SCIENCE · SAFETY · POLICY

The Psychedelic Gap

Controlled-trial successes and real-world complexities

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01 · THE TENSION

Two pictures of the same drugs

In the controlled trial

- Selected participants
- Known drug and dose
- Structured set and setting
- Preparation + integration
- Short-term endpoints

In the real world

- Comorbidity, polypharmacy
- Variable purity and dose
- Often unsupervised use
- Little prep or integration
- Effects unfold over months

What works in a trial does not always hold up once these drugs are out in the world.

02 · THE OPTIMISTIC PICTURE

Controlled trials look remarkable

2 ✓

positive Phase 3 trials for treatment-resistant depression (psilocybin)

67%

of MDMA-therapy patients no longer met PTSD criteria (Phase 3)

−6.0 pts

lower Hamilton Anxiety vs placebo, held to 12 weeks (LSD, GAD)

9.7% vs 23.6%

heavy-drinking days: psilocybin vs placebo (alcohol)

40.5% vs 10%

6-month smoking abstinence: psilocybin vs patch

18×

higher odds of complete cocaine abstinence vs placebo

Large, rapid effects under medical supervision, plus ~80% durable response at 6 months in cancer distress.

03 · THE FINE PRINT

...from a controlled world

The same results depend on five conditions holding at once.

1. **Selected patients**
2. **Fixed, known dose**
3. **Set & setting**
4. **Prep + integration**
5. **Short endpoints**

Change any one of these, and the picture can change.

04 · THE REAL WORLD

A different lens on the same drugs

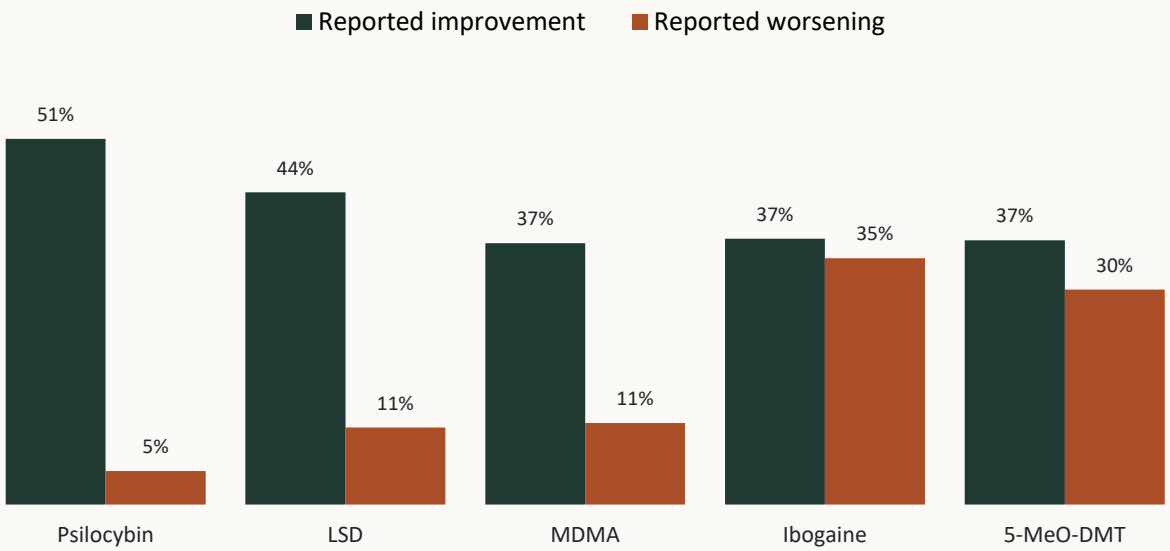
WHERE THE DATA COME FROM		WHAT SURFACES
Poison centers	→	Acute psychological distress
Emergency department visits	→	Prolonged / destabilizing effects
Observational cohorts	→	Cardiovascular events in at-risk patients
Community & national surveys	→	Lasting distress; impaired functioning

These are the outcomes controlled trials tend to miss.

05 · A POPULATION-LEVEL SIGNAL

Feeling better vs. feeling worse, by drug

2025 NSIHT, nationally representative US adults; self-reported change in mental health after use.



≈ 11 : 1

psilocybin: better vs. worse

≈ 1 : 1

ibogaine & 5-MeO-DMT: about even

The common drugs skew strongly toward benefit; ibogaine and 5-MeO-DMT sit close to even. Cross-sectional, self-reported.

06 · ADVERSE EVENTS, COMPARED

Adverse events: the trial versus the real world

In clinical trials

- Serious AEs: none in healthy volunteers; ~4% with prior psychiatric illness
- Common AEs mostly transient: headache ~40%, nausea ~24%, anxiety ~22%
- No deaths, HPPD, or lasting psychosis in modern trials
- But AE monitoring was systematic in only ~24% of studies

In naturalistic use

- ≥1 of 13 adverse effects: 76%–95% of recent users
- Wider range: cardiac symptoms, suicidal thoughts, prolonged effects
- Cardiac symptoms ~44–51% for ibogaine & 5-MeO-DMT
- Self-attributed, in unscreened and unsupervised settings

More adverse events, and a wider variety, outside the trial (Hinkle et al., JAMA Psychiatry 2024; Simonsson et al., JAMA Netw. Open 2026).

07 · BOTH DIRECTIONS

Real-world use cuts both ways

Outside the clinic, the same drug helps some people and hurts others.

HARMS

9.8%

sexual or physical violence during use
Chwyl et al., World Psychiatry 2026

8.9%

functional impairment >1 day (2.6% sought help)
Simonsson, Hendricks et al., J. Affect. Disord. 2023

2.8×

more difficulties with ≥4 adverse childhood experiences
Olofsson et al., Int. J. Drug Policy 2026

BENEFITS

51%

improved mental health after psilocybin (NSIHT)
Simonsson et al., JAMA Netw. Open 2026

↓ distress

and suicidality across 190,000+ US adults
Hendricks et al., J. Psychopharmacol. 2015

18%

reported a major positive life change
Carlisle et al., Sci. Rep. 2026

08 · WHY TRIALS MISS IT

What controlled trials aren't built to capture

Trials use pure drug, known doses, screened patients, and short follow-up, so they rarely encounter:

- **Toxicity from adulterants & unknown street doses**
- **Interactions with other medications**
- **Harms in the patients trials exclude**
- **Delayed effects beyond the follow-up window**
- **Rare or population-specific harms**

As access expands: post-approval surveillance · standardized adverse-event reporting · harm-reduction frameworks

A recognized surveillance gap (Simonsson, Johnson & Hendricks, "A Call for Action," JAMA Health Forum 2024).

Efficacy in ideal conditions doesn't guarantee effectiveness, or safety, at scale.

So the work now is to build the research, surveillance, and policy that let the good results reach people safely.

09 · CLOSING THE GAP

What research needs to do

Pragmatic trials	Representative patients: serious mental illness, comorbidity, complex trauma
Real-world evidence	Registries and cohorts that follow people past the trial window
Surveillance built in	Poison-center and safety partnerships in place from the start
Standardized safety	Common adverse-event definitions and reporting across studies
Durability	Longer follow-up, and whether effects need maintenance

09 · CLOSING THE GAP

What policy and practice need to do

Prepare state systems now	Work out who pays, how Medicaid covers it, and which providers deliver it, before approval arrives
Build oversight early	Provider credentialing, safety protocols, informed consent, and a way to report complaints
Communicate risk honestly	Give the public straight information on both benefits and harms
Watch use outside clinics	Track the use already happening; give providers and patients accurate risk information
Coordinate federally	Get FDA, SAMHSA, NIH, and the states aligned early

Drawn from the SAMHSA technical-assistance paper on psychedelics as medicine (2026).

IMPLICATIONS

What each of you can do

FDA

Track adverse events after approval; set labels and prescribing rules to fit real-world use

NIH

Fund trials in everyday patients, and studies that follow people after the trial ends

SAMHSA & states

Set provider training and credentialing, plan Medicaid coverage, communicate risks and benefits

Industry & academia

Build real-world evidence and safety-monitoring partnerships; report benefits and harms plainly

TAKEAWAY

The trials are promising. The real world is messier. We should plan for both.

These therapies could help a lot of people. Getting there safely means building the real-world evidence, surveillance, and policy to match the trials.

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Sources: Simonsson et al., JAMA Netw. Open 2026 · Hinkle et al., JAMA Psychiatry 2024 · Chwyl et al., World Psychiatry 2026 · Simonsson & Hendricks, J. Affect. Disord. 2023 & 2025 · Olofsson et al., Int. J. Drug Policy 2026 · Carlisle et al., Sci. Rep. 2026 · Hendricks et al., J. Psychopharmacol. 2015 · SAMHSA 2026