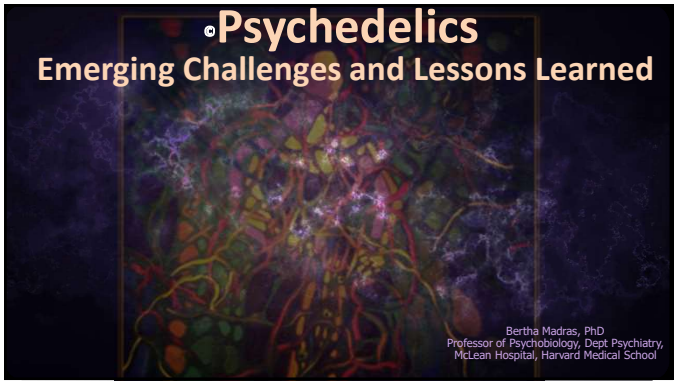


1

Why is this Topic Timely?

To learn

- status of medicalizing Schedule 1 drugs, others

To prepare

- Policy development, renderjudgements

2

Introduction

Controlled Substances	• Drug scheduling and Definitions of Abuse Liability
Medicalization of psychoactive substances: unmet needs	• **Opioids** • **Marijuana** • **Ketamine** • **Hallucinogens**
How Good is the Science?	• Four Challenges and Representative Clinical Trials
Unintended Consequences	• Have we learned anything?
PHPs and Schedule I drugs	• Is it prime time for policy?

3

Controlled Substances: Drug Schedules

Schedule I no currently accepted medical use, high abuse potential severe	Psilocybin, LSD, Marijuana, MDMA, Peyote, Heroin, Mephedrone, MDPV, cannabinoids
Schedule II high potential for abuse, severe psychological or physical dependence, medical use	Cocaine, Methamphetamine, Methadone, Hydromorphone, Meperidine, Hydrocodone, Oxycodone, Fentanyl, Dexedrine, Adderall, Ritalin
Schedule III moderate to low potential for physical psychological dependence	< 90 mg Codeine per dose (Tylenol with codeine), Ketamine, Anabolic Steroids, Testosterone
Schedule IV low abuse, addiction potential	Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien, Tramadol
Schedule V lowest potential for abuse	Antidiarrheal, Antitussive, Analgesics, Cough preparations, Lomotil, Motofen, Lyrica, Parepectolin

4

How do Drugs Become Classified in Restrictive Categories?

Eight Factor Analysis Drives Scheduling

Required Under CSA (21 USC 811(c))

1. Actual or relative potential for abuse
2. Known pharmacology
3. Current scientific knowledge of substance
4. History and current pattern of abuse
5. Scope, duration, and significance of abuse
6. Public health risk
7. Psychic or physiological dependence liability
8. If immediate precursor of a controlled substance

5

How is Abuse Liability Defined?

- Use in amounts that create health or safety hazard (self, others)
- Use of substance on own initiative, not on medical advice
  - Significant diversion from legitimate channels
- Substances' actions are like other substances with potential for abuse
- Evidence of actual abuse of substance indicates potential for abuse

Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No 91-1444, 91st Cong., Sess.1 (1970) reprinted in U.S.C.C.A.N. 4566,4603

6

Medicalization of Psychoactive Substances

Lessons from the past, present

- Opioids
- Marijuana
- Ketamine
- Hallucinogens

7

Opioids

- Root Causes
- Current Crisis
- Lessons Learned

8

Generational Forgetting

For Decades, Prescription Opioids Avoided for Chronic Pain: no good evidence

9

Weak Scientific Literacy

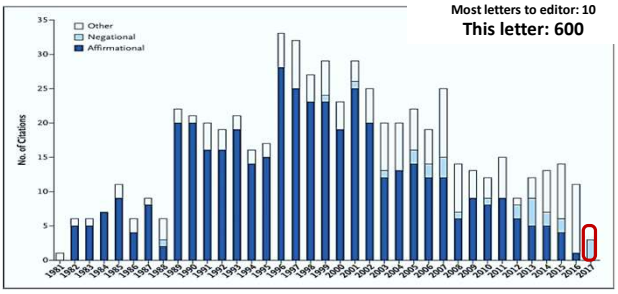
ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients[1] who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,[2] Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

Jane Porter, Hershel Jick, M.D. Addiction Rare in Patients Treated with Narcotics. N Engl J Med 1980; 302:123
Portenoy RK, and Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 1986; 25: pp. 171-186

10

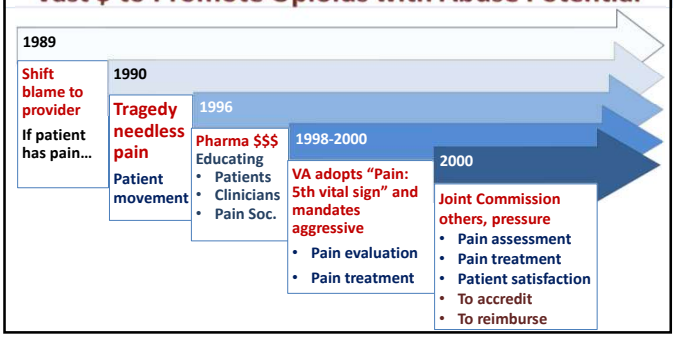
Advocates Reigned, Skeptics Ignored



Leung PTM, et al., A 1980 Letter on the Risk of Opioid Addiction. N Engl J Med. 2017 Jun 1;376(22):2194-2195

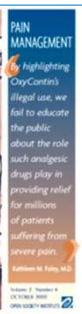
11

Vast $ to Promote Opioids with Abuse Potential



12

Political "Humanitarian Pleas"



IDEAS for an Open Society

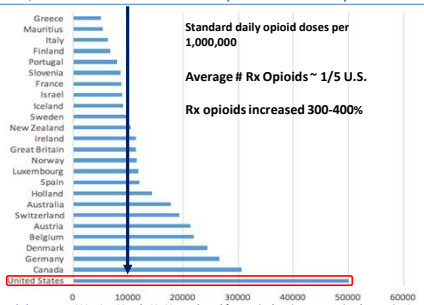
PATIENTS IN PAIN

Casualties of the war on drugs

13

U.S. Leads the World in Prescription Opioid Daily Doses

Yet, U.S. doesn't have more pain than European nations



Standard daily opioid doses per 1,000,000

Average # Rx Opioids ~ 1/5 U.S.

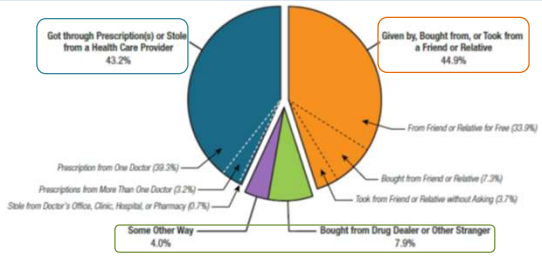
Rx opioids increased 300-400%

Source: K. Humphreys, www.thelancet.com 390: 437-439. July 29, 2017. Adapted from United Nations International Narcotics Control Board. 2016 Narcotic drugs: estimated world requirements for 2017; statistics for 2015. Vienna, Austria

14

Diversion of Medications not Anticipated

Source of Misused Pain Relievers (88% from prescriptions)



8.7 Million People Aged 12 or Older Who Misused Pain Relievers in the Past Year

2021NSDUHFFRRev010323.pdf

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Legal Marijuana

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Marijuana Movement Began "Medicalization For Compassionate Use"
What Has Happened?

More Products	More use	More Associated
❑ Illicit production ❑ Unregulated potency High %THC ❑ THC analogs ❑ Routes of delivery: Vaping, edibles, beverages, creams ❑ Advertising, "dispensaries" ❑ vaping, edibles, beverages, creams	❑ Daily by teens ❑ Among adults of child-bearing years ❑ By elderly ❑ By pregnant women	❑ Psychosis (ED) ❑ Violence ❑ Traffic accidents, fatalities ❑ Child poisonings ❑ Hyperemesis syndrome ❑ Addiction, even among users for medical purposes

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Were these Qualifying Medical Conditions Proven by Quality Clinical Trials? NO

Cannabis has been disingenuously hyped as a treatment/cure for

opioid addiction, glaucoma, disease of cancer, Crohn's disease, PTSD, Parkinson's disease, Alzheimer's, Autism, ALS, hydrocephalus, or use "any other medical condition" such as pain, sleep, depression, anxiety,

and many other conditions for which evidence does not exist

18

Does Marijuana Fulfill FDA Criteria?

Purity: NO	A specific medical condition to use marijuana NO
Dose, Standard doses: NO	What patients may benefit; tested in children NO
	Reported adverse effects – acute and chronic NO
Quality control: NO	How the drug should be taken (eat, drink, vape?) NO
Clinical trials: LIMITED	A safe drug dose for a specific medical condition NO
	How the drug is made (pill, liquid) NO
Safety, side effects: NO	Active and inactive ingredients NO

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FDA Has Approved Cannabinoids

- **Marinol:** AIDS appetite; cancer chemotherapy
- **Nabilone:** AIDS appetite; nausea for cancer chemotherapy
- **Syndros (dronabinol oral solution):** cancer and AIDS
- **Sativex (THC/CBD):** Other nations, multiple sclerosis-not in United States
- **Epidiolex (CBD):** Rare forms of epilepsy

NO BOTANICAL MARIJUANA APPROVED

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Hallucinogens in Medicine

Intersection of Science, Policy, Reality

Large public health burden: chronic brain disorders

Treatment needs: inadequate or unmet

Indications: "conditions of internalizing disorders"

Drug Policy: All premises now questioned

Vivien Felsen Vivien Felsen

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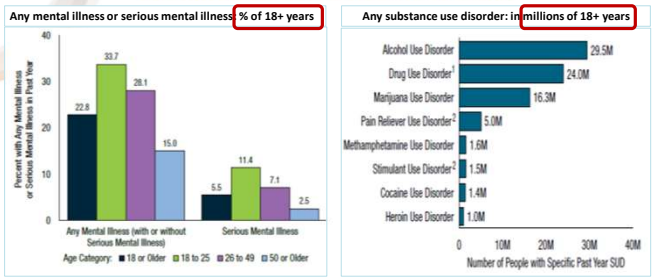
Millions of People with Major Mental Illness or Substance Use Disorders or Both



Substance Abuse and Mental Health Services Administration. (2022). *Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health* (HHS Publication No. PEP22-07-01-005, NSDUH Series H-57). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report

22

How Effective are Conventional Anti-depressants?

effective, but…imperfect

1. Responders and non-responders

- *Non-responders with MDD*: ~33%-50% don't respond to anti-depressants
- *Partial responders*: some
- *Treatment-resistant depression (TRD):* unresponsive to 2 or more antidepressants

2. Time to respond is long

- ~3-4 weeks to alleviate MDD symptoms

3. Side effects

- headache, gastrointestinal symptoms, anxiety, agitation, sexual dysfunction

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Hallucinogens

Dissociatives	• **Ketamine** • **Phencyclidine (PCP, angel dust)**
Psychedelics	• **Psilocybin (magic mushrooms)** • **Mescaline/peyote** • **LSD** • **DMT/ayahuasca (N,N-dimethyl-tryptamine)**
Other types	• **MDMA (Ecstasy, hallucinogen-stimulant)** • **Salvinorin A** • **Ibogaine (dissociative)**

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Ketamine for Major Depressive Disorder, TRD

Ketamine i.v.

Surgical anesthetic: humans, animals, Anti-depressant

- **Systematic review, meta-analysis of 7 RCTs, 12 open label trials**
- positive effect of ketamine on MDD (OR at 7 days: 6·33

FDA-approved TRD

Esketamine nasal spray

(Spravato)

- **Systematic review of 5 RCTs (3 RCTs) assessed outcome at 28 days**
- significant positive effect
- relapse-prevention: positive effect
- open-label, long-term trial: positive effect on TRD
- limited to medical facilities, used as nasal spray
- patients wait 2 h medical facility potential side effects

Marwaha S, Palmer E, Suppes T, Cons E, Young AH, Upthegrove R. Novel and emerging treatments for major depression. Lancet. 2023 Jan 14;401(10371):141-153

25

Esketamine FDA-Approved for Treatment Resistant Depression

- Symptoms improve after 24 hours, effects wane at 7 days
- May endure in some people for 6 weeks
- FDA requires drug maker to develop **Risk Evaluation and Mitigation Strategy (REMS)**

Inpatient Healthcare Setting	Outpatient Healthcare Setting	Pharmacy	Patient
• Certification in REMS required to treat patients	• Certification in REMS required to treat patients	• Certification in REMS required to treat patients	• Must be enrolled in REMS to receive treatment in Outpatient Healthcare Setting

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Lesson Learned: No "Standard of Care" for Rogue Ketamine "Clinics"

Rogue Ketamine Clinics

No standard for drugs

procured outside medical norms

Licensing criteria

35% require treatment training

12% require physicians

No Contraindications

Psychiatric conditions

Cardiovascular disease

No guidance on

- Youth
- Older adults
- Pregnant women
- Safety sensitive job

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Psychedelics

- History, What are they?
- Effects, biology, consequences
- Medicines: what is status?
- Hallucinogens: merger of medical, commercial products

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What are Psychedelics/Hallucinogens?

Hallucinogens

- change/distort perception of surroundings
- sensations and images that seem real but are not
- change/distort their internal thoughts and feelings
- Distort sensory reality: synesthesia, visual hallucinations

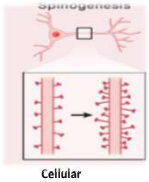
Psychedelics are hallucinogens…and some able to

- "mind-revealing": some describe as spiritual, mystical
- "ego dissolution": decreased boundary between self/world; connectedness

Nichols DE, Hallucinogens. Pharmacology & Therapeutics 2004;101(2):131-181.

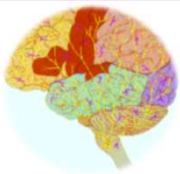
29

Mechanisms of Psychedelics?



Cellular

- Increased 5-HT2A receptor activity
- Increased cortical glu transmission
- Increased neuroplasticity



Network

- Decreased brain modularity
- Changed network connectivity

Behavioral

- Increased psychological flexibility
- Insight
- Acceptance
- Mystical-type state
- **Bad Trip**

Aday et al., Emerging Chalenges fro Psychedelic Therapy JAMA Psychiatry Published online April 19, 2023

30

Do Hallucinogens Have Long Term Effects?

(infrequent)

Persistent Psychosis: continuing mental problems, including:

- visual disturbances
- disorganized thinking
- paranoia
- mood changes

Hallucinogen Persisting Perception Disorder (HPPD):

- reoccurrences of hallucinations, other visual disturbances
- without warning, a few days or >year after drug use
- both more often with history of mental illness
- can happen to anyone, even one time use

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Early Use of Hallucinogens in Psychiatry

Symptoms: anxiety, depression, neuroses, distress, AUD, schizophrenia

- Repeated low LSD doses to reveal unconscious traumatic memories
- Unconscious content reflected orientation of the therapist

Uncontrolled case series

- Osmond and Hoffer: 50% of patients given LSD remained alcohol abstinent 6 months
- Some reported 70% symptom improvement *neurotic disorders*
- Some reported LSD reduced *anxiety, distress in terminal cancer*

Critics argued studies too small, poorly controlled, biased outcomes

- Positive results not replicated in later controlled trials

32

EFFECTS OF MESCALINE AND LYSERGIC ACID (d–LSD–25)[1]

PAUL H. HOCH, M.D., JAMES P. CATTELL, M.D.,
AND
HARRY H. PENNES, M.D.
New York City

HOCH PH, CATTELL JP, PENNES HH. Effects of mescaline and lysergic acid (d-LSD-25). Am J Psychiatry. 1952 Feb;108(8):579-84.

- ***Mental symptomatology markedly aggravated***
- ***Disorganizes psychic integration of a person***
- ***More apparent in schizophrenics than normal***

drugs are very important in producing schizophrenic-like reactions in normal individuals, in magnifying the schizophrenic structures in schizophrenic patients, and in studying the personality structure of different individuals

do not believe that the evidence available today would permit their reliable use for any of these clinical approaches. It is undeniable that the drug precipitates an overt schizophrenic psychosis in some individuals

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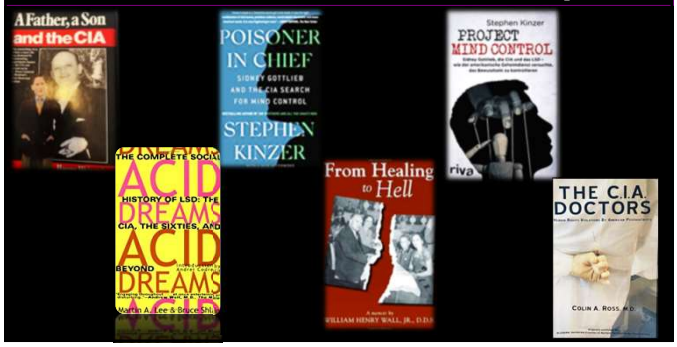
Unethical Research Unintended Consequences



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Psychedelic Research Abandoned

Psychedelic drug research abandoned	Psychedelics drew exuberant advocacy	Clinical trials performed with ZERO oversight	Some patient outcomes grim	Clinical use became supervised
Not because of Nixon's 'War on Drugs'	Drugs used in unsupervised clinical practice, for spiritual enlightenment	Therapeutic use of psychedelics Bias was a norm	Some became more ill Some irreversibly	to avoid 1950, 1960s research/social misadventures

Hall W. Why was early therapeutic research on psychedelic drugs abandoned? Psychol Med. 2022 Jan;52(1):26-31.

35

1. How Solid is the Science? Trials

Trials cannot be blinded

Double-Blinding intended to limit *conscious, unconscious bias of a clinical trial*

- Recruitment Bias?
- Informed consent reveals expectations?
- Expectations queried? of therapist of patient
- Therapy protocols? Same for drug, placebo?
- End-points assessment? Side effects?
- Assessment over what period?

Aday JS, clinical trials. Psychopharmacology (Berl). 2022 Jun;239(6):1989-2010.Breeksema JJ, Kuin BW, Kamphuis J, van den Brink W, Vermetten E, Schoevers RA. Adverse events in clinical treatments with serotonergic psychedelics and MDMA: A mixed-methods systematic review. J Psychopharmacol. 2022 ;36(10):1100-1117.
Liechti, M. E. (2017). Modern clinical research on LSD. Neuropsychopharmacology, 42(11), 2114-2127.

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1. How Solid is Recent Science? (Trials)

Inclusion/exclusion criteria, Selection bias, Generalizability?

Recruited subjects

- **Intrigued with hallucinogens?**
  prior hallucinogen use 1.9-100%
- **Selection bias?**
  choose 50/1000
- **Diversity?**
  Caucasian, educated, urban
- **Aware of expected outcomes**

Excluded subjects

- Co-morbid psychosis
- Suicidality
- Known risk factors
- Family history
- Preexisting psychiatric condition

limit true risk of drugs

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Prior Hallucinogenic Use

Study	Type	Condition	Test Drug	Prior Use
Mitchell et al 2021	RCT III	PTSD[a]	MDMA	39%
Mithoefer et al 2019	RCT II	PTSD	MDMA	30%
Wolfson et al 2020	RCT	EOLA[b]	MDMA	56%
Carhart-Harris et al. 2021	RCT II	Depression	Psilocybin	27%
Davis et al. 2020	RCT	MDD[c]	Psilocybin	1.9%
Carhart-Harris et al. 2016, 2018	Open-label	TRD[d]	Psilocybin	35%
Ross et al, 2016	RCT	EOLA	Psilocybin	60%
Grob et al, 2011	RCT	EOLA	Psilocybin	67%
Johnson et al 2014	Open-label	Tobacco cessation	Psilocybin	67%
Moreno et al 2006	Dose-escalation	OCD[e]	Psilocybin	100%
Schmid et al. 2020	Observation	EOLA	LSD	39%

[a]Post-traumatic stress disorder; [b]End of life anxiety [c]Major depressive disorder [d]Treatment-resistance depression [e]Obsessive-compulsive disorder

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Subject Expectancy Effects

Given obvious psychoactive effects of psychedelic drugs

those receiving drug likely know they received drug

- may show greater treatment response

those receiving placebo may know they received placebo

- disappointment may decrease their placebo response

Sumner, McMillan, Spriggs, . . . Muthukumaraswamy. Ketamine Enhances Visual Sensory Evoked Potential Long-term Potentiation in Patients With Major Depressive Disorder. Biol Psychiatry Cogn Neurosci Neuroimaging 5, 45-55 (2020).

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Therapeutic Alliance

Therapeutic alliance	• one of strongest mediators of success in psychotherapy
If on placebo	• What is content of psychedelic therapies?
32 therapists: who do psychedelic-assisted therapy	• 88% had taken psychedelics • all had favorable views of its use • *risk of over-enthusiasm and advocacy*

(Aday et al., Psychedelic Med, 2023)

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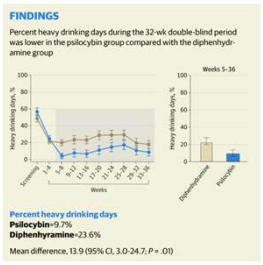
Psilocybin for Alcohol Use Disorder



Caveats

- 95% of participants in second session correctly guessed if given psilocybin or placebo (Benadryl)
- All participants: "had meaningful social support" (inclusion criterion)
- mean income was $100K

Slide Courtesy of Dr. Wilson Compton, NIDA

Bogenshutz, et al. "Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder" *JAMA Psychiatry* 2022;79(10):953-962.

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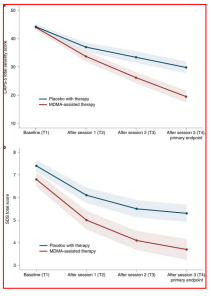
MDMA-assisted Therapy for PTSD



- MDMA vs. placebo for severe PTSD (n=90)
- MDMA sessions at weeks 1, 5, 9 (18 weeks)
- MDMA reduced PTSD symptoms and social disability
- 33% on MDMA achieved remission vs. 5% on placebo
- No SAEs in MDMA group, heart conditions were excluded
- *90% correctly guessed if they were given MDMA or placebo*

Mitchell JM, et al. *Nature Medicine* (2021)

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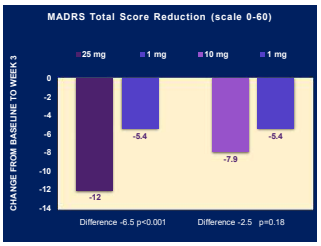
Psilocybin for Treatment Resistant Depression

3 dose trial in 233 patients

Effectiveness: Depression Scores Reduced
25 mg dose (*not 10 mg)* reduced depression score significantly more than 1 mg dose at 3 weeks

Secondary end points: not significant
- **Response:** ≥50% reduction from baseline to week 3
- **Remission:** total score ≤10 week 3
- **sustained response:** weeks 3 through 12

- **Response not sustained at 12 weeks**



Goodwin, et al. *NEJM* (2022)

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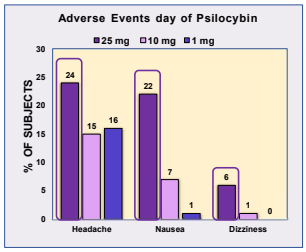
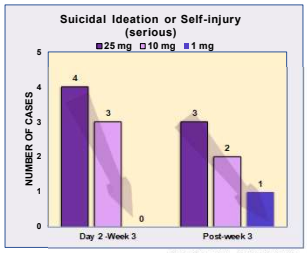
Psilocybin for Treatment Resistant Depression: Adverse Events

Adverse events day of use
- Headaches, nausea, dizziness
- Highest # in therapeutic dose (25 mg)

Serious adverse events
- Suicidal ideation, self-injury, hospitalization
- Four (5%) in 25 mg, 10 mg dose; 1 in low-dose group





Goodwin, et al. *NEJM* (2022)

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Trial of Psilocybin versus Standard of Escitalopram for Depression

Exclusion criteria
- Immediate family or personal history of psychosis
- History of serious suicide attempts
- *Previous use of escitalopram excluded*
- *But previous use of psilocybin allowed*
- Suspected, known preexisting psychiatric condition that could jeopardize rapport

Conclusions
- Results: no significant difference in antidepressant effects psilocybin, escitalopram
- Secondary outcomes: generally favored psilocybin, but analyses lacked correction for multiple comparisons

Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, Martell J, Blemings A, Erritzoe D, Nutt DJ. **Trial of Psilocybin versus Escitalopram for Depression**. N Engl J Med. 2021 Apr 15;384(15):1402-1411.

45

2. Can Protocols be Scaled with Fidelity?

FDA approval: Contingent on same conditions as clinical trials, REMS

- **Academic setting:** Expectations outlined
- **Session:** lasts up to eight hours
- **Intensive care:** supportive, psychotherapy, contacts
- **Therapist-monitors:** 1-2 with human relation skills
- **Therapist-monitors:** know altered states
- **Setting:** Living-room, headphones, blinders, music
- **Set/setting:** appropriate for diverse populations?
- **Next day session:** guides talk experience, help patients "make sense of it
- **Potential risks:** outside protocol?

SET (person's mindset)

- Mood
- Background
- Psychology unique to subject
- Physiology unique to subject

SETTING (environment)

- Music playlist
- Living room, sofa
- Earphones
- Hand-holding

Baryshnikov et al. . Diagnostic conversion from unipolar depression to bipolar disorder, schizophrenia, or schizoaffective disorder: A nationwide prospective 15-year register study on 43 495 inpatients. Bipolar Disord. 2020 Sep;22(6):582-592. Rubin-Kahana et al. Posttraumatic Stress Disorder After a Psychedelic Experience, a Case Report. J Addict Med. 2020 Sep

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Scalability

Screening

- few chosen are carefully selected; ***in clinical practice?***

High selectivity ratio

- recruited subjects believe will respond; ***in clinical practice***?

In naturalistic setting

- will recruitment be as cautious?

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Psychedelic Clinical Trials (~200 est.) (excluding ketamine, cannabinoids)

INDICATION	Psilocybin	MDMA	LSD	9 Others
Major depressive disorder or depression	20	-	-	-
Treatment-resistant depression	12	-	-	1
Alcohol use disorder	10	1	-	-
Eating disorder/body dysmorphia/anorexia	7	1	-	-
Obsessive compulsive disorder	5	-	-	-
Bipolar disorder, other psychiatric disorders	5	2	-	-
PTSD	4	21		--
Autism	4	-	1	2
Anxiety disorder, burnout	2	4	1	-
Substance use disorder	-	6	-	-
Opioid Use Disorder	4	1	-	-
Meth. Use Disorder	2	-	-	-
Cocaine use disorder	2	-	-	-
Smoking cessation	2	-	-	-

- **Demoralization**
  - hopelessness
  - inability to cope
  - feelings of inadequacy
- **Enhancement of spirituality**

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3. Reality of Unintended Consequences?
Legalization Movement Piggy-backing on Medical Research

- **Will states follow California MMJ? From ballot to physicians recommend?**
- **Will advocates promote compassionate access without FDA approval?**
- **Will psychedelics get ahead of efficacy, safety evidence?**

Prediction? Majority of states will legalize psychedelics by 2034 - 2037

Siegel JS, Daily JE, Perry DA, Nicol GE. Psychedelic Drug Legislative Reform and Legalization in the US. JAMA Psychiatry. 2023 80(1):77-83.

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Have We Learned Anything from Marijuana?
Legalization Supporters Cite Emerging Research of Potential Medical Uses

Psychedelic reform bills increased *from 5 in 2019 to 36 in 2022*

10 bills signed into law: 32 still active

25 states considering 74 bills: 69 legislative initiatives, 5 ballot votes

Legal "medical hallucinogens", decriminalized: Oregon and Colorado

- ***Medical oversight***: 23% specify
- **Training and/or licensure required**: 35% specify

Siegel JS, Daily JE, Perry DA, Nicol GE. Psychedelic Drug Legislative Reform and Legalization in the US. JAMA Psychiatry. 2023 80(1):77-83.

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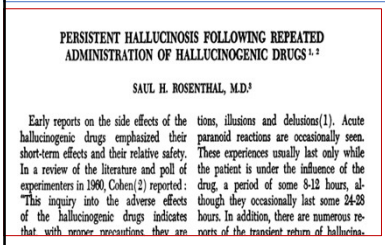
Early Warnings of Public Hallucinogen Use

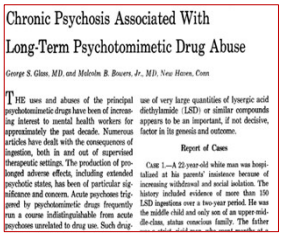


PERSISTENT HALLUCINOSIS FOLLOWING REPEATED ADMINISTRATION OF HALLUCINOGENIC DRUGS[1, 2]

SAUL H. ROSENTHAL, M.D.[3]

Early reports on the side effects of the hallucinogenic drugs emphasized their short-term effects and their relative safety. In a review of the literature and poll of experimenters in 1960, Cohen(2) reported: "This inquiry into the adverse effects of the hallucinogenic drugs indicates that with proper precautions they are

tions, illusions and delusions(1). Acute paranoid reactions are occasionally seen. These experiences usually last only while the patient is under the influence of the drug, a period of some 8-12 hours, although they occasionally last some 24-28 hours. In addition, there are numerous re-



Chronic Psychosis Associated With Long-Term Psychotomimetic Drug Abuse

George S. Glass, M.D. and Malcolm B. Bowers, Jr., M.D. New Haven, Conn

THE uses and abuses of the principal psychotomimetic drugs have been of increasing interest to mental health workers for approximately the past decade. Numerous articles have dealt with the consequences of ingestion, both in and out of supervised therapeutic settings. The production of prolonged adverse effects, including extended psychotic states, has been of particular significance and concern. Acute psychoses triggered by psychotomimetic drugs frequently run a course indistinguishable from acute psychoses unrelated to drug use. Such drug-

use of very large quantities of lysergic acid diethylamide (LSD) or similar compounds appears to be an important, if not decisive, factor in its genesis and outcome.

Report of Cases

CASE 1.—A 23-year-old white man was hospitalized at his parents' insistence because of increasing withdrawal and social isolation. The history included evidence of more than 150 LSD ingestions over a two-year period. He was the middle child and only son of an upper-middle-class, status conscious family. The father

ROSENTHAL SH. Persistent Hallucinosis Following Repeated Administration Of Hallucinogenic Drugs. Am J Psychiatry. 1964 Sep;121:238-44.
Glass GS, Bowers MB Jr. Chronic psychosis associated with long-term psychotomimetic drug abuse. Arch Gen Psychiatry. 1970 Aug;23(2):97-103

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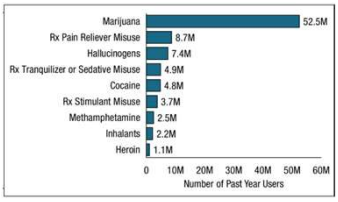
Hallucinogen Use is Increasing

Past Year Hallucinogen use: 12 y and older



Patrick ME et al (2022). Monitoring the Future Panel Study annual report: National data on substance use among adults ages 19 to 60, 1976-2021.

% Past Year Drug Use Among 12th graders

DRUG	PREV.
Alcohol	46.5%
Vaping, Any	31.5%
Marijuana/Hashish	30.5%
Hallucinogens	4.1%
LSD	2.5%
MDMA (Ecstasy)	1.1%
Ketamine	0.9%
PCP	0.7%
Salvia	0.6%

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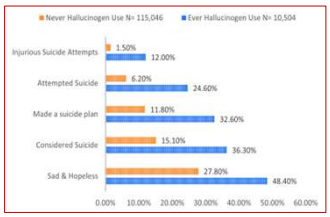
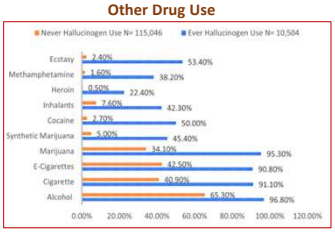
Youth who Use Hallucinogens: Risks

Depression, Suicide



Other Drug Use



Youth Risk Behavior Surveillance System (YRBSS)

Rabinowitz J, Lev-Ran S, Gross R. The association between naturalistic use of psychedelics and co-occurring substance use disorders. Front Psychiatry. **2023** Jan 10;13:1066369.

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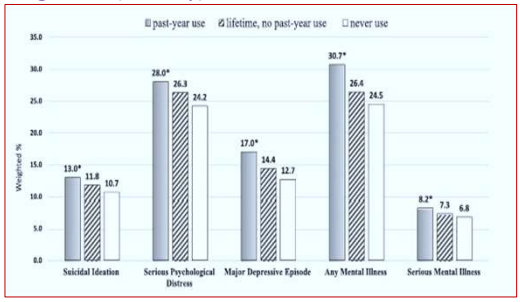
Young Adult (18-25 y) LSD Use & Mental Health Problems



Han B, Blanco C, Einstein EB, Compton WM. Mental health conditions and receipt of mental health care by illicit LSD use status among young adults in the United States. *Addiction* 2022;117(6):1794-1800.

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Medical Community Steps Up

- **July 2022 American Psychiatric Association position:** "clinical treatments should be determined by scientific evidence in accordance with applicable regulatory standards; not by ballot initiatives or popular opinion."
- **Legislative initiatives have minimal involvement of physicians**: contrast to FDA regulation of esketamine, which includes *extensive guidelines regarding medical diagnosis prior to initiation and oversight during treatment.*

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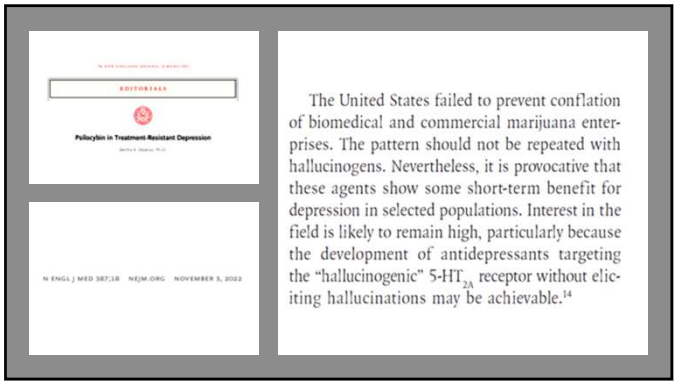
EDITORIALS

Psilocybin in Treatment-Resistant Depression

N ENGL J MED 387;1:8 NEJM.ORG NOVEMBER 3, 2022

The United States failed to prevent conflation of biomedical and commercial marijuana enterprises. The pattern should not be repeated with hallucinogens. Nevertheless, it is provocative that these agents show some short-term benefit for depression in selected populations. Interest in the field is likely to remain high, particularly because the development of antidepressants targeting the "hallucinogenic" 5-HT_{2A} receptor without eliciting hallucinations may be achievable.[14]

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Why is Medicalization of Psychedelics a Crucial Topic For NOAP?

Psychedelic effects

- can be intoxicating, psychotomimetic, many hours

Safety-sensitive positions

- Health professionals are in safety-sensitive positions

Safety-sensitive workers

- are obligated ethically, legally to mitigate identifiable safety risks

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Why is Psychedelic Medicalization a Crucial Topic for NOAP?
Only FDA-approved Medications Should be Acceptable

FDA approval	• No psychedelic FDA-approved for any medical condition-except eskatamine
Psychedelic complex challenges	• can use be balanced with safety/cognitive facilities/advocacy?
Fitness to work	• Is hallucinogenic use compatible with monitoring, safe practice?
PHP obligations to others	• Compatible with patient safety?
Physicians in position to counsel youth, others on hallucinogens	• What to say?

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- 'the chemical opening of doors into the Other World', and belief that drugs can procure 'what Catholic theologians call a gratuitous grace'.

…Aldous Huxley

- Chemically induced hallucinations, delusions and raptures may be frightening or wonderfully gratifying
- in either case they are in the nature of confidence tricks played on one's own nervous system. …Arthur Koestler

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Thank You!

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A Sobering View
Dr. Jerry Rosenbaum, Director,
Center for the Neuroscience of Psychedelics
Massachusetts General Hospital

HTTPS://VIMEO.COM/769140075/896e7a6180

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