RMPDS 18th Annual
Scientific Meeting

Comparable but not Identical: The Unique Surveillance Needs of Psychedelics

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Overview

- History & pharmacology
- The importance of effectiveness data
- Need for purpose built systems

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Thank you to our wonderful team!

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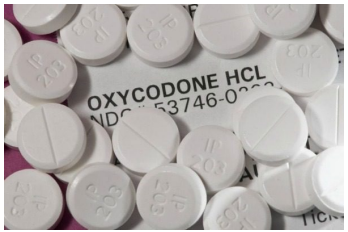
Psychedelics are following a similar path as previously illicit drugs turned therapeutics

- Long history of advocacy for new drugs in hopes for safer and more effective alternatives.
- Opium→morphine→heroin→oxycodone



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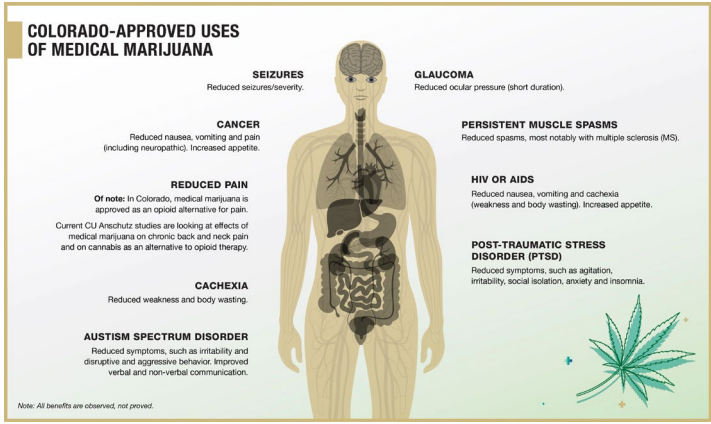
- Cannabis



5.7 million

Opioid Use Disorder

1.8 million

Methamphetamine Use Disorder

19.2 million

Cannabis Use Disorder

8.8 million used a psychedelic in the last year

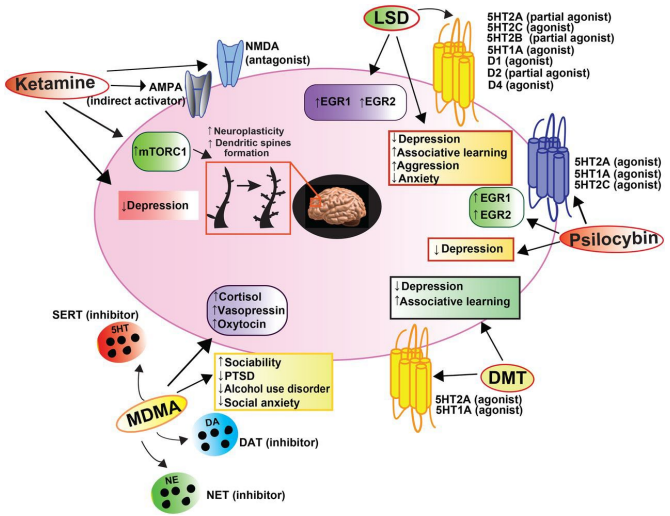
SAMHSA, NSDUH, July 2024

MDMA, LSD, and psilocybin have similar regulatory histories.

But will the differences in pharmacology lead to the same results?

Psychedelics Do Not Affect Dopamine to the Same Effect as Traditional Illicit Drugs

- Cocaine & methamphetamine lead increases in dopamine by causing release and direct inhibition of dopamine transporter.
- Psilocybin work directly on 5HT2A.
- LSD works directly on 5HT2A with some dopamine receptor agonism.
- MDMA increases reuptake and release of serotonin, norepinephrine, and some dopamine.
- Ketamine/esketamine block NMDA receptors leading to increases serotonin.

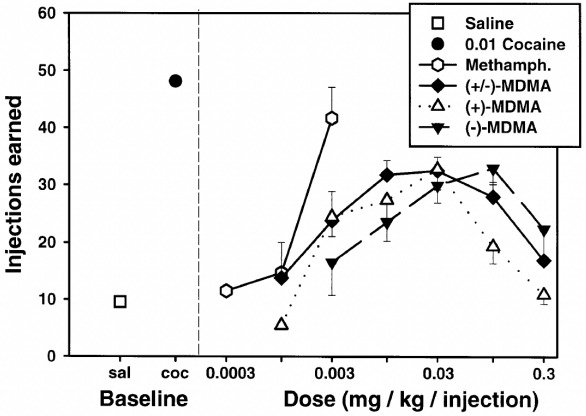


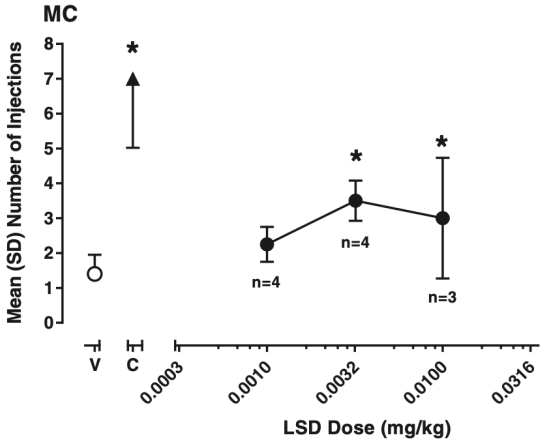
De Gregorino, 2021

All lead to some increase in dopamine.

Addictive Potential Appears Lower

- MDMA and LSD availability leads to less self-administration than cocaine or methamphetamine in monkeys.
- MDMA and psilocybin cause dopamine release the mesolimbic reward pathway, but opposes dopamine reward in ventral striatal regions (not seen with cocaine or amphetamine).

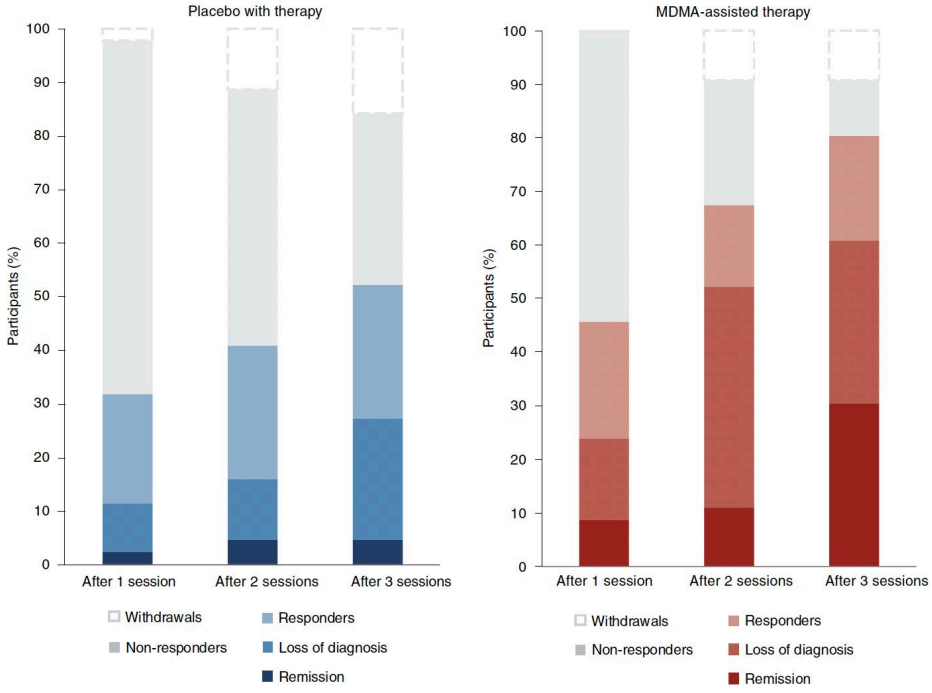




Fantegrossi, 2002, Shin, 2008, Goodwin, 2016.

The Effect Size for Psychedelics May Be Huge

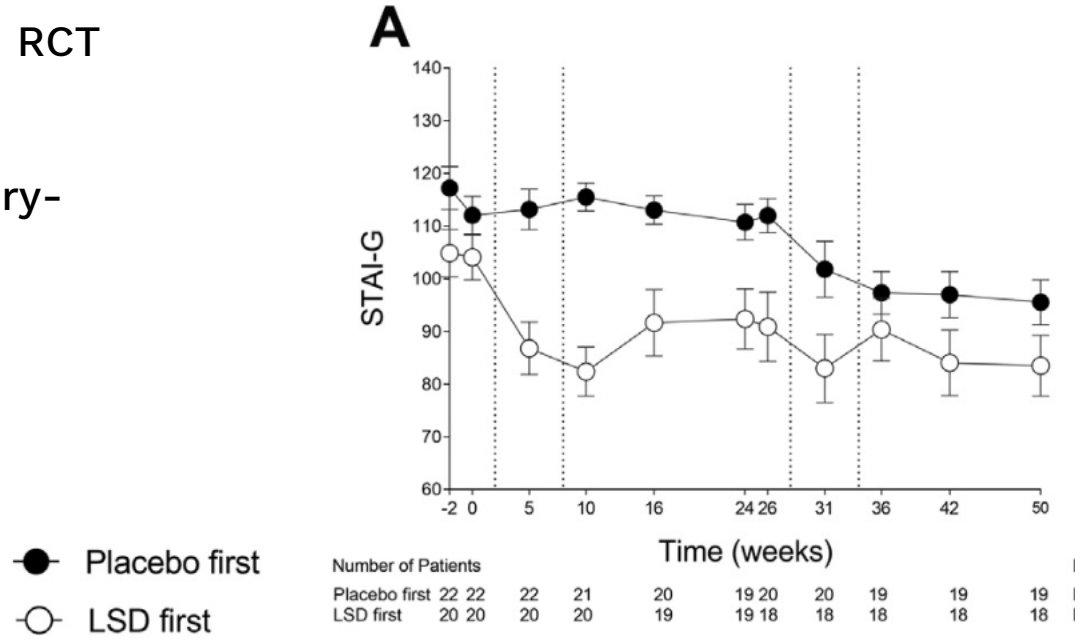
- 22.8% of US adults had any mental illness in 2023.
- 5.7% had severe mental illness in 2023.
- 4.7 million US veterans report a service related disability, costing the US government $73 billion/year.
- SSRIs are effective in approximately 50% of patients with PTSD.



SAMHSA, 2024, Mitchell, 2023.

LSD May Improve Anxiety in a Durable Manner

- Phase II placebo controlled RCT
- 200 mcg LSD in 2 sessions
- State-Trait Anxiety Inventory-Global (STAI-G) primary endpoint



Holze, 2023.

Adverse Effects May be Manifestations of the Underlying Disease

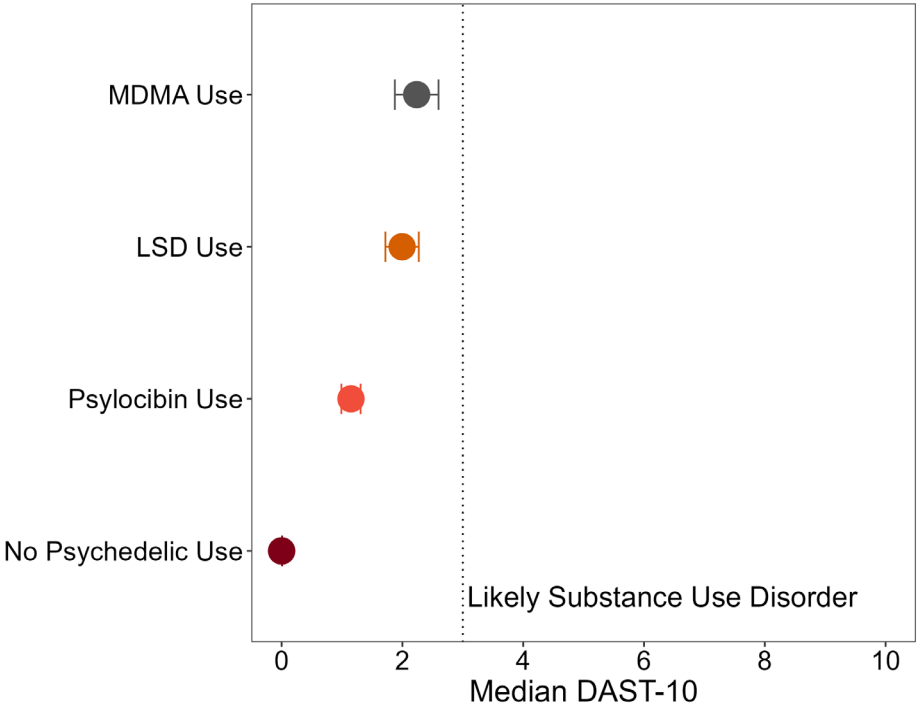
- 13.1 million Americans had serious thoughts of suicidal.
- 2.4 million made a plan, but didn’t act.
- 1.1 million had thoughts, made a plan, and attempted suicide.
- Integration therapy facilitates reframing negative experiences into opportunities for growth.
- Hallucinations are expected, but may persist.


We love you, call collect
WEP-1101
ART LINKLETTER
AND HIS
DAUGHTER DIANE
WORDS BY
MARTIN WARK
BACKGROUND MUSIC BY
RALPH CARMICHAEL
PRODUCED BY
IRVIN S. ATKINS
Art Linkletter and his daughter, Diane, narrate an anguished cry for communication between the generations
WORD

Thus, we must monitor rates of AEs in non-treated in the real world.

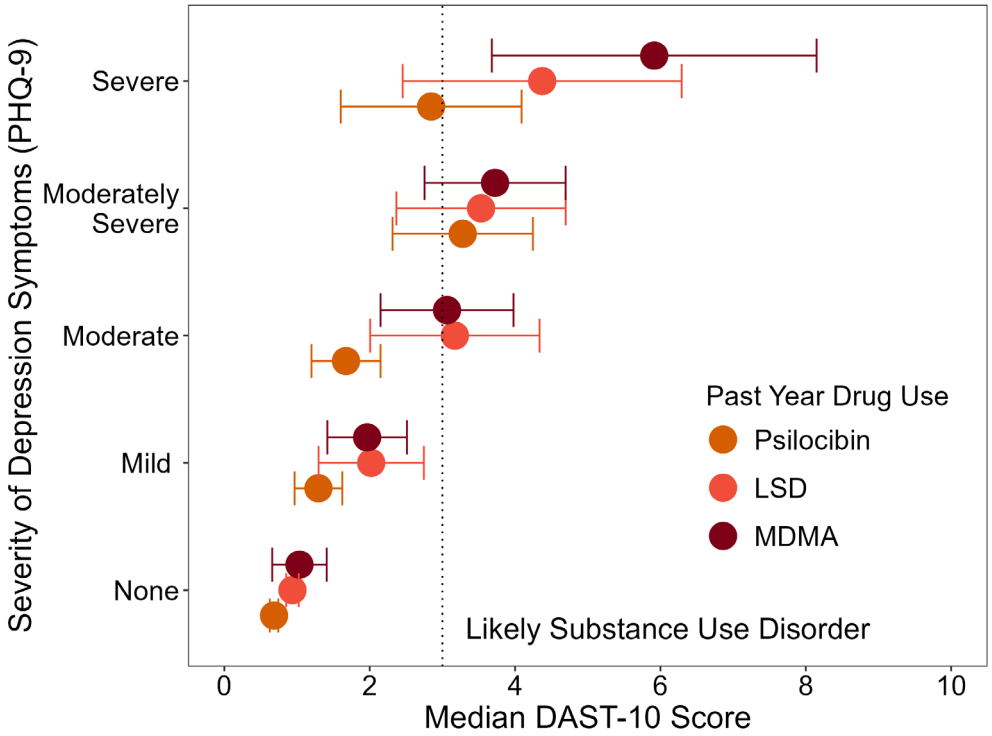
And we must account for confounders and modifiers.

The rate of SUD varies by psychedelic



NMURx, 2023

Risk varies by disease severity



We can’t fully understand safety of these drugs without understanding effectiveness.

1. What is the rate of events in the general population that don’t use?
2. What is the rate of events in those treated?
3. Do these rates change over the course of treatment?
4. Have events increased or decreased?

There are not adequate systems to assess real world safety and effectiveness of these drugs.

Hospital Records Don’t Capture Psychedelic Related Visits

- ICD codes over endorse most illicit drugs.
- Only 26% of ED visit with a cannabis ICD code are cannabis attributable visits.
- ICD codes for psychedelic AEs don’t adequately capture cases.
- There were only 9 cases of psychedelic poisoning in NHAMCS from 2015-2021 (3 mushrooms, 3 LSD, 3 "other psychodysleptics”).
- Methods to ensure sensitivity and specificity must be robust.

NPDS Does Not Adequately Capture Product or Intent

- More people call the poison center when a new drug becomes available.
- New illicit brands are common.
- Was the drug used through an approved program?
- Was the patient using to treat a medical condition?
- Did they mix it with another drug?

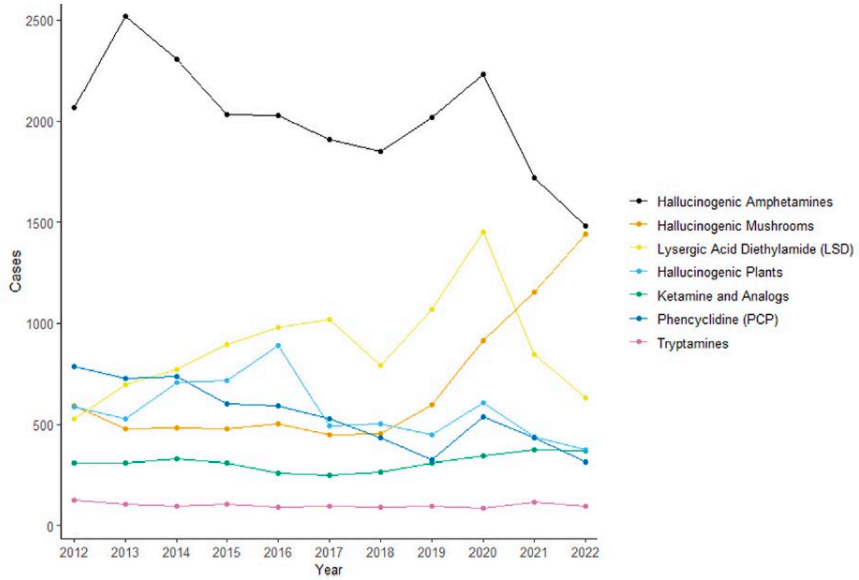


Figure 1. Annual exposures to psychedelic substances reported to US poison centers.

Simon, 2024.

Patient Registries Can Capture Approved Use

- Observational studies that collect uniform clinical data
- Predetermined outcomes in the real-world can be assessed
- Can be effective at measuring effectiveness in the real-world

- Possible Problems
  - Lack of independence
  - Don’t capture data on use outside of approved programs
  - Can be biased in populations enrolled
  - Failure to capture confounders
  - Failure to validate key data points

NSDUH is a cornerstone of surveillance

- NSDUH is the most important national data source on drug use prevalence.
- It is not designed to parse products.
- It is not designed to assess local availability or local policy.
- It does not parse psilocybin from other psychedelics.
- It does not identify reasons for use.
- The scope is not designed for monitoring of new product safety

FAERS Provides Important Reconciled Data

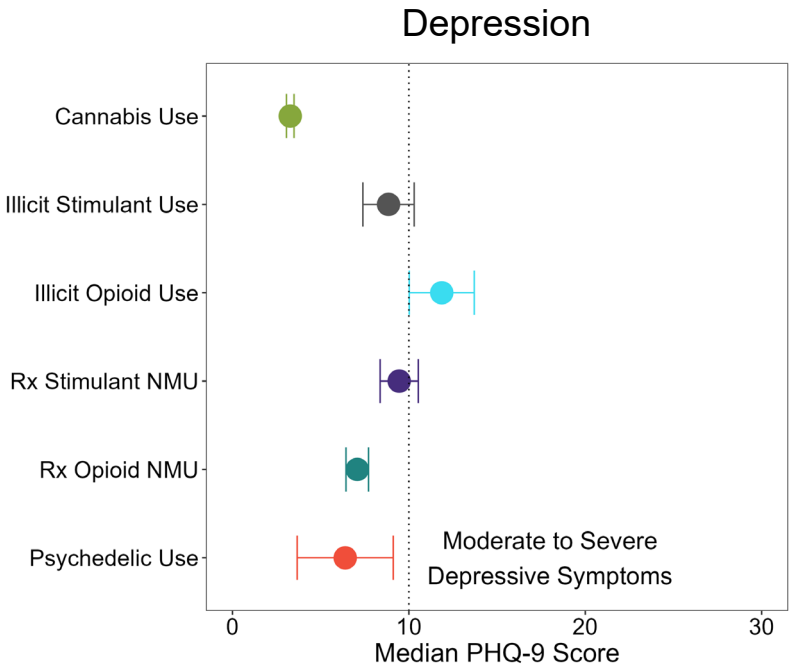
- Excellent source for rare AEs
- Pharmacovigilance follow up

- Potential Problems
  - Only utilized for approved pharmaceuticals
  - Biased by physician and patient drug preferences
  - Doesn’t capture diversion
  - Won’t capture AEs that occur in the non-treated
  - Not designed to capture abuse/misuse

Real world evidence programs must be purpose built.

FDA RWE Framework, 2018.

Cross sectional data demonstrate lower depression scores amongst psychedelic users

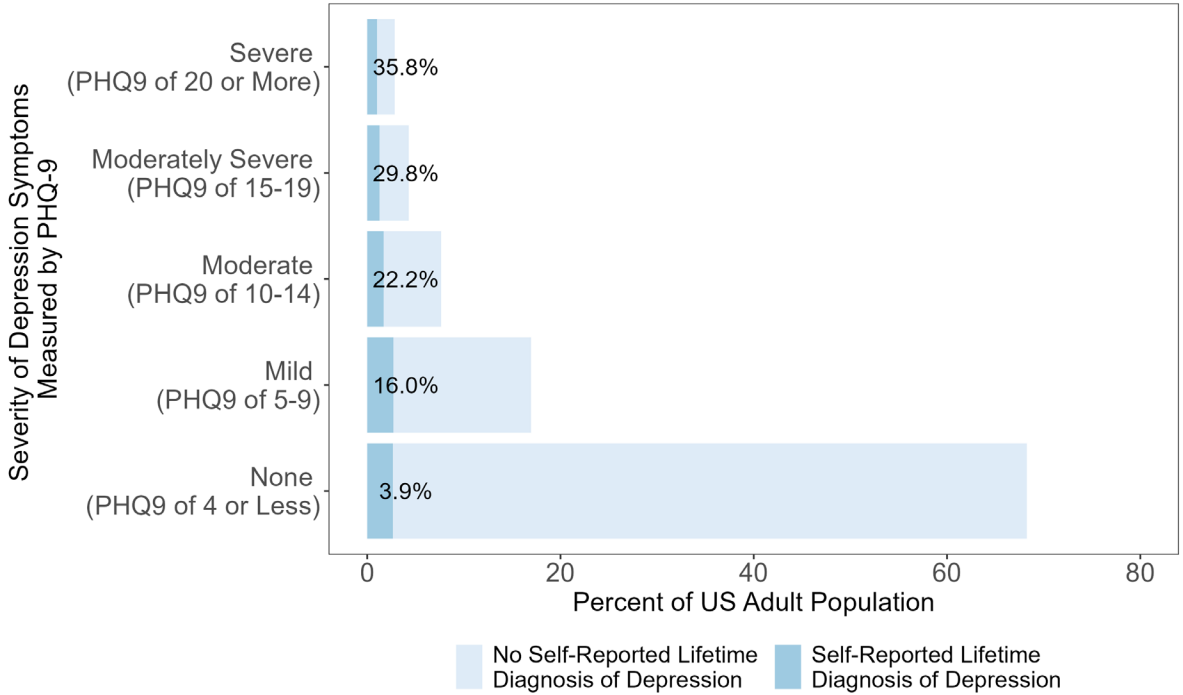


NMURx, 2023

Real World Evidence Must. . .

- Be timely
- Be drug and dose specific
- Capture timing of exposure
- Capture untreated
- Capture variable use patterns
- Stratify by symptoms and other patient characteristics
- Use validated outcome tools
- Be generalizable
- Track trajectories outcome over time

We Must Capture Symptom Burden

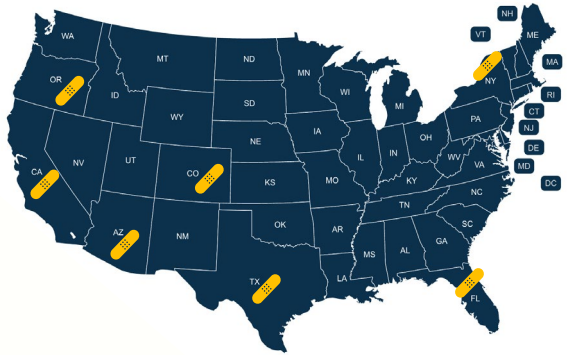


NMURx, 2023

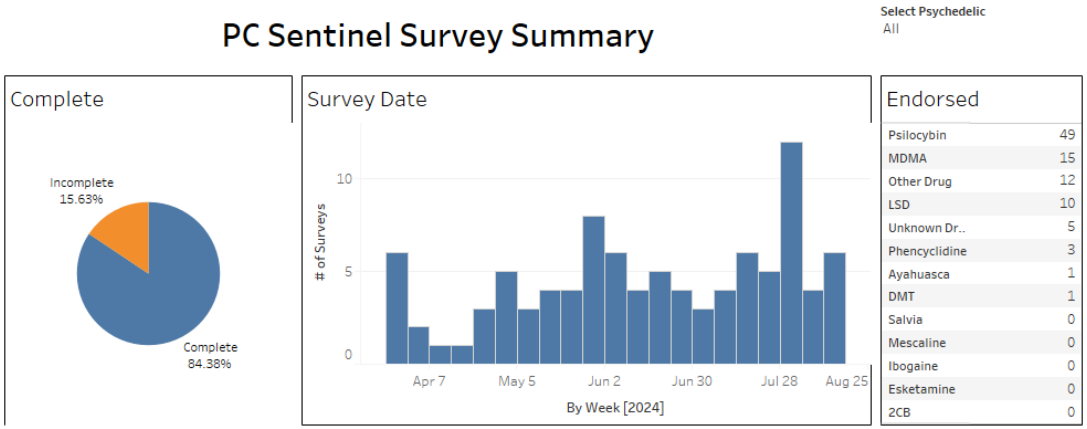
A general drug use survey can't give us detailed use patterns or patient trajectories.

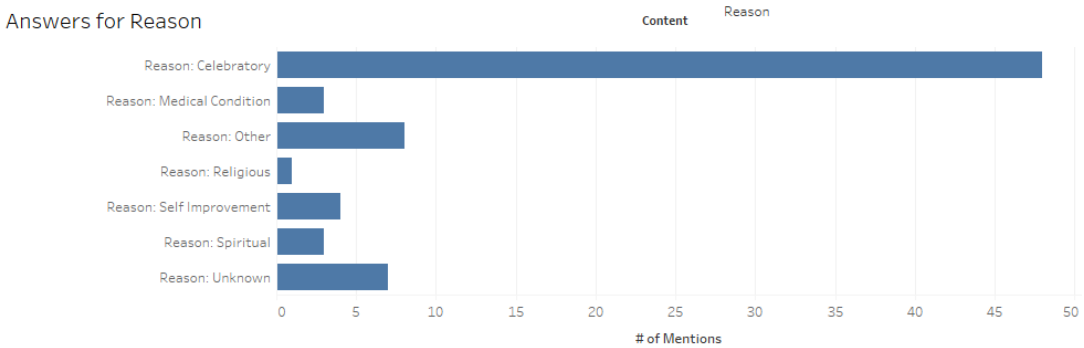
Healing Center Program

- Captures data on safety and effectiveness from patients entering treatment in ketamine, esketamine, and psilocybin treatment centers.
- Median age: 38 (IQR: 19-63)
- 78% report fair or poor health at baseline.
- 61% report major depression is the reason for treatment.
- Comorbid disease is the norm
  - 89% have depression
  - 83% have anxiety
  - 55% have PTSD
  - 11% have history of addiction
  - 16% have chronic pain



Reason for Use Should Be Sought





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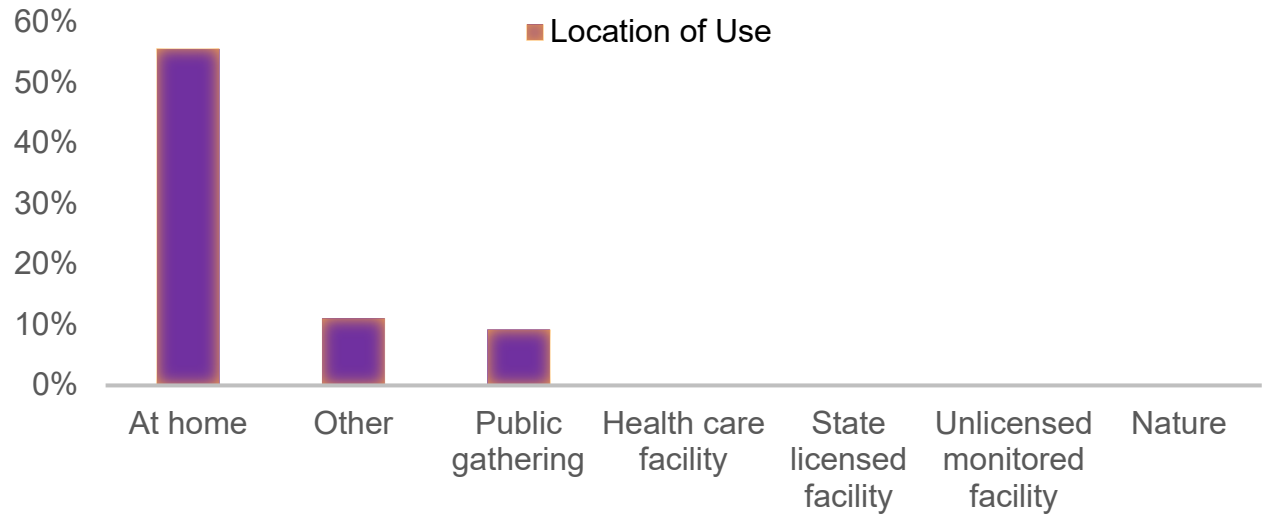
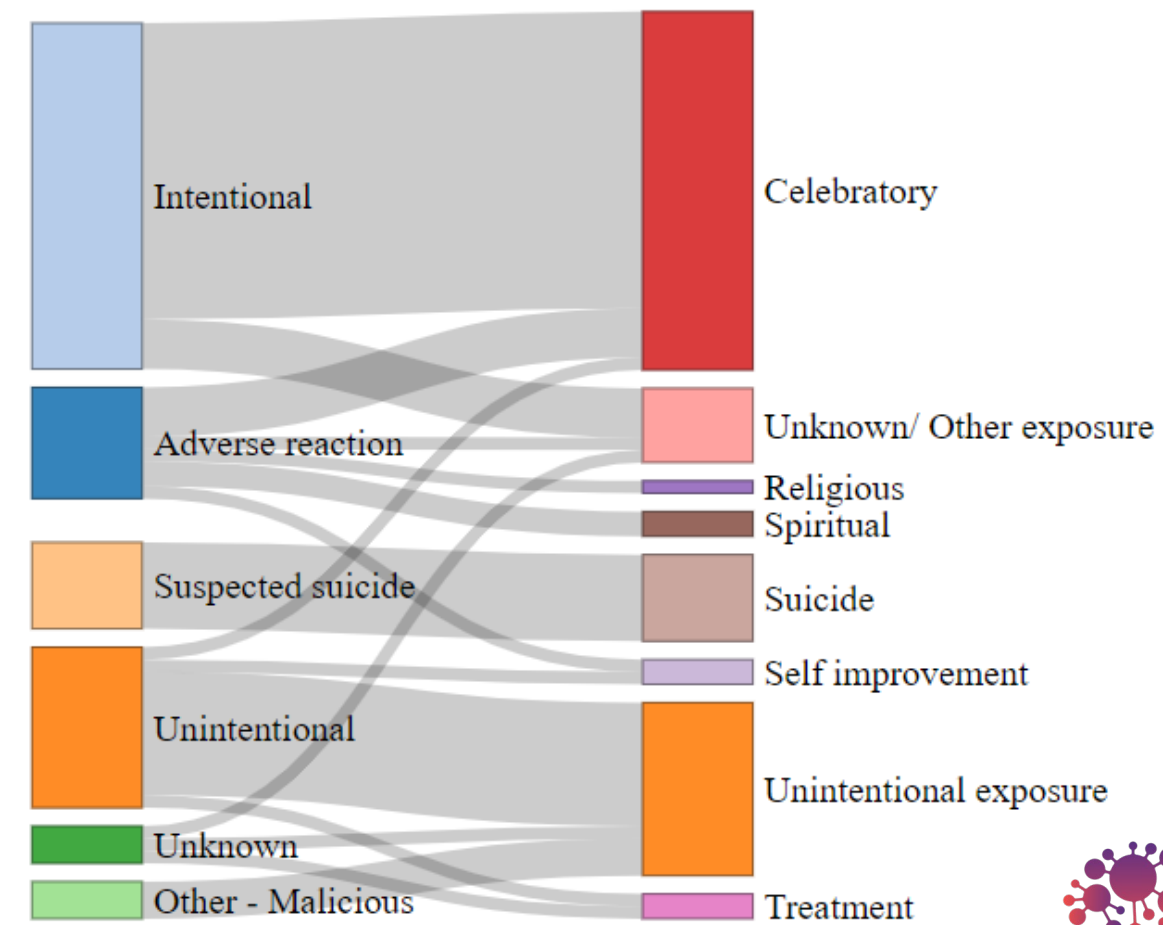
Source of Illicit Drug Must be Captured

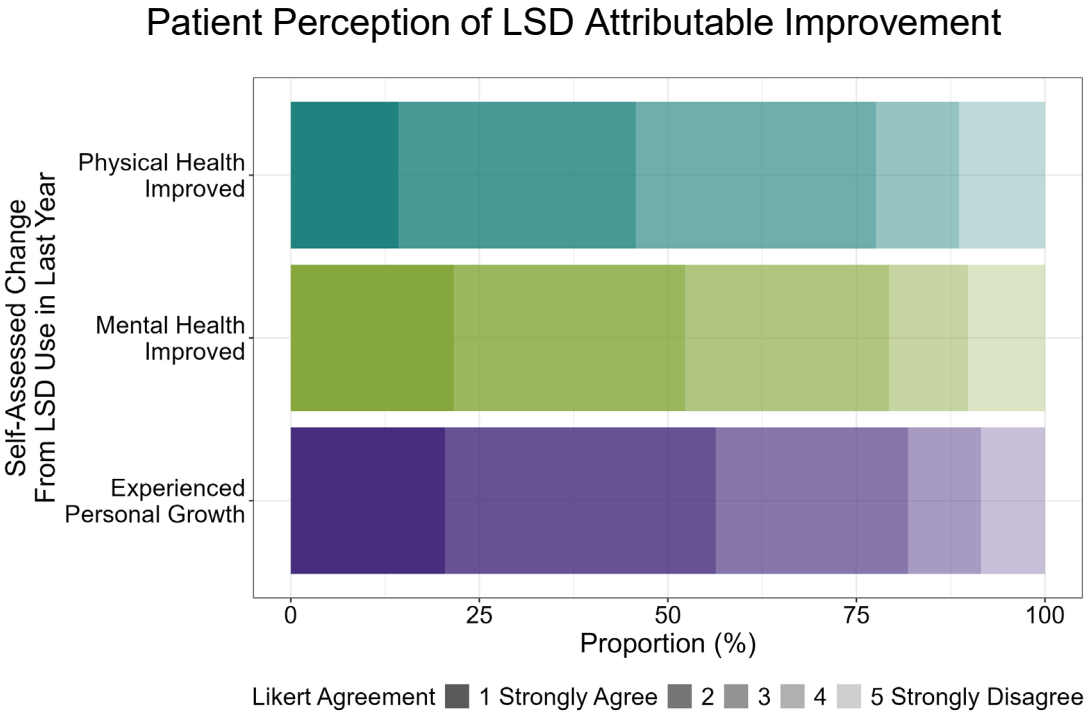
- We do this through triangulation with surveys and the Sentinel Poison Center Program.
- Augmented data collection at time of poison center call.




NPDS
PC Sentinel
Intentional
Adverse reaction
Suspected suicide
Unintentional
Unknown
Other - Malicious
Celebratory
Unknown/ Other exposure
Religious
Spiritual
Suicide
Self improvement
Unintentional exposure
Treatment

National Survey Investigating Hallucinogen Trends (**NSIHT**) can fill the gaps in prevalence knowledge about safety and effectiveness in the general population.

NSIHT is Purpose Built



Summary

- Population and individual patient surveillance tools are necessary.
- Tools must be purpose built.
- Consistency in outcomes across tools allows for triangulation of findings.

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Thank you and enjoy the afternoon!

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