Psychedelics In Psychiatric Practice

A Carlat Webinar

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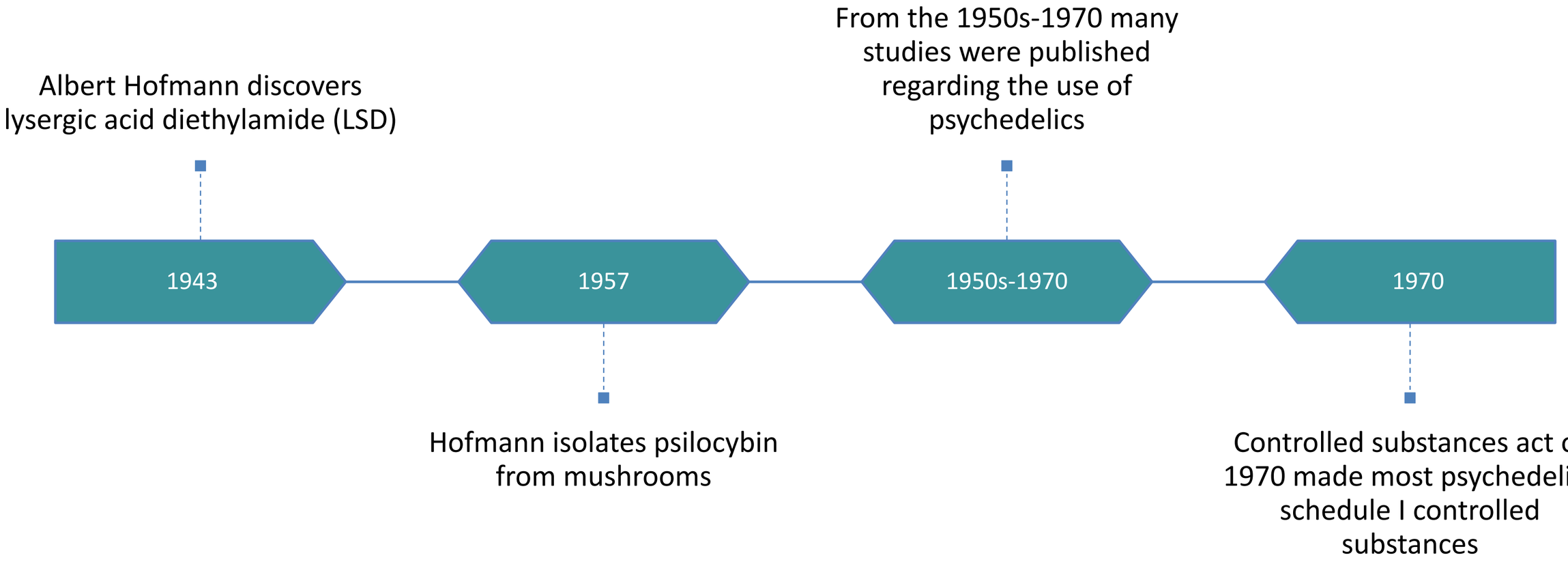
Conflicts and Disclosures

None

Learning Objectives

1. Understand the historical basis for using psychedelics to treat mental illness
2. Describe the therapeutic potential of psychedelic medicine
3. Explain the data supporting the use of psychedelics in major depressive disorder and differences in the mechanism of action compared to standard antidepressants
4. Identify the challenges associated with the development and clinical use of psychedelics

Hallucinogens Over the Years



Dyck E. CMAJ. 2015 Aug 4;187(14):1079-80

What Is a Psychedelic?

- Drugs that alter consciousness and perception
- Classic psychedelics: tryptamines and phenethylamines
- Atypical Psychedelics: MDMA and the dissociative anesthetics

Mendes FR et al. Addiction Neurosci September 2022

How Do Psychedelics Work?

- Classic psychedelics activate the serotonin 2A receptor
- Atypical psychedelics work by blocking NMDA receptors (ketamine) or by modulating dopamine, norepinephrine, serotonin, and oxytocin (MDMA)

Pandis C et al, Psychopathology 2019;52(3):161-173

Potential Therapeutic Uses

Medication is typically delivered in the context of psychotherapy before, during, and after treatment

- Mood Disorders: depression, anxiety
- PTSD
- OCD
- Pain and inflammation
- Cancer related psychological distress
- Addiction: alcohol use disorder, smoking cessation, cannabis use disorder, stimulant use disorder

Psychedelic Assisted Psychotherapy

- Delivered in a controlled setting
- 1-2 facilitators providing psychological support
- The initial session is followed by a brief course of therapy
- It’s unclear if the pairing is necessary
- Indirect support for psychedelic-assisted therapy comes from studies on follow up CBT after ketamine treatment

Wilkinson ST et al, Psychother Psychosom 2021;90(5):318–327

Mystical Experiences and Treatment Effect

- Therapeutic benefit correlates with the level of mystical experience
- It’s unclear if an altered state of consciousness is required
- Reduced activity in the default mode network allows the brain to form new connections
- These connections are formed in the context of psychotherapy and may explain the ability to prolong the effects
- In animal models blocking the serotonin 2A receptors still alleviated depressive behaviors

Wade BSC et al, Psychol Med 2022;52(12):2376–2386)
Hesselgrave N et al, Proc Natl Acad Sci U S A 2021;118(17):e2022489118

Psilocybin

- Plant alkaloid that acts as a serotonin 2A agonist
- Isolated from tropical and subtropical mushrooms found in South America, Mexico, and the United States
- Common street names include magic mushrooms and shrooms

Effects of Psilocybin-Assisted Therapy For Depression

- RCT of 24 participants with MDD
- Two psilocybin sessions
- Participants were randomized to begin treatment immediately or after 8-week delay
- Mean GRID Hamilton Depression Rating scores at baseline 22.8
- GRID-HAMD at weeks one and four 8.0 and 8.5 in the immediate treatment group
- Effect sizes 2.5 and 2.6

Davis AK et al. JAMA Psychiatry. 2021;78(5):481-489

Trial of Psilocybin vs Escitalopram for Depression

- Phase-II double blind randomized controlled trial
- Participants with long-standing moderate to severe MDD
- Compared psilocybin with escitalopram over a 6-week period
- Participants received either two separate doses of 25 mg of psilocybin 3 weeks apart or daily escitalopram with two separate doses of 1 mg psilocybin 3 weeks apart
- The results favored psilocybin over escitalopram they were not significantly different

Carhart-Harris R et al. N Engl J Med 2021;384:1402-11.

Single-Dose Psilocybin-Assisted Therapy in MDD

- Double blind RCT 52 participants with MDD
- Randomized to single dose of psilocybin or placebo
- Change in baseline BDI and MADRS at 14 days were the primary end points
- The psilocybin group showed a decrease in symptom severity at 14 days with an effect size 0.97
- 54% of the psilocybin group met MADRS remission criteria

Von Rotz R et al. EClinicalMedicine. 2022 Dec 28;56;101809

Psilocybin and Treatment Resistant Depression

- Only presented in abstract but showed positive results
- Large industry sponsored RCT 223 participants who failed 2-4 antidepressants
- Compared to placebo those who received psilocybin had a sustained response 3 months after the initial dose (20.3% vs 10.1%)

Goodwin G et al, Poster Presentation, APA New Orleans 2022

Psilocybin-Assisted Therapy in Life-Threatening Cancer

- 68 participants with terminal cancer in three small, randomized crossover trials
- Two studies were positive, with 70% showing large responses after a single dose
- Benefits were maintained at 6 months
- A long-term follow up (4.5 years later) was conducted with 15 of the original 16 patients in one cross over trial

Dodd S et al, CNS Spectr 2022;11:1–11
Agin-Liebes GI et al. J Psychopharmacol. 2020 Feb;(2):155-166

Microdosing Psilocybin

- Microdosing is defined as taking 5%-10% of the standard dose
- Low doses may provide benefits without intense hallucinatory experiences, based on some evidence
- One study found after 4 weeks of microdosing positive changes occurred with respect to well-being, anxiety, depression and emotional stability
- Microdosing challenges include legality, and participants reporting impairment in areas usually seen as a benefit of microdosing
- Different individuals can have vastly different experiences

Kaertner LS et al. Sci Rep 2021;11(1):1941
Anderson T et al. Harm Reduct J 2019;16(1):43

MDMA: 3,4-Methylenedioxymethamphetamine

- Known as “ecstasy” or “molly”
- Similar in structure to methamphetamine and mescaline
- Causes the release of monoamines through reversal of transport proteins and reuptake inhibition (serotonin and norepinephrine primarily)
- Modulates glucocorticoids through the HPA axis, decreases amygdala and hippocampal activity, and increases PFC activity
- New data indicating efficacy in the treatment of PTSD

MDMA Benefits for Fear Extinction in Exposure Therapy

- Increases blood flow to the vmPFC that decreases amygdala activation
- Increases cortisol which interacts with glucocorticoid receptors in the hippocampus improving memory
- Elevates BDNF improving memory
- Elevates oxytocin to decreases activity in the amygdala and enhance connectedness with the therapist
- Increased serotonin resulting in prosocial behavior and positive affect

Initial MDMA Trials

- The first data came from six small randomized controlled trials involving 105 participants
- Military and civilians with PTSD
- When the data is pooled it registered a large effect size
- One year later remission rates increased from 56% to 67%

Jerome L et al, Psychopharmacology (Berl) 2020;237(8):2485–2497

Phase III RCT Granting MDMA Breakthrough Status

- Randomized double blind Phase III trial of 89 participants
- Treatment is safe and well tolerated
- 67% reached full remission from PTSD
- New studies are looking at MDMA for alcohol use and eating disorder

Mitchell JM et al, Nat Med (2021);27:1025–1033

MDMA Risks

- Reports of death from hyperthermia, cardiotoxicity, and seizures
- Psychiatric side effects include worsening mood, suicidality, and psychosis/mania
- It’s unknown if these same risks carry over for doses used clinically

Costa G and Gołembiowska K, Exp Neurol 2022;347:113894

Abuse Potential

- Psilocybin, MDMA are Schedule I drugs
- These drugs do not seem to hijack the reward center like opioids
- Repeated use of psilocybin does not lead to physiological dependence or withdrawal
- Psilocybin is decriminalized in 9 US cities and readily available in nonmedical settings in Oregon

Summary

- There is a renewed interest in psychedelics as a treatment for psychiatric disorders
- Investigations are underway for several psychiatric disorder including depression and PTSD
- Psychedelic-assisted psychotherapy is a new method of delivering medication
- Psychedelics come with risk including adverse effects and legal consequences