MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Welcome!

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Massachusetts General Hospital

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Nuts and bolts

- CME is claimed via your attendance
- Psychologists and SW credit: sign in **each day**
- Evaluations!

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Psychedelics – Intro & Pharmacology

Disclosures

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If you have disclosures, state:

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

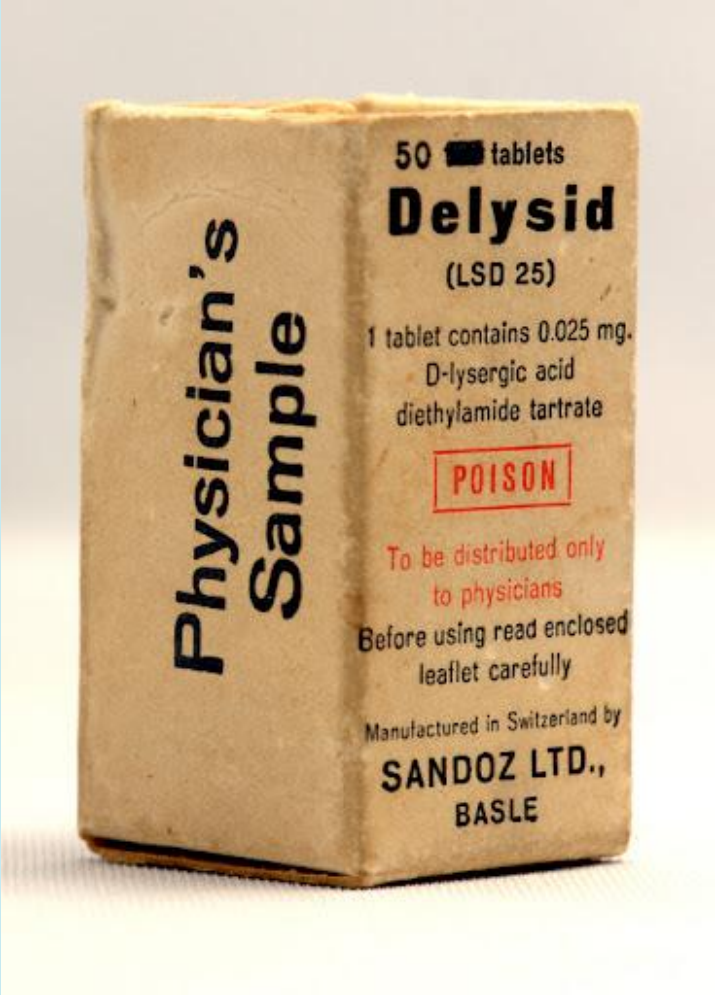
Compass, Cybin – personal stock

Apex Labs – SAB

Tryp Therapeutics – research support

Psychedelics in western medicine

- Hashish, chloroform, ether (1890s)
- Narcoanalysis (barbiturates, 1920s)
- Confessions in Mescaline Inebriation (1931)
- First clinical study with LSD (1947)
- First use of LSD in therapy (1950)



Psychedelic therapy 1950s-1970s

- Thousands of participants enrolled in clinical studies, mostly utilizing LSD
- Promising results, particularly in alcohol use disorder and end of life-related depression and anxiety
- However, lower quality research, heterogeneity of studies
- Ultimately a casualty of moral panic over LSD in the USA and Europe

The return of psychedelics

- 1994: DMT study by Rick Strassman
- 2006: “psilocybin can occasion mystical type experiences” (Griffiths, Johns Hopkins)
- 2010s-present: Research grows
- 2019-present: starting with Imperial College (UK) and Johns Hopkins (USA), psychedelic research centers open
- 2021: first Phase III study results reported (MDMA-assisted therapy for PTSD); MGH opens Center for Neuroscience of Psychedelics
- 2024: FDA rejects New Drug Application for MDMA

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The Pharmacology of Psychedelics

What do psychedelics do?

Classical Psychedelics

- Change in consciousness
- Deeply felt personal meaning
- Ego dissolution
- Increased connectedness
- Enriched sensory/phenomenal experience
- Visual hallucinations

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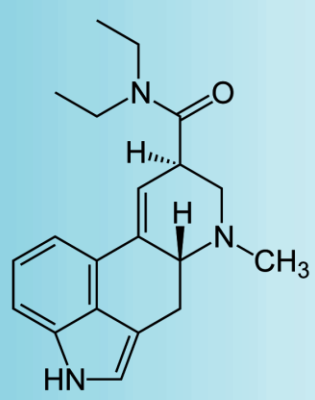
MDMA/empathogens

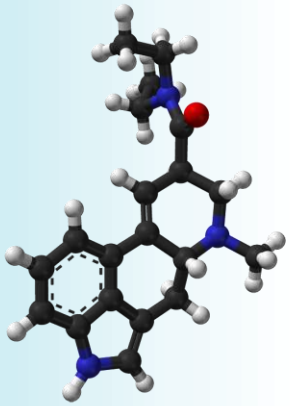
- Change in consciousness
- Increased trust, empathy
- Euphoria
- Social connectedness
- Sensory enhancement

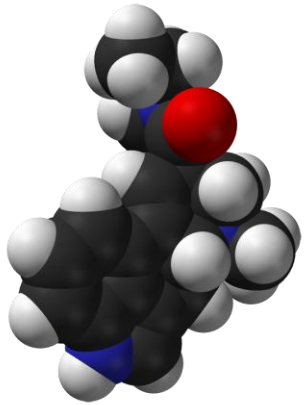
Both: durable changes over time (?)

Tryptamines

- Most studied class in modern era
- All share structural backbone with serotonin (5-hydroxytryptamine)
- Psilocybin (4-phosphoryloxy-DMT)
- DMT, 5-MeO-DMT
- LSD







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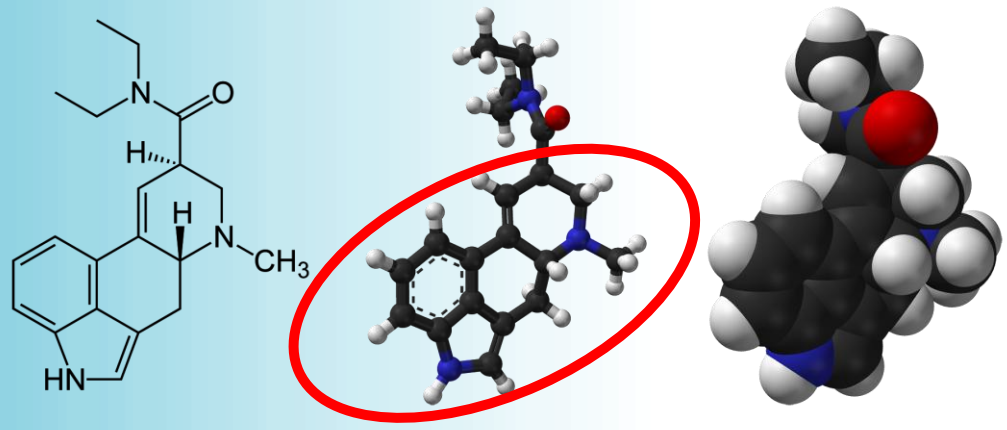
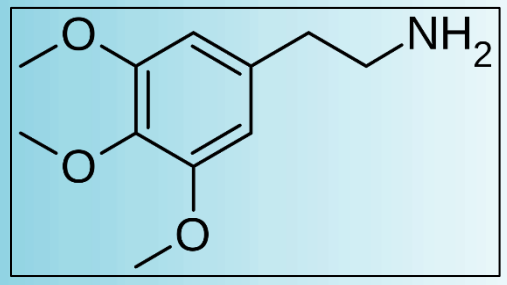


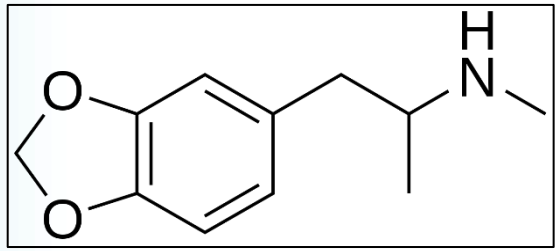
Phenethylamines

- Substituted phenethylamines include a wide array of drug classes
- Psychedelics include mescaline, MDMA
- Other than MDMA, less well-researched

CNS stimulants, decongestants, antidepressants, anti-Parkinson agents, vasopressors, bronchodilators, and neurotransmitters epinephrine, norepinephrine and dopamine



Mescaline

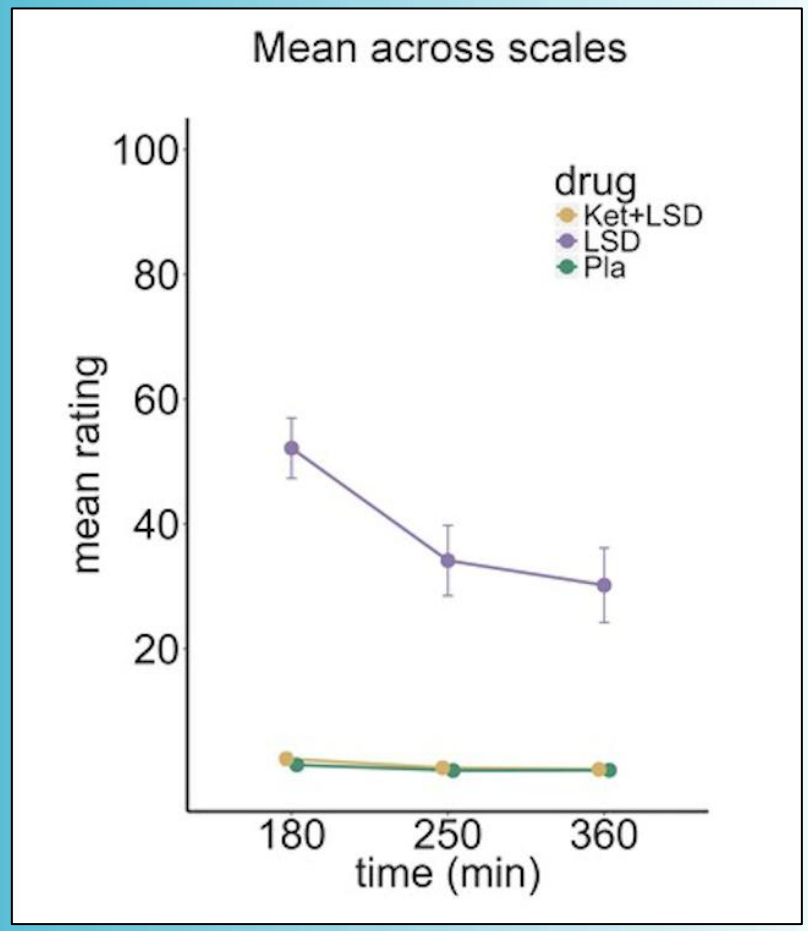


MDMA

Pharmacology

Classical Psychedelics

- Agonist or partial agonist activity at 5HT-2A receptor
- Ketanserin (2A antagonist) blocks effects of psilocybin, LSD
- Atypical antipsychotics more effective blockade/abortive than haloperidol



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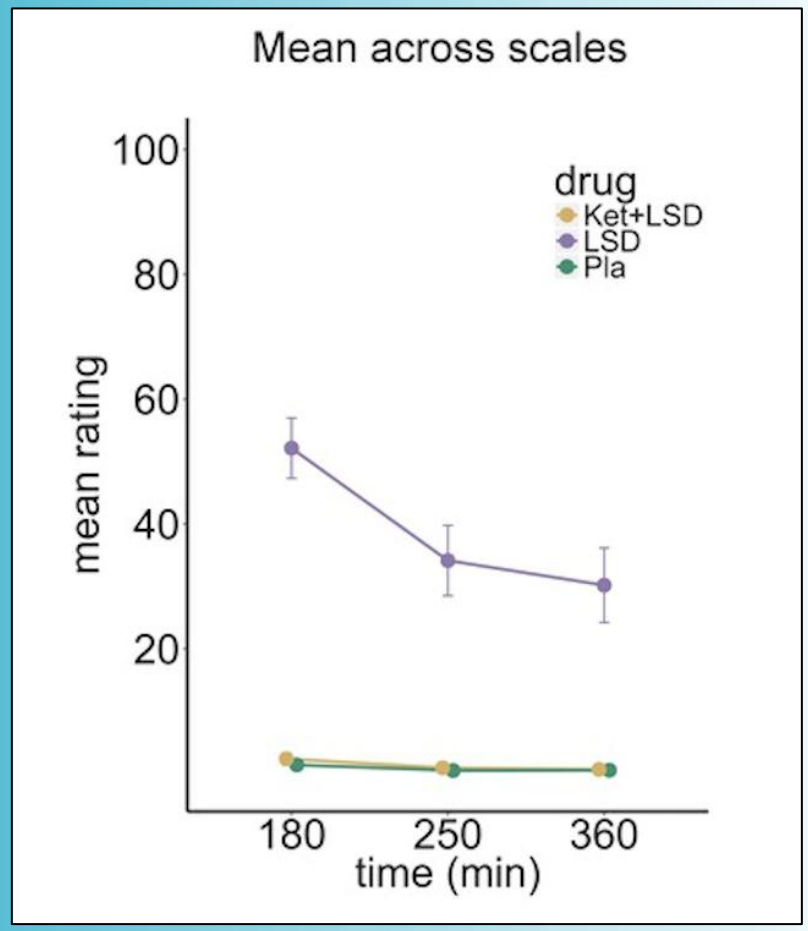
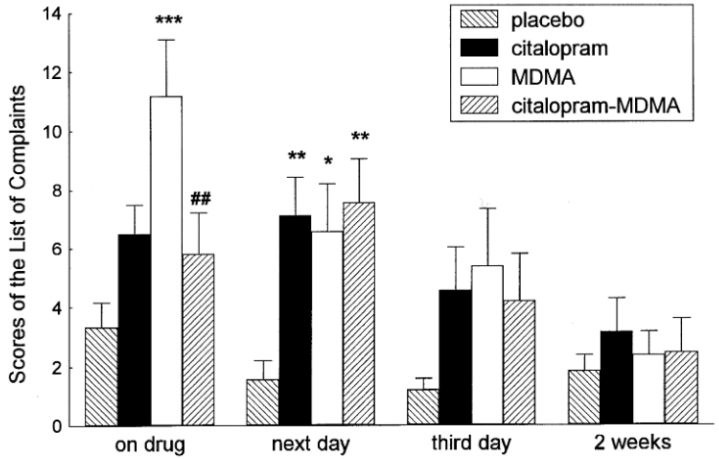


Empathogens (MDMA)

- Monoamine releaser
- 5HT release (primary)
- DA and NE (secondary)
- SSRIs/SNRIs block (most) MDMA effects



Liechti et al., *J Psychopharmacol*, 2000

Physiologic and psychologic adverse effects

Classical psychedelics

Acute adverse effects

- Headache, fatigue, nausea common
- Mild sympathetic increase
- Psychiatric: transient anxiety, psychological discomfort, delusional thinking
- Safe in overdose

Chronic adverse effects

- 5HT2B receptors and cardiac disease: theoretical – microdosing?

Passie *CNS Neuroscience and Therapeutics* 2008

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MDMA

Acute adverse effects

- Bruxism, hyperthermia, SIADH
- Nausea, appetite suppression
- Sympathomimetic >> classical psych's
- Psychiatric: anxiety
- Overdose possible

Chronic adverse effects

- ?Neurotoxicity – controversial, not proven
- Decreased 5HT-R density w heavy chronic use

Passie *CNS Neuroscience and Therapeutics* 2008

Autonomic effects

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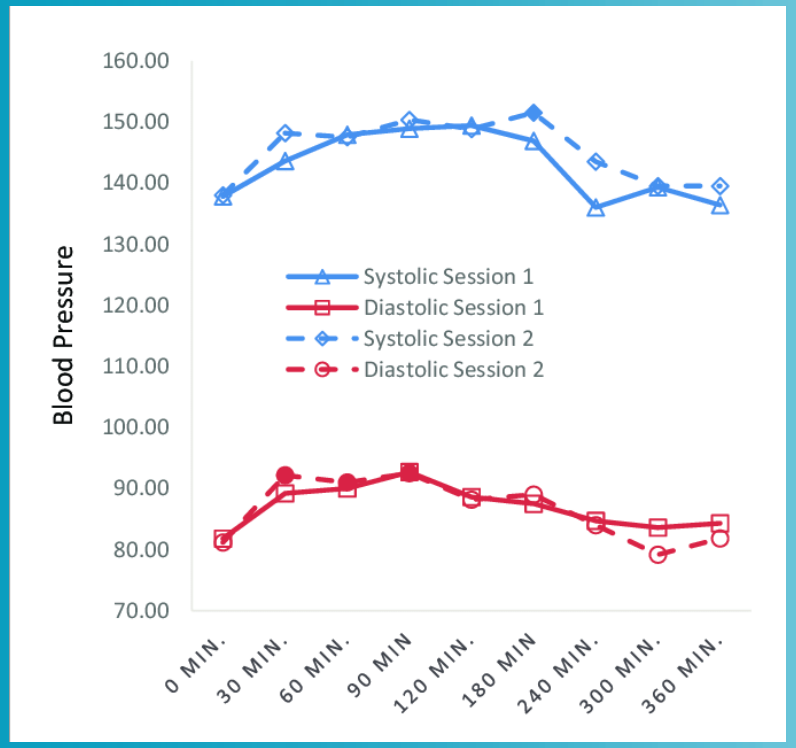
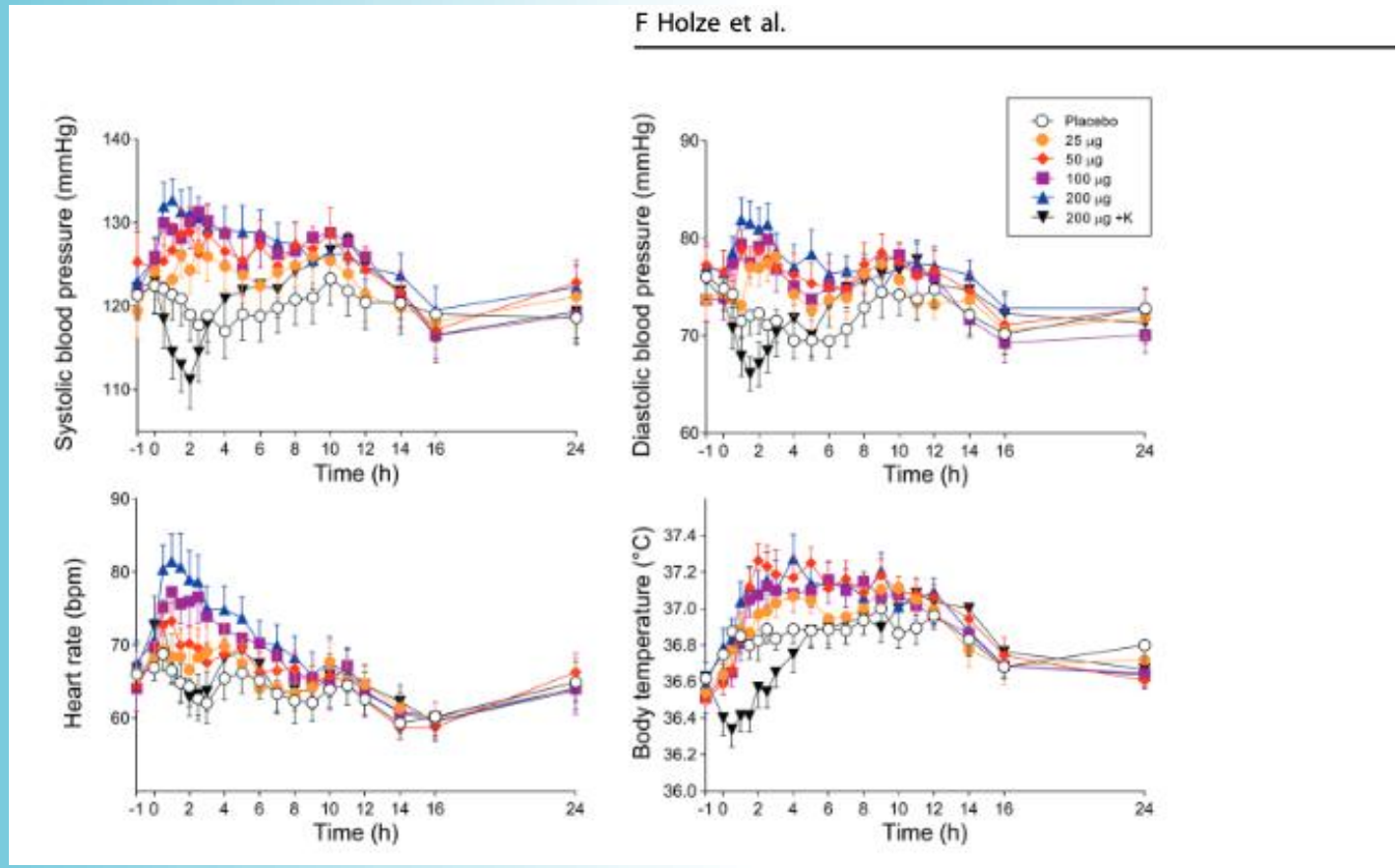


Psilocybin ☝

LSD 👇



Bogenschutz *Psychopharmacology* 2015,
Holze *Neuropsychopharmacology* 2021

Tachyphylaxis and addictive potential

- For classical psychedelics, tachyphylaxis occurs within 3-4 days of daily administration, lasts days to weeks
- Cross-tolerance between different agents
- Correlates with downregulation of 5HT-2A receptors in animal models
- Biological (and psychological) dependence on psychedelics is not observed
- For MDMA, abuse/addiction potential is higher, likely due to dopaminergic effects

Psychedelics and psychiatric medications

- Classic psychedelics + SSRIs = OK
- MDMA is fully blocked by SSRIs and SNRIs
- Ayahuasca: **contains MAOI** 💀
- Ibogaine: QT prolongation <-> methadone et al.
- Lithium: increased risk of seizure?
- Second generation antipsychotics fully antagonize psychedelic, partial blocking of effect with haloperidol

Liechti et al, Neuropsychopharmacology 2000; Nayak et al, *Pharmacopsychiatry* 2021; Schmid et al *J Pharmacol Exp Ther* 2015; Vollenweider et al *Neuroreport* 2008

Thank you

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MGH Center for the Neuroscience of Psychedelics

Leadership

- **Jerrold Rosenbaum, MD**
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  MGH Department of Psychiatry
- **Sharmin Ghaznavi, MD, PhD**
  CNP Associate Director and Director of Cognitive Neuroscience
  MGH Department of Psychiatry
- **Bruce Rosen, MD, PhD**
  Scientific Director, Neuroimaging
  Athinoula A. Martinos Center for Biomedical Imaging
- **Jacob Hooker, PhD**
  Director, Translational Biomarkers
  Athinoula A. Martinos Center for Biomedical Imaging
- **Stephen Haggarty, PhD**
  CNP Scientific Director, Chemical Neurobiology
  MGH Department of Neurology
- **Franklin King, MD**
  CNP Director of Education and Therapist Training
  MGH Department of Psychiatry
- **Jeremy Ruskin, MD**
  Founder, MGH Cardiac Arrhythmia Service