



# What a Long Strange Trip It's Been: Novel Treatments in Psychiatry

Elizabeth D. Weed, MSW, PharmD, BCPP

[weede@musc.edu](mailto:weede@musc.edu)

# Objectives



Define Psychedelics



Understand how psychedelics and MDMA theoretically work



Understand the history of psychedelics and research in the U.S.



Understand therapy-assisted interventions and its role in the medication intervention



Understand your role as a licensed clinician in these novel treatments

# Current Situation

## 5<sup>th</sup> cause of global disability-adjusted life years

- Mental health and substance abuse disorders

## Depression is common world-wide

- More than 300 million people are impacted
- Associated with high rates of suicide
- Leading cause of disability worldwide

## Suicide

- 2<sup>nd</sup> leading cause of death in those 15-29 years old
- 2<sup>nd</sup> leading cause of death in the military personnel with PTSD

## Cancer patients

- Depression is an independent risk factor for early death
- Associated with decreased treatment adherence and prolonged hospitalization

## Post-Traumatic Stress Disorder (PTSD)

- 8 million adults have PTSD during a given year
- 10% of women 4% of men develop PTSD sometime in their lives

# Medication Treatment in Psychiatry: Side Effects

## Antidepressants

- Sexual dysfunction, nausea, diarrhea, head aches, anticholinergic, sleepiness, increased BP, drug interactions, QTc prolongation, lower seizure threshold, etc...

## Mood stabilizers or anticonvulsants

- Toxicity, liver issues, kidney issues, weight gain, etc...

## Antipsychotics

- Sleepiness, weight-gain, metabolic issues, tardive dyskinesia, hypotension, QTc prolongation, etc...

## Benzodiazepines

- Sedation (falls), anterograde amnesia, risk of abuse, impaired cognition, respiratory depression, rebound anxiety, interferes with fear extinction in PTSD

## Stimulants

- Headache, rebound symptoms, irritability, decreased appetite, headaches, increased BP, anxiety

# Non-Medication Treatment

- Therapy – interpersonal, cognitive behavioral, exposure, Eye Movement Desensitization and Reprocessing (EMDR), behavioral therapy, group therapy
- Lifestyle modifications – diet, exercise, stress management
- Light therapy, breathing exercises
- Hypnosis
- Electroconvulsive therapy
- Other

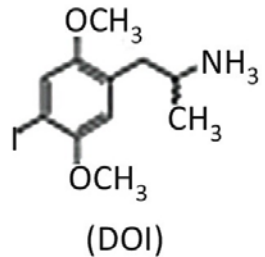
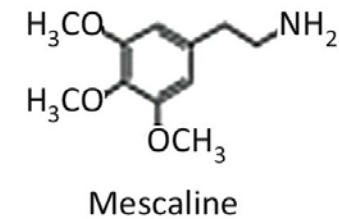
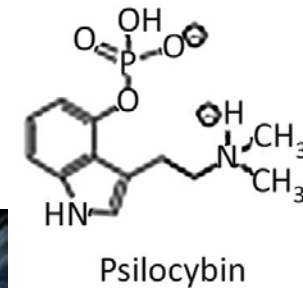
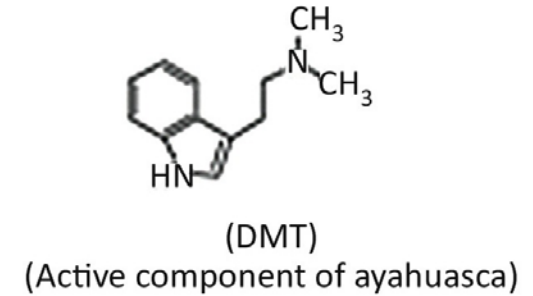
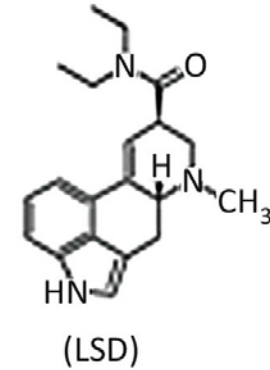


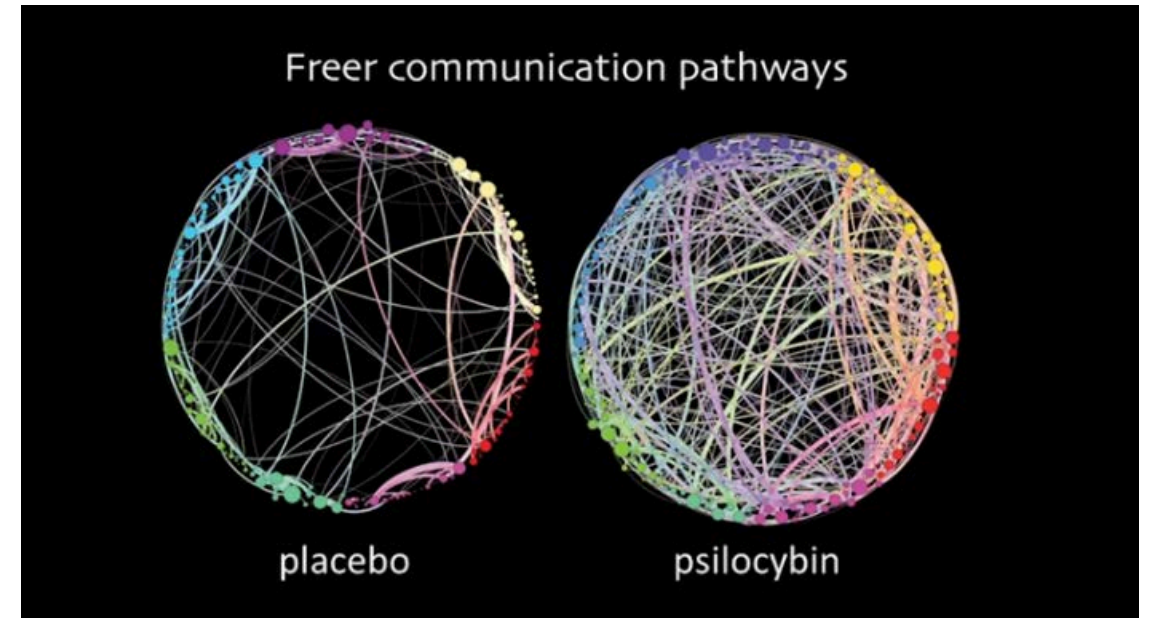
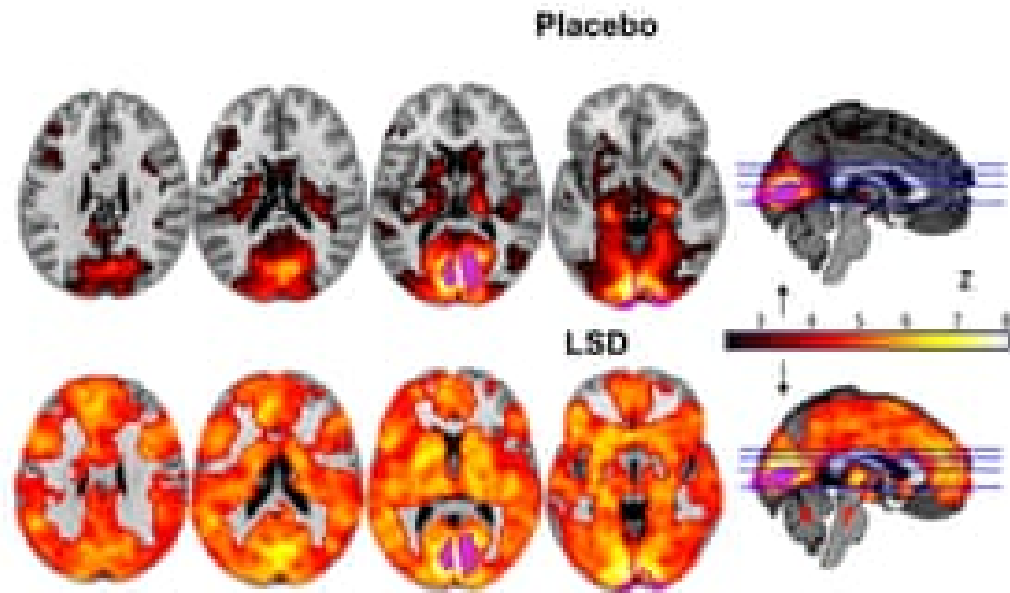
# The Novel Treatments

The Classic Psychedelics

# The Psychedelics or Serotonergic Hallucinogens

- 5HT2A agonists
  - LSD – Lysergic acid diethylamide
  - Psilocybin – magic mushrooms
  - Ayahuasca – from the Amazon
  - DMT – Dimethyltryptamine
  - Mescaline

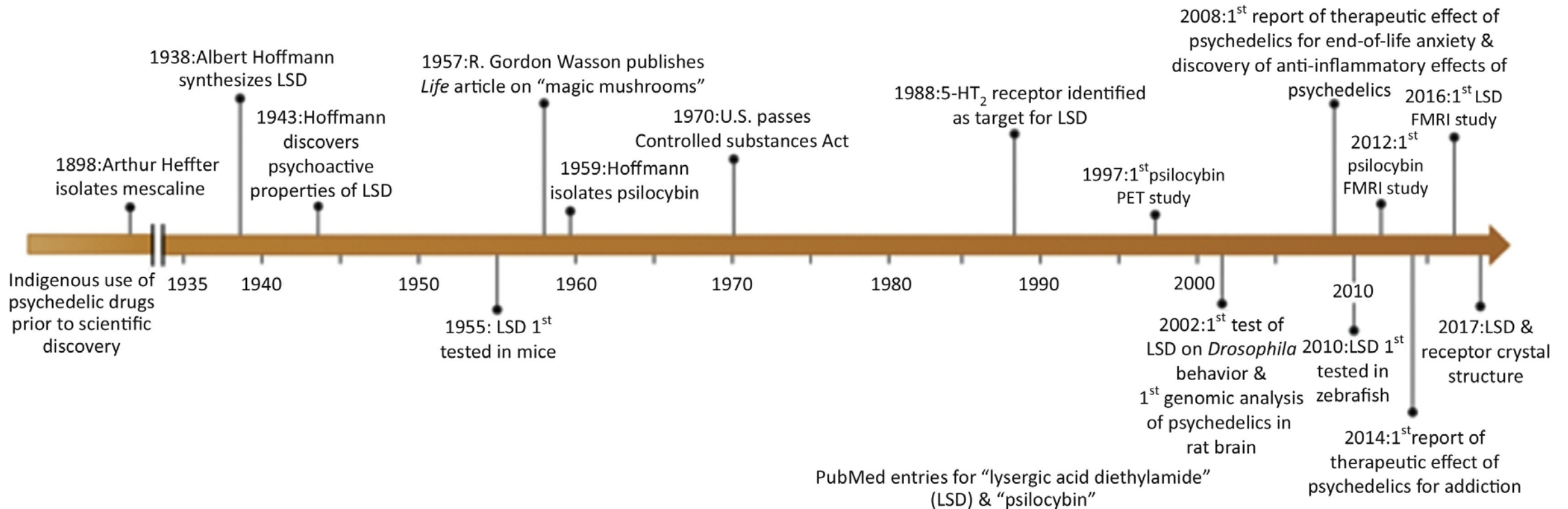




How They Work - Brain Changes



# History of Psychedelic Research



# Research: Things To Think About

- Type of trial
  - Randomized, controlled trial
  - Single-blinded, double-blinded, open-label, case series, observational
- Duration or length of the trial
- Number of patients
- Who is enrolled or excluded?
- Measurements
  - Example: Ham-D rating or Vanderbilt rating scale, HAM-A
- Funding source of trial

# Research Studies Before 1970

## Psychotic patients

- Inpatient hospitals

## Medication dosage range

- LSD: unknown to 10 – 120 mcg
- Mescaline: unknown to 500 - 750 mg

## Dosage frequency

- Unknown or once or several times

## Exacerbated symptoms

- LSD hallucinations were more visual compared to auditory hallucinations in schizophrenia

## Worsening response

## Therapeutic value questioned

# An Inkling: Therapy and Psychedelics

- As early as 1936, a psychiatrist at a London hospital gave to an unknown number of students, patients, and colleagues mescaline and noted that:

*There is reason to suppose that patients in such a state may be very susceptible to psychotherapeutic influence...If it is so, the intoxication could be made use of as a sort of forced or concentrated analysis.*

- Erich Guttman



# Psychotherapy – Assisted Interventions

The context in which the medication is given is important: therapy plays a prominent role

# “Psycholytic” Method: Studies Before 1970

- **Low dose** LSD increased to an “adequate reaction” used within psychotherapy
  - Loosen ego defenses and accelerate access to traumatic material
  - Aim of therapy was to understand the experience in terms of its emotional meaning, not worry about it’s objective validity
- “Psychoneurotic” participants
- Medication - LSD Dosage
  - 25 to 400 mcg
- Dosage frequency
  - Unknown, once, daily, weekly or biweekly for up to 30 times
- Marked improvement, majority improved, full recovery in many
- In one study, 4 out of 5 depressed patients improved with a follow-up of 6-18 months

# “Psychedelic Approach”: Studies Before 1970

- **High dose** administered once
  - Allows for the person to have a single experience that is so profound that his life experience leads to continual growth
- The Therapy
  - Group approach: psychiatrist, psychologist, psychiatric nurse, and music therapist
- Diagnosis
  - Neurosis, some with alcohol addiction
- Medication - Dosage
  - LSD: 3mcg/kg to 1500 mcg
  - LSD + mescaline: 100 – 200 mcg + 200-400 mg mescaline
- Dosage frequency
  - Once
- 84% and 92% of patients showed improvement in two different trials
  - Improvement may depend on the subject's willingness to face himself, accept what he encounters and then act on it

## Direct Approach: Studies Before 1970

- Therapist sits with patient through the session
  - responding accordingly to their emotional needs
- Diagnosis: severe neurosis
- Medication - Dosage
  - LSD: Unknown
- Dosage frequency
  - Weekly for 20 session
- 93% (57 out of 60) response rate



# Terminally Ill Cancer Patients: Studies Before 1970

- Dosage of LSD
  - Cancer: 100 mcg
  - LSD as pain reliever
- Patients reported increased openness with more positive attitudes their condition
- More focus on patient's attitude toward illness
- Daily interviews provided for one week prior to medication administration
  - Purpose: establish trust and discuss personal issues



# Set and Setting

The environment becomes Important

# Another Approach: Studies Before 1970

- The therapy
  - Extensive preparation - 4 to 8 weeks of interviews prior to medication administration
  - Male and female therapist spent the day with patient on day of medication
    - Therapist role: companion and emotional support
  - Shared expectation that the patient would have their own experience that would prove useful in altering their life
  - Environment: music and visual stimuli (personal photographs)
- Neurotics, depressives
  - outpatient
- Medication - Dosage
  - LSD + mescaline: 200 – 300 mcg + 200-400 mg mescaline (if necessary)
- Dosage frequency
  - Once
- 80% (62 out of 77) improvement after 6 months
- 81% of the total (197 out of 243) showed improvement

# Substance – Assisted Psychotherapy: 1970s and 80's

- Diagnosis: life-threatening cancer with anxiety and depression
- LSD Dosage range
  - 200 – 500 mcg LSD
- Therapy
  - A series of interviews (drug-free) over 2-3 weeks (about 10 hours contact time) before the medication administration
    - Establish therapeutic relationship and prepare the patient
    - LSD and its effect on the psyche is discussed
    - Post – session follow-up: discussion of the experience and enduring psychological effects occur
- The Setting
  - Physically safe and supportive environment
    - Music, personal items
    - 2 therapists (one male and one female)
- 2 new things
  - Measurements: Emotional Condition Rating Scale
  - Therapist assisted during the medication session

# The Psychotherapeutic Intervention: How Does It Work?

LSD loosens the ego and reduces defensiveness

Increases capacity to relive experiences and release feelings

Therapist-patient relationship is enhanced

Unconscious material surfaces more readily

Another hypothesis came from cancer studies

- Attenuation anticipation – a concept in which patients may benefit from an experience in which they are not able to anticipate pain and death, while at the same time experience an immediate expansion of their sensory world

# Sterile or Antiseptic To Sensory Comfort

Medication and dose is initially the primary focus

Then...

The context in which the medication is given becomes very important

- Developing the therapeutic relationship
- Creating a positive, supportive environment
- Pre-, during, and post-sessions become important
- Set and setting seems to be a powerful influencer of the participant's hallucinogen experience

# But....Main Problem with Studies

Methodology in the studies was sub-optimal

Treatment groups not well-defined

No control group typically

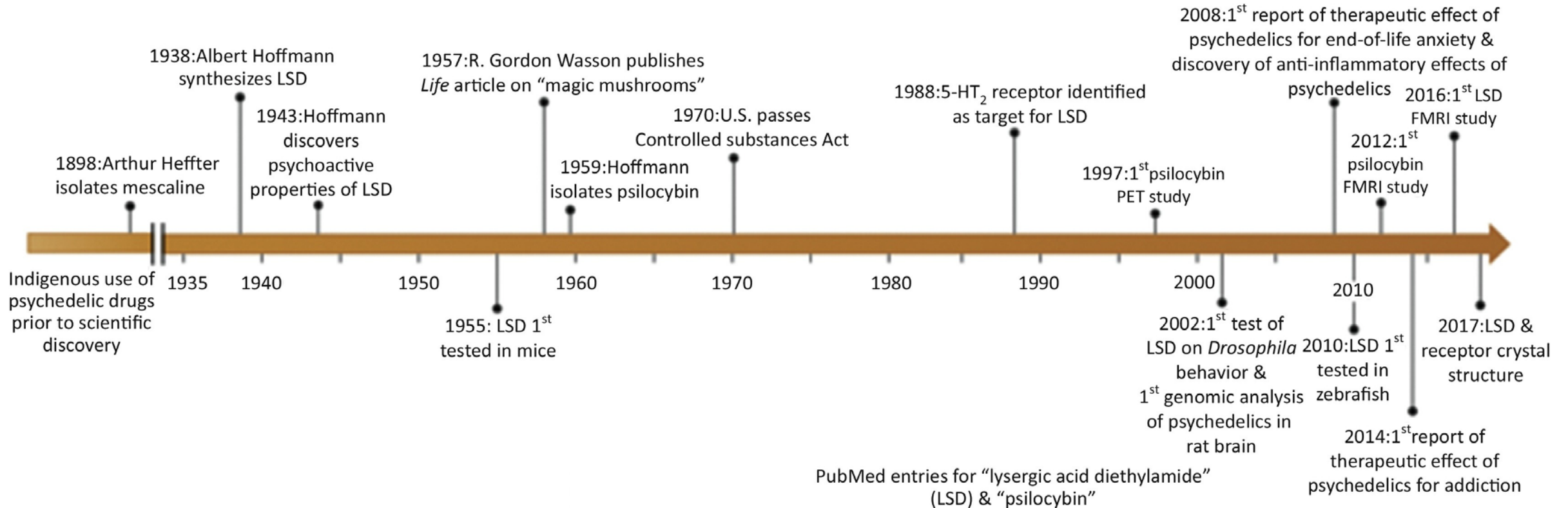
Outcome measures not validated

Inconsistent reporting of outcome data or adverse outcomes

Side effects not always reported

And the biggest problem is.....

# History of Psychedelic Research







## Science and Culture Clash: Schedule I Drug:

- Drugs with no currently accepted medical use and a high potential for abuse
  - Lysergic acid diethylamide (LSD)
  - Mescaline
  - Dimethyltryptamine (DMT)
  - 3,4-methylenedioxymethamphetamine (MDMA) - ecstasy

# Research Studies After The 1970s: A Resurgence

## 3 Trials in 1990s

- Healthy volunteers
- Germany, United States, Switzerland
- Mescaline, DMT, psilocybin

## Since 2006

- Psilocybin, Ayahuasca, LSD
- Major depressive disorder, alcohol dependence, life-threatening cancer with anxiety and depression, obsessive compulsive disorder, tobacco addiction
- Study methodology is improving
- Small studies
- Objective measurements are used

# Psilocybin

- Experimental sessions
  - 2 sessions, 6 hours each, several weeks apart
  - Took place in specifically prepared hospital room
- Psilocybin Dosage
  - Comparison 0.2 mg/kg vs. 250 mg niacin
  - Compare low dose 1 or 3 mg/kg vs high dose 22 or 30 mg/kg
- Patients with life-threatening cancer anxiety and depressive disorders
- Results: depression reduced by nearly 30% after one month and significant reduction in anxiety at one month and 3 months after the 2<sup>nd</sup> session
- Other study: After 6 months, 78% of patients showed a 50% reduction in depressive symptoms and 65% showed symptom remission, while 82.5% showed a 50% reduction in anxiety and 56.5% with symptom remission
  - Improvement in quality of life
- Mystical experience scores showed a significant correlation with positive outcomes

# Ayahuasca

- Dosage: 0.36 mg/kg vs. placebo
- Duration of Treatment 1 dose
  - Session last about 8 hours
- Environment/Therapy
  - Patients informed of the effects of the drug
  - 2 investigators provided support – stayed in room next door
  - Comfortable living-room like environment, predefined playlist of music, dimmed lighting
  - Eyes closed – visions may play a role in therapeutic effect
- Participants – 35 patients with treatment resistant depression
- Results: 7 days after session, 64% showed response (> 50% reduction in symptoms) and 26% of those in placebo group
  - HAM-D, MADRS scores
- Another trial with lower dose and 6 patients - reduction in depressive symptoms at day 7 with symptoms increasing on day 14, then a reduction on Day 21



# What We Know

# Psilocybin Adverse Events

## Transient experiences

- Nausea, vomiting, headache, tremor, and breathing difficulties
- Moderate increases in diastolic and systolic blood pressure
- Mild anxiety and panic – responded to follow-up therapy

In all studies, no report of serious medical complications

# Ayahuasca Adverse Events or Safety Profile

## Reported from long-term ritual use

- Not associated with increased psychiatric symptoms including personality or substance use disorders
- Nausea, vomiting, gastrointestinal discomfort
- Dysphoric reaction with anxiety and psychotic-like features
- Not considered addictive

## Rare side effect

- Prolonged psychotic – like reaction

# LSD Adverse Effects or Safety Profile

Recreational use vs. controlled medical setting

Up to 10 – 24 h post-LSD administration

- Difficulty concentrating, headache, dizziness, lack of appetite, dry mouth, nausea, imbalance, and feeling exhausted.
- Headaches and exhaustion may last up to 72 h

Flashbacks typically reported

- Usually episodic and short (seconds or minutes) replications of elements of previous substance-related experiences

No severe adverse reactions were reported in modern LSD studies

- When used in medical settings and according to safety guidelines, LSD is relatively safe

LSD is physically non-toxic, but there are psychological risks especially when used recreationally



# Therapeutic Environment

---

- May reduce psychological distress
- Furniture is comfortable
- Keep in mind perceptual changes occur during the session
  - No sharp corners, windows, no phones
- Private restroom – no interaction with non-study personnel



# Role of Social Worker or Licensed Clinician

- Characteristics of those involved in monitoring during a session
  - Have significant human relation skills
  - Personal experience with meditation, yoga, and breathing exercises
  - To maximize the potential for the mystical experience – have an ability to relate and interact with the participant concerning spiritual issues
  - Be friendly, welcoming and compassionate
- Lead monitors tend to be clinical social worker or psychologist
  - Clinical sensitivity is more important than the degrees
  - 2 monitors are recommended – both genders
- Establish relationship with participant
  - 8 contact hours over at least 4 meeting
  - Discuss the meaningful aspects of the participant's life, including spiritual and philosophical beliefs
    - Reduces the likelihood of paranoia during the session
  - Convey that all aspects of the person's life are welcome
- If trust is not developed, more meetings must be had or session must be cancelled

# Reminder

Indigenous cultures have used hallucinogens for millennia

Hallucinogen have typically been restricted to sacramental and healing contexts, with these two often being inseparably intertwined.

# Something Different

3,4-methylenedioxymethamphetamine (MDMA)

# MDMA: How Does It Work?

## MDMA promotes empathy and compassion

- Increases feelings of interpersonal closeness
- increases ability to tolerate distressing memories
- May temporarily reduce avoidance, allowing patients to revisit trauma and fully engage in exposure

## Stimulates the release of neurochemicals

- Serotonin, dopamine, norepinephrine

## Elevates levels of oxytocin

- Associated with bonding in mammals

# MDMA

August 16, 2017 - FDA designates MDMA-assisted psychotherapy as a breakthrough therapy

- FDA agrees this treatment may have a meaningful advantage and greater compliance over available medications for PTSD
- Indicates intent that the FDA will help to review this treatment **faster** than other candidate therapies

Phase 3 trials in Charleston as well as other cities

- Would allow for MDMA as a prescription

Volunteers needed who are at least 18 years old diagnosed with PTSD and in good health

- <https://mdmaptsd.org/>

# MDMA-Assisted Therapy

Three 90 minute psychotherapy sessions prior to the MDMA session

- Build therapeutic alliance and prepare patient

MDMA Session – 2 to 3 sessions about 8 hours each

- 1 dose followed 1.5 to 2 hours later with optional additional dose
- Dose: 30 mg, 75 mg or 125 mg
- Non-directive or client-directed therapy

Follow-up included an overnight stay onsite

7 days of telephone contact

90 min psychotherapy psychotherapy sessions

Total 18 hours of non-drug therapy

16-24 hours of MDMA-assisted therapy

# MDMA Adverse Effects

## In session

- Anxiety, fatigue, muscle tension, perspiration
- Vital signs transiently increased

## 7 days later

- Anxiety, fatigue, insomnia, headache

Most events were mild, decreasing in severity with time

No suicidal behavior

Abuse or compulsive seeking of MDMA is low



# Therapist Background: MDMA- Assisted Psychotherapy

- Have a client-centered orientation
  - Be comfortable following and supporting the participant's own emotional process
- Maintain a high level of empathic presence throughout the therapy session
- Be prepared to teach a method of stress reduction
  - Example: diaphragmatic breathing
- Be well versed in a method of addressing somatic manifestations
- Holotropic Breathwork training is an excellent preparation for therapists
- Training and experience in Internal Family Systems Therapy (IFS) or some other
- A background in Sensorimotor Psychotherapy or other techniques recognizing sensorimotor-level psychological influence
- Training or background in Hakomi and other mindfulness based

# Summary

- Candidates - No history of psychosis or mania
  - Medically stable – no high blood pressure
  - No antidepressants or St. John's wort, or 5HT over the counter medication
- No serious or long-standing adverse events in a controlled environment
- Dosing is infrequent and therapy assisted
- Results are immediate compared with typical medications
- Schedule 1 Drug
  - Phase 3 trials – MDMA (recruiting) and Psilocybin (still planning)
- Spiritual/profound element - mystical or spiritual type experience may account for some of the benefit
- Environment – should be soothing and comfortable
- Therapeutic relationship very important – trust must be established
- Neuroplasticity

# Resources

Certificate in  
Psychedelic Assisted  
Therapies and Research

- <https://www.ciis.edu/research-centers/center-for-psychedelic-therapies-and-research/about-the-certificate-in-psychedelic-assisted-therapies-and-research>

Psychedelic Support -  
Professional Training

- <https://psychedelic.support/professional-trainings/>

Multidisciplinary  
Association for  
Psychedelic Studies

- <https://psychedelic.support/professional-trainings/>

MDMA Assisted  
Therapy: a social  
worker's perspective

- <https://psychedelic.support/resources/mdma-assisted-psychotherapy-trauma/>

How Change Your Mind  
by Michael Pollan

- <https://michaelpollan.com/books/>



Questions?

# Bibliography

- Dos Santos RG, Bouso José Carlos, Alcázar-Córcoles Miguel Ángel, Hallak JEC. Efficacy, tolerability, and safety of serotonergic psychedelics for the management of mood, anxiety, and substance-use disorders: a systematic review of systematic reviews. *Expert review of clinical pharmacology*. 2018;11(9):889-902. doi:10.1080/17512433.2018.1511424.
- Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, Klinedinst MA. [Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial](#). *J Psychopharmacol*. 2016 Dec;30(12):1181-1197. doi: 10.1177/0269881116675513. PubMed PMID: 27909165; PubMed Central PMCID: PMC5367557.
- Johnson M, Richards W, Griffiths R. [Human hallucinogen research: guidelines for safety](#). *J Psychopharmacol*. 2008 Aug;22(6):603-20. doi: 10.1177/0269881108093587. Epub 2008 Jul 1. Review. PubMed PMID: 18593734; PubMed Central PMCID: PMC3056407.
- Mithoefer M. A manual for MDMA-assisted psychotherapy in the treatment of PTSD (version 8). 2016. <http://www.maps.org/research/mdma/mdma-research-timeline/4887-a-manual-for-mdma-assistedpsychotherapy-in-the-treatment-of-ptsd>
- Mithoefer MC, Grob CS, Brewerton TD. [Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA](#). *Lancet Psychiatry*. 2016 May;3(5):481-8. doi: 10.1016/S2215-0366(15)00576-3. Epub 2016 Apr 5. Review. PubMed PMID: 27067625.
- Palhano-Fontes F, Barreto D, Onias H, Andrade KC, Novaes MM, Pessoa JA, Mota-Rolim SA, Osório FL, Sanches R, Dos Santos RG, Tófoli LF, de Oliveira Silveira G, Yonamine M, Riba J, Santos FR, Silva-Junior AA, Alchieri JC, Galvão-Coelho NL, Lobão-Soares B, Hallak JEC, Arcoverde E, Maia-de-Oliveira JP, Araújo DB. [Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial](#). *Psychol Med*. 2019 Mar;49(4):655-663. doi: 10.1017/S0033291718001356. Epub 2018 Jun 15. PubMed PMID: 29903051; PubMed Central PMCID: PMC6378413.
- Reiche S, Hermle L, Gutwinski S, Jungaberle H, Gasser P, Majić T. [Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: A systematic review](#). *Prog Neuropsychopharmacol Biol Psychiatry*. 2018 Feb 2;81:1-10. doi: 10.1016/j.pnpbp.2017.09.012. Epub 2017 Sep 22. Review. PubMed PMID: 28947181.
- Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, Mennenga SE, Belser A, Kalliontzi K, Babb J, Su Z, Corby P, Schmidt BL. [Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial](#). *J Psychopharmacol*. 2016 Dec;30(12):1165-1180. doi: 10.1177/0269881116675512. PubMed PMID: 27909164; PubMed Central PMCID: PMC5367551.
- Rucker JJH, Iliff J, Nutt DJ. [Psychiatry & the psychedelic drugs. Past, present & future](#). *Neuropharmacology*. 2018 Nov;142:200-218. doi: 10.1016/j.neuropharm.2017.12.040. Epub 2017 Dec 25. Review. PubMed PMID: 29284138.
- Rucker JJ, Jelen LA, Flynn S, Frowde KD, Young AH. [Psychedelics in the treatment of unipolar mood disorders: a systematic review](#). *J Psychopharmacol*. 2016 Dec;30(12):1220-1229. doi: 10.1177/0269881116679368. Epub 2016 Nov 17. Review. PubMed PMID: 27856684.
- Sanches RF, de Lima Osório F, Dos Santos RG, Macedo LR, Maia-de-Oliveira JP, Wichert-Ana L, de Araujo DB, Riba J, Crippa JA, Hallak JE. [Antidepressant Effects of a Single Dose of Ayahuasca in Patients With Recurrent Depression: A SPECT Study](#). *J Clin Psychopharmacol*. 2016 Feb;36(1):77-81. doi: 10.1097/JCP.0000000000000436. PubMed PMID: 26650973.
- World Health Organization. Depression. <https://www.who.int/news-room/fact-sheets/detail/depression>. Published March 2018. Accessed September 25, 2019.
- United States Drug Enforcement Administration.. Drug Scheduling. <https://www.dea.gov/drug-scheduling>. Accessed September 27, 2019.