MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Welcome!

Franklin King IV, MD

Director, Training and Education, Center for Neuroscience of Psychedelics

Massachusetts General Hospital

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Nuts and bolts

- CME is claimed via your attendance
- Psychologists and SW credit: sign in **each day**
- Write your name in your book
- Please silence your phones (and alarms)
- Questions for Q&A via link on the slides
- Ask the Psych Academy for lunch options
- Evaluations!

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A Brief History of Psychedelics in 20 minutes

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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

All relations approved by MGH Office of Interaction with Industry

Psychedelics are not new

- Psychedelics are **not** “novel agents”
- Used across cultures and continents for thousands of years
- Generally used as medicines within a sacred context combining elements of therapy, medicine, and religion
- Broader context of:
  - Psychoactive plants as medicines
  - Elevating non-ordinary states of consciousness as integral aspects to the human experience

Mescaline

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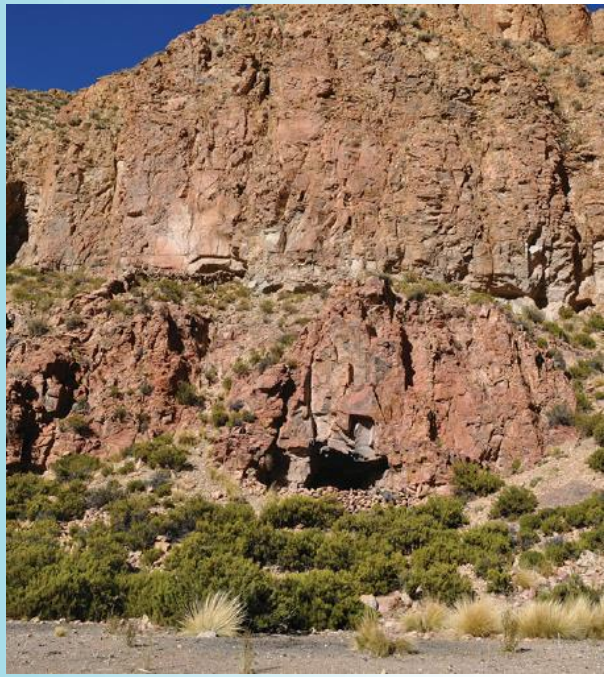
- Peyote buttons found in Rio Grande valley, 5700 years ago
- San Pedro cactus in Peru from 3300 years ago

El Seedi, *J* Ethnopharmacol, 2005; Davis *Botanical Museum Leaflets*, 1983

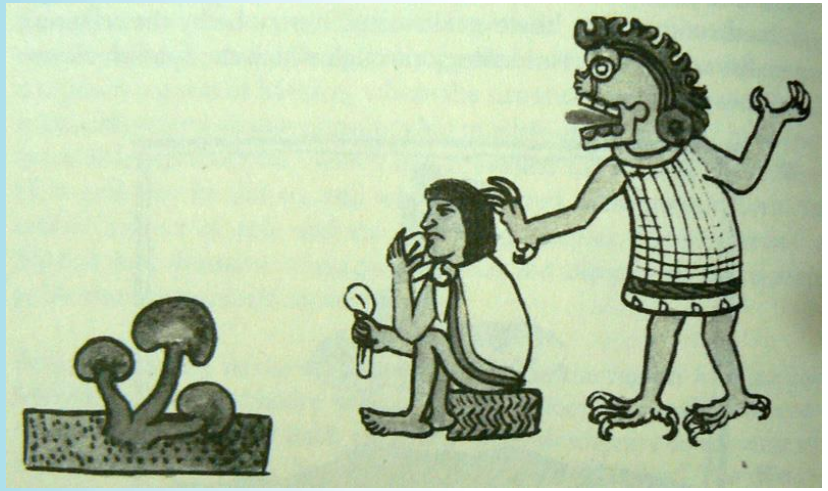
DMT

- Many diverse plants contain DMT
- Ayahuasca (at least 1,000 years ago in Bolivia), *Banisteriopsis* and *Psychotria*
- Jurema (northeastern Brazil) - *Mimosa*
- Tepezcohuite (Mexico) – *Mimosa*
- Cohoba or yopo (Caribbean) - *Anadananthera*



Psilocybin

- Extensively used and deeply embedded within Mesoamerican cultures
- Various names, teonanacatl (flesh of the gods), temicxoch (dream flowers)
- Aztecs also consumed morning glory seeds (ololiuqui)
- Brutally suppressed by invading Europeans



Ibogaine

- Shrub native to central and western Africa
- Used likely for millennia
- Highly potent
- Primarily used in large doses in coming of age ceremonies

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)

Psycholytic therapy

- Arose in context of psychoanalysis-dominated era
- Goal to use LSD as an adjunct to therapy, rather being a cure itself
- Amplication of psychodynamic processes and reduction of ego defenses
- Many, frequent, moderate dose LSD sessions embedded within extensive, traditional psychotherapy paradigm
- Predominant model in Europe

Psychedelic therapy

- Inadvertent discoveries that LSD led to significant patient improvement in cancer and alcoholism by inducing mystical and/or religious experiences
- Concurrent refocus within psychology on transcendent states (Maslow, head of APA)
- Growing awareness of Indigenous practices using psychedelics in ritual context

Psychedelic therapy

- One of the predominant forms in North America by latter 1960s
- Explicit purpose to induce mystical or transcendent experience
- Single, high dose session
- Manipulation of expectation and environment to prime this occurrence

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 are psychedelics?

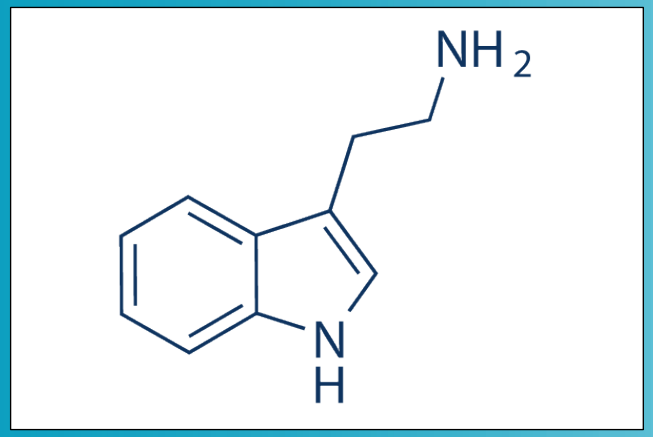
- Psychedelic, 1956 = “mind-manifesting”
- Change in consciousness, experience often described as profound, transformative, with spiritual or mystical importance, and/or personal meaning
- “Ego dissolution” – decreased boundary between self and world, increased connectedness
- Increased sensory experiences: synesthesia, visual imagery and/or hallucinations

How do psychedelics differ?

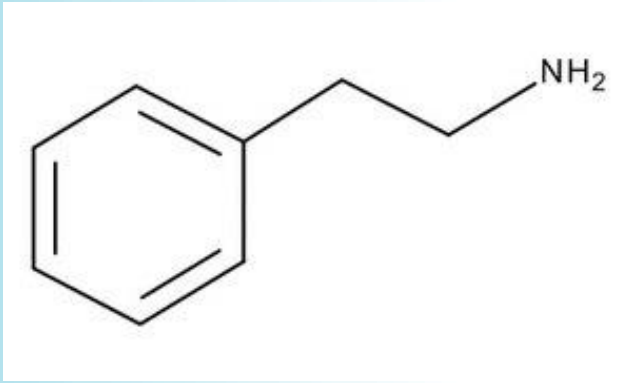
- Time: LSD and mescaline (8-12 hours), psilocybin and ayahuasca (4-6 hours), DMT and 5-MeO DMT (10-20 minutes)
- Quality:
  - Measures: ASC, MEQ, HRS
  - Visual aspects
  - Ego dissolution/consciousness change
  - Prosociality (MDMA, MDA - “empathogens”)
- Oral bioavailability: DMT – 100% metabolized by gut monoamine oxidase, most others with good oral bioavailability

Classes of Psychedelics

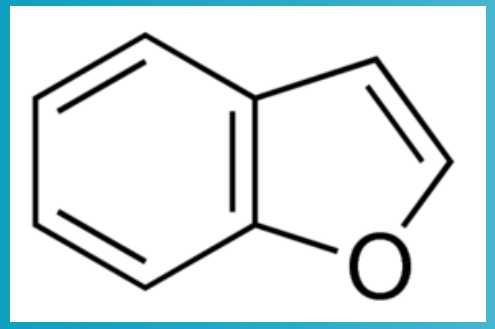
Tryptamines



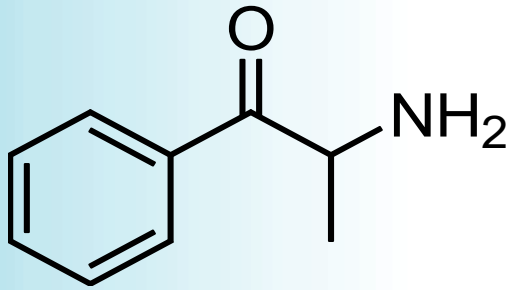
Phenethylamines



Benzofurans

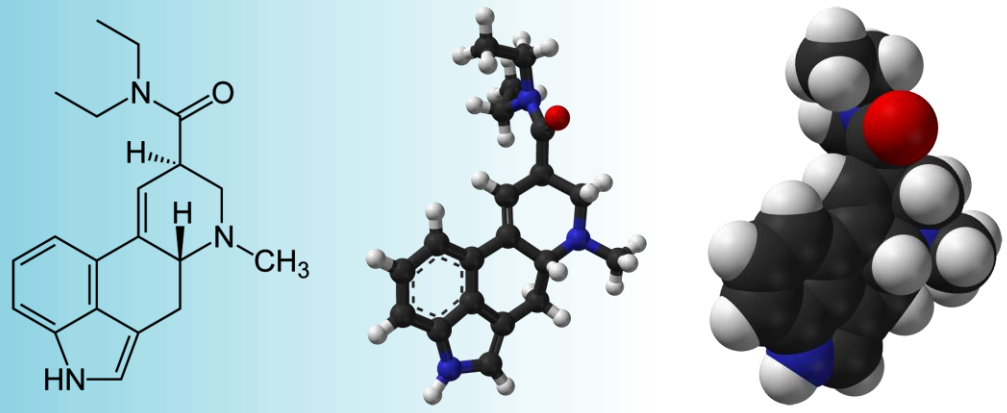


Cathinones



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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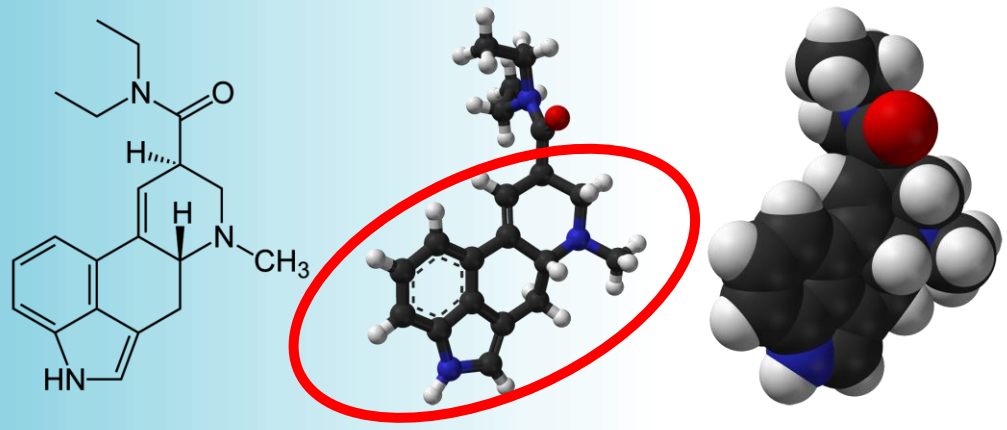
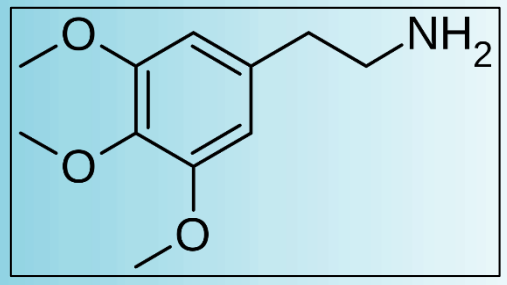


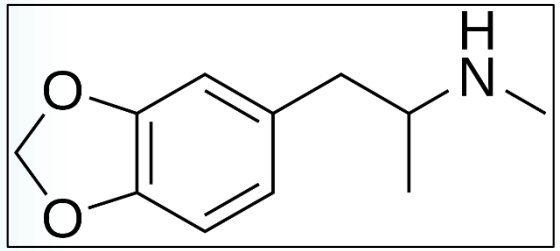
Phenethylamines

- 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

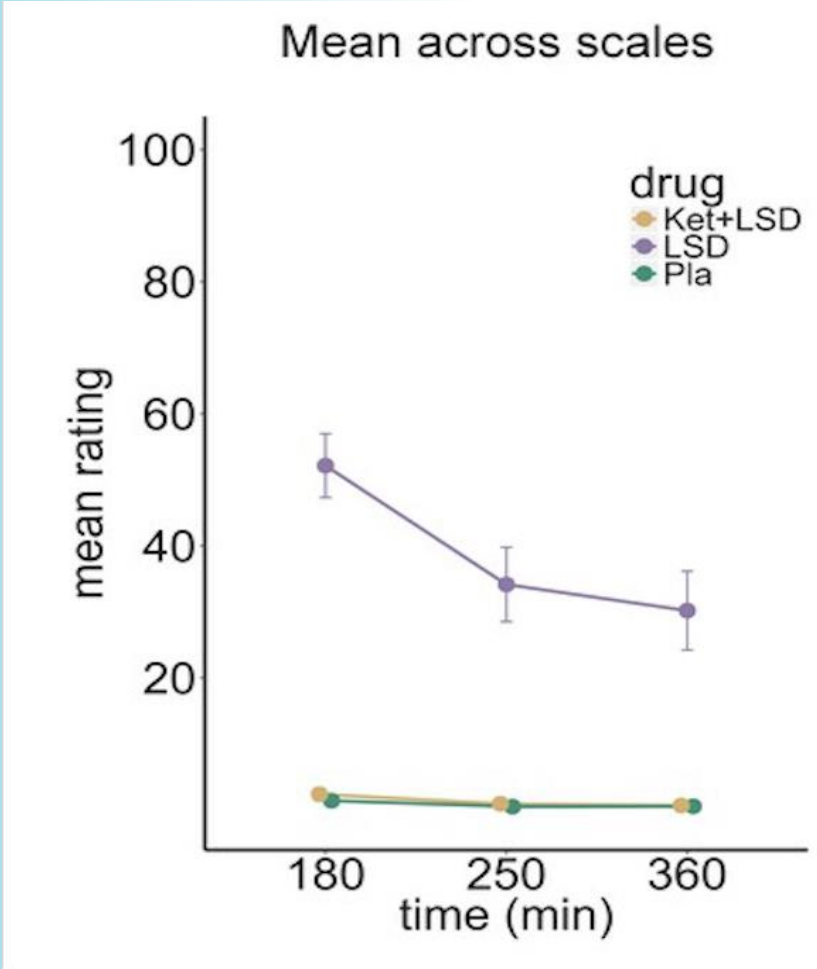
Phenethylamines

- "2C" compounds, eg, 2C-B (psychedelic + empathogenic)
- Also include psychedelic agents with higher risk for adverse effects
  - **DOM**: "STP", extremely potent, long lasting, mistakenly taken as LSD in late 1960s
  - **NBOMe's**: group of compounds highly potent, sometimes misrepresented as LSD -> overdose
    - Toxicity: tachycardia, fever, hypertension, seizures, hyperthermia

Wood et al, Clin Toxicol, 2015

Pharmacology

- Primary effect via agonist or partial agonist activity at 5HT-2A receptor
- Blocked by ketanserin and other 5HT-2A antagonists
- Prevention of psychedelic effect shown for psilocybin, LSD



Vollenweider et al, *Neuroreport*, 1998; Preller et al, *Curr Biol*, 2017; Preller et al, *Elife*, 2018

The 5HT-2A receptor

- Excitatory (G-protein coupled receptor, causes neuron to depolarize, release cortical glutamate)
- Expressed throughout the brain, but more densely expressed in certain areas
- Activation associated with neuroplasticity (increase in dendritic spines, synaptic proteins etc)

Martin et al, *EBioMedicine*, 2016

Safety & physiologic effects

- Subjective physical effects:
  - Headache, nausea, fatigue most common (<50%)
- Sympathetic changes:
  - ↑BP, ↑HR (mild), ↑temperature (mild)
  - Mydriasis, increased reflexes
- Well tolerated in medically ill subjects (advanced cancer, geriatric patients)
- Toxicity: no LD50 established for humans, likely in grams or kilograms
- No evidence for mutagenic effects or neurotoxicity, including high dose exposures

Passie *CNS Neuroscience and Therapeutics* 2008

Autonomic effects

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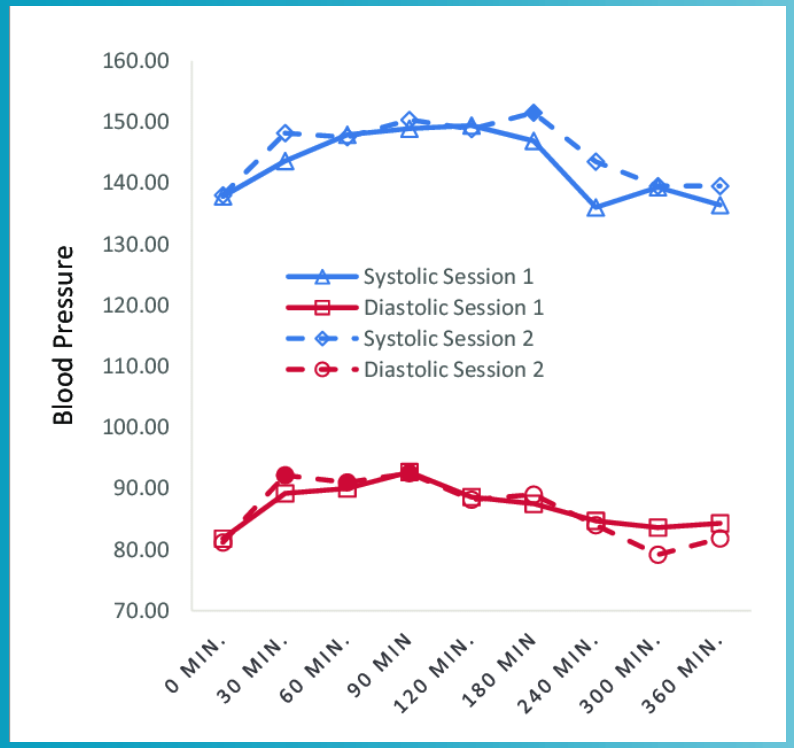
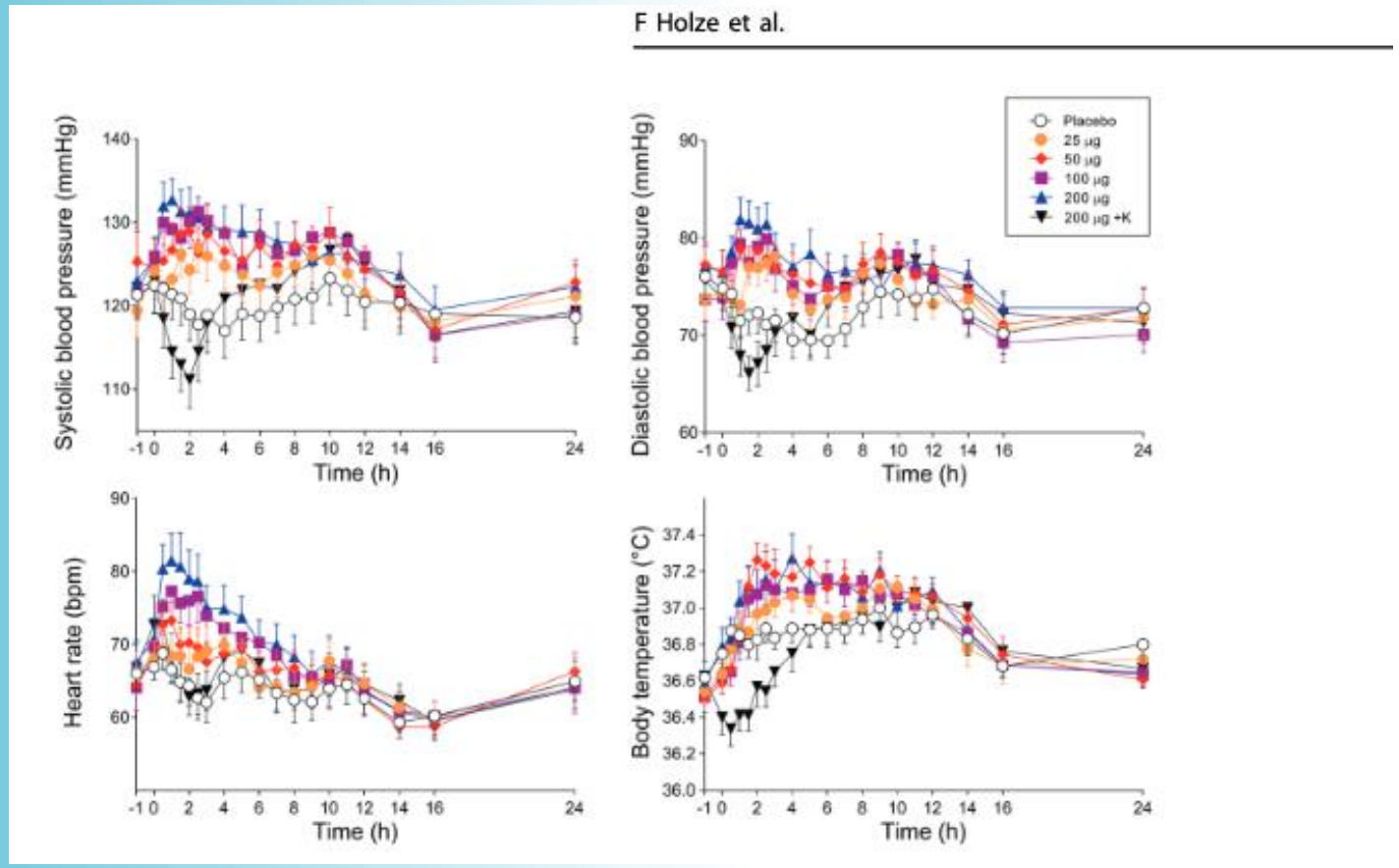


Psilocybin ☝

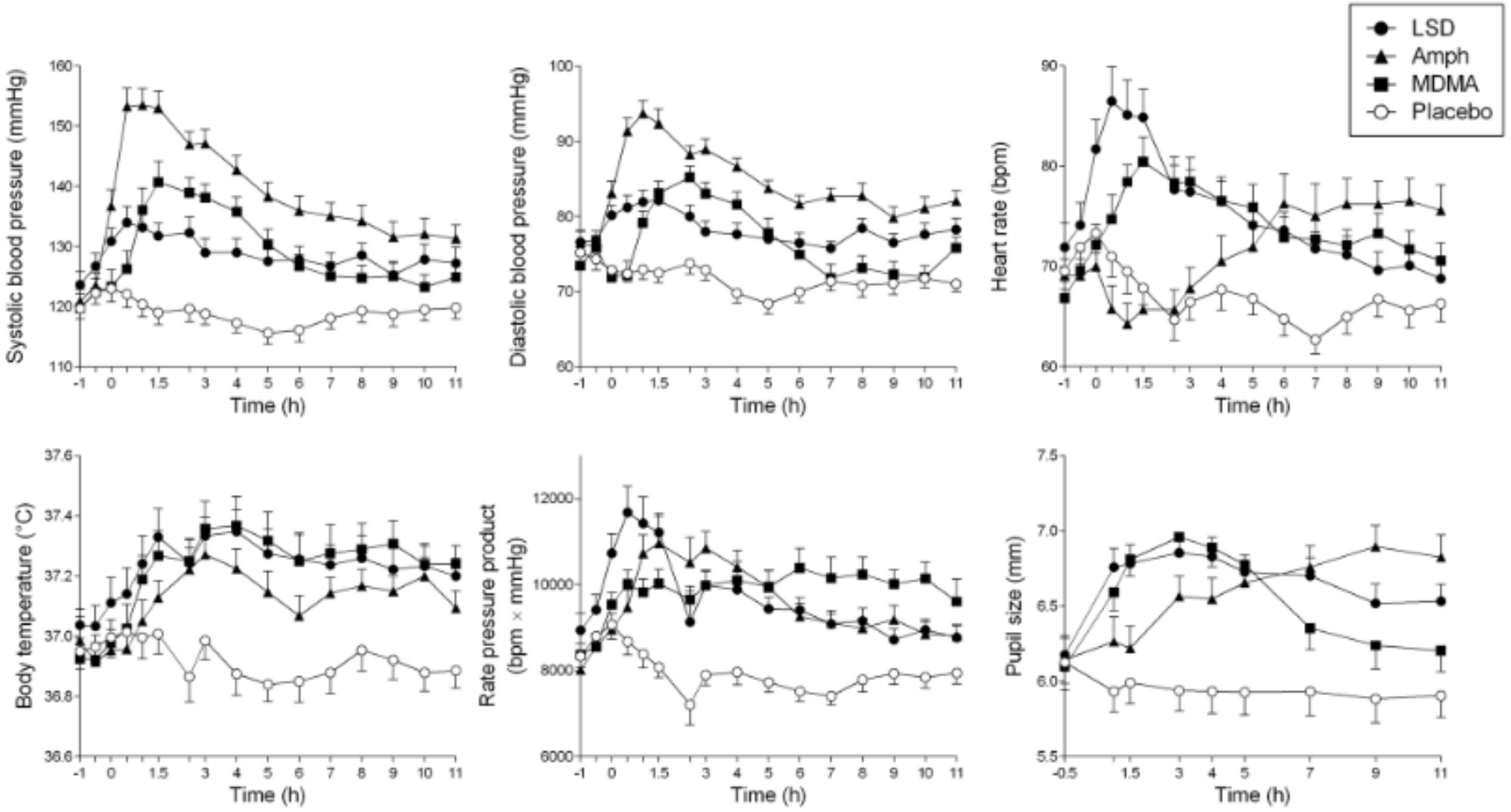
LSD 👇



Bogenschutz *Psychopharmacology* 2015,
Holze *Neuropsychopharmacology* 2021

Autonomic effects

Distinct acute effects of LSD, MDMA, and D-amphetamine
F Holze et al.



Holze *Neuropsychopharmacology* 2019

Tachyphylaxis

- Tachyphylaxis occurs within 3-5 days of daily administration
- Cross-tolerance between different agents
- Correlates with downregulation of 5HT-2A receptors in animal models
- Biological dependence on psychedelics is not possible

Psychedelics and psychiatric medications

- SSRIs tapered off for most psychedelic studies
- Long been thought to blunt the effects of psychedelics
- Recent (but small) studies suggest SSRIs may neither block subjective nor therapeutic effects
- More research needed on this question due to impact on accessibility of psychedelic treatments

Becker et al *Clin Pharmacol Ther* 2021
Goodwin et al, *Neuropsychopharmacology* 2023

Psychedelics and psychiatric medications

- 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

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  CNP Associate Director and Director of Cognitive Neuroscience
  MGH Department of Psychiatry
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