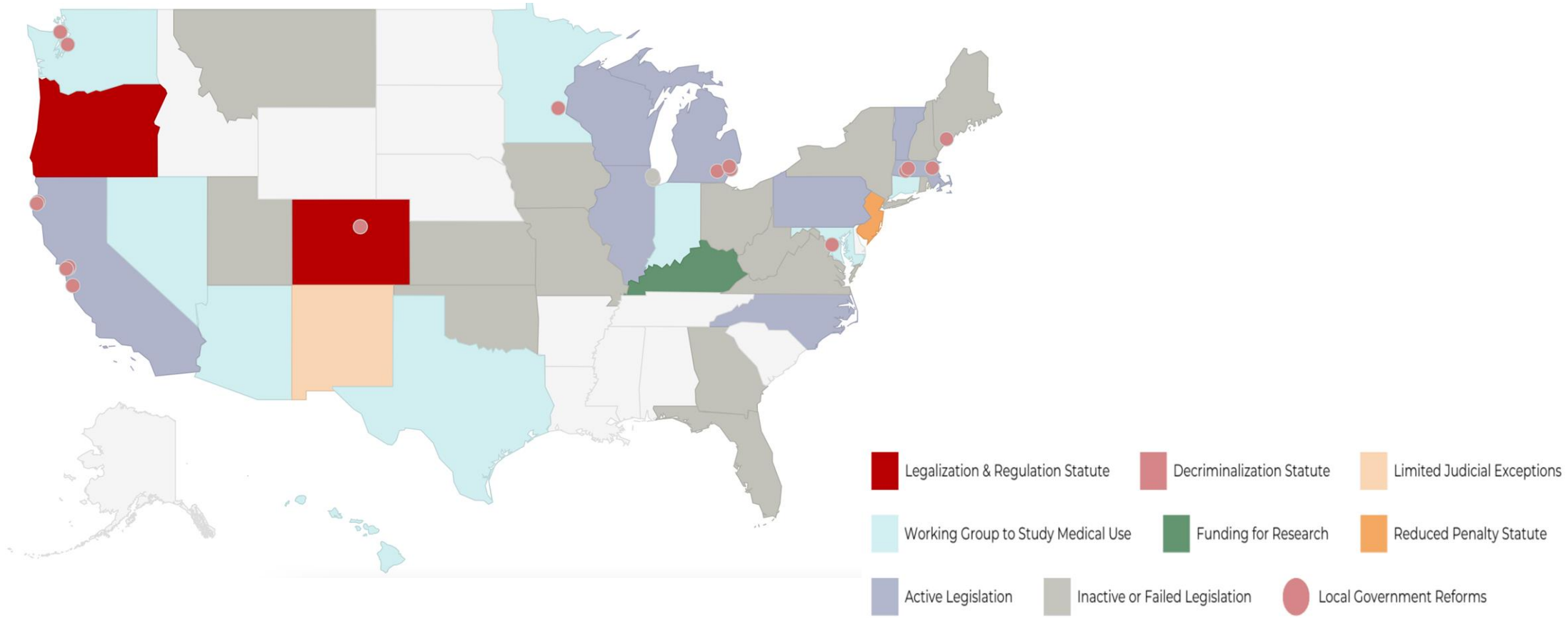
Dose	IV: 0.2 - 0.4 mg/kg bolus
Onset	Within 2 minutes
Peak	5-10 min
Duration	30 min

- Difficult to study as a brew due to inconsistency of preparations
- Ethical concerns about use of frog venom
- Has been studied as IM, IV, and inhalation
- inhalation of vaporized 5-MeO-DMT engenders a potent range of experiences ranging from spiritual ecstasy and enlightenment, to feelings of near-death anxiety and panic

Scheduling of Substances

SCHEDULE	DRUG EXAMPLES	FDA DESCRIPTION
I	LSD, MDMA, **Psilocybin**, Mescaline, Heroin	no currently accepted medical use and a **high potential for abuse**
II	Cocaine, Morphine, PCP, Methamphetamine	high potential for abuse, with use potentially leading to severe psychological or physical dependence.
III	Ketamine, Hydrocodone, Anabolic Steroids	moderate to low potential for physical and psychological dependence
IV	**Xanax**, Valium, Rohypnol	**low potential for abuse** and low risk of dependence
V	Codeine-based cough medicines	Very low potential for abuse

Legal Status of Psychedelics in the US



Source: Psychedelic Alpha, https://psychedelicalpha.com/data/psychedelic-laws

Ketamine is NOT a psychedelic

Ketamine is a dissociative anesthetic, which can elicit a *psychedelic-like* experience

- 1965- Ketamine was discovered to be a dissociative anesthetic
- 1970- FDA approved for use in Vietnam veterans for acute pain
- 1990- Ketamine introduced for chronic pain
- 2018- FDA grants Ketamine “breakthrough therapy designation” for treatment resistant depression

KETAMINE - “Special K”

Ketamine

- Ketamine **blocks** the NMDA receptors part of the glutamatergic system (excitatory system of the brain) located in your limbic system, which is responsible for learning, memory, and emotional regulation
- Ketamine blocks the NMDA receptors on GABA neurons.
- GABA are inhibitory neurons.
- Because the inhibitory neurons are blocked, **a glutamate surge** is created.
- This surge triggers increased neural connectivity, potentially improving mood and cognition.
- Ketamine also binds receptors for dopamine D2, adrenergic, HCN1, cholinergic, and opioid, as well as affecting sodium channels

Image: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8156539/

Ketamine-Assisted Therapy

Dose	Low dose: 0.5-0.8mg/kg IV; 50-75 mg lozenges; 30-50 mg IM; 60 mg IN Moderate dose: 0.8-1.2mg/kg IV; 100-200 mg lozenges 50-100 mg IM; 80 mg IN High dose: 1.2-2.5mg/kg IV; 300-500 mg lozenges 150-200 mg IM; 100 mg IN
Onset	IV: 2-3min; IM: 3-5 min; Oral: ~30 min; IN: ~5-10 min
Peak	IV: varies; IM: ~30 min; Oral: ~45 min; IN: ~20min
Duration	IV:~20 min after stopping IV; IM: 1-2hr; Oral:1-3hr; IN: 45-60 min

Psycholytic Dosing

- Lower doses, focus on therapy framework with drug as a catalyst

Psychedelic Dosing

- Higher doses, focus on transformational power of the drug experience and dissociation

Key takeaway: experience varies individually

KETAMINE IN THE NEWS

Forbes

CBC

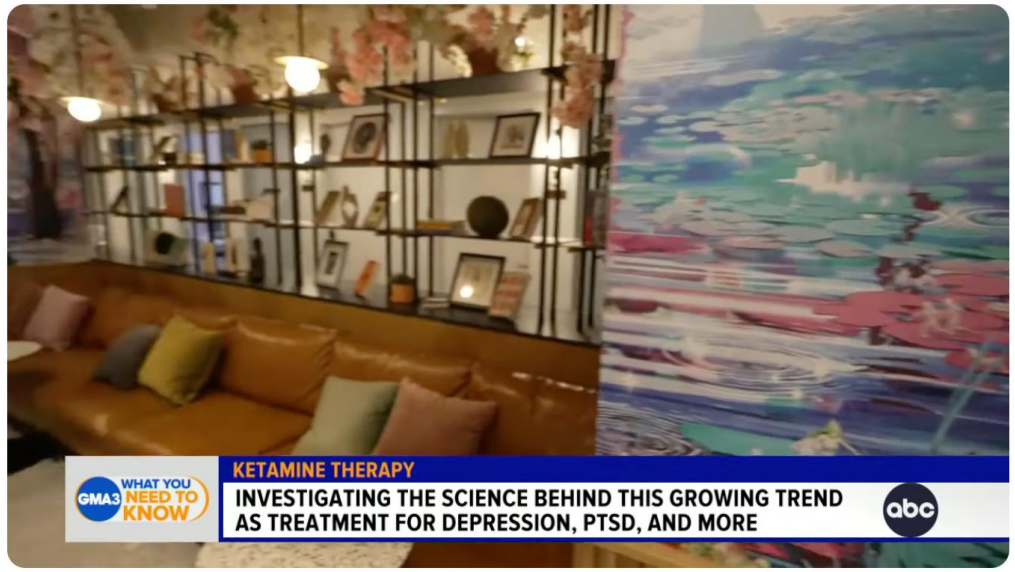
BUSINESS INSIDER

The New Yorker

Harvard Health

Medscape

The New York Times



What you need to know about ketamine therapy

The Good, The Bad, & The Ugly

- Promising results
- Racemic ketamine is off patent therefore less research incentives
  - High cost and variability of therapy means less research focused on therapy component
- Ugly media coverage of Matthew Perry's death - shows lack of general education of public and reporters

Los Angeles Times

Psychology Today

THE WALL STREET JOURNAL.

Future Of Psychedelic Medicine

- Can’t patent natural substances - so biotech companies are looking for patentable molecules, exploring shorter acting psychedelics to fit into the clinical model
- Other companies looking to remove the “trip” all together
- *How important IS the altered state of consciousness?*
- *What SHOULD we be focusing on?*

“The tragedy that I see is that DARPA could have a winner right now with MDMA for PTSD,” says Doblin. “But DARPA is trying to say screw the psychedelic experience and let’s invest in non-psychedelic psychedelics while 20 vets a day are killing themselves.”

Ethical Considerations

- INFORMED CONSENT
  - Physical touch
  - Not all memories under a psychedelic are true memories!
- ACCESS & PRICING
  - New treatments are expensive, but is insurance coverage for the medicine all we need?

Paradigm Shift for Existing Mental Health Care Delivery

- Need more research focused on therapy
- Need more research on impact of group therapy
- Adolescents deserve better first line treatments
- When talking about mental health care, the route of administration of the medicine IS the provider - how can we help our providers today so that these medicines become as effective as they can be?

Q & A

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Microdosing information: Microdosing Institute

Clinical Trials near you: https://classic.clinicaltrials.gov/ct2/home