

#PeptideWC2022



# THE BIOCHEMISTRY BEHIND LOW DOSE PSYCHEDELICS

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# What is a Psychedelic?

For the purpose of today's presentation, we will be discussing 5HT2A agonist ligands.



## Ergolines

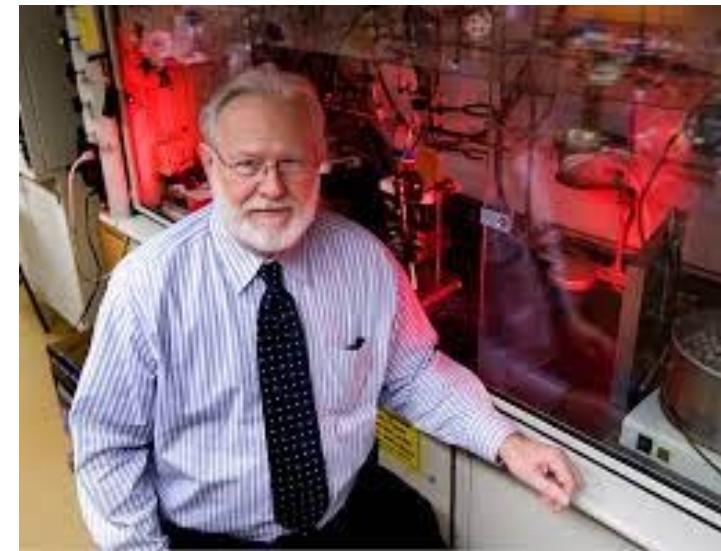
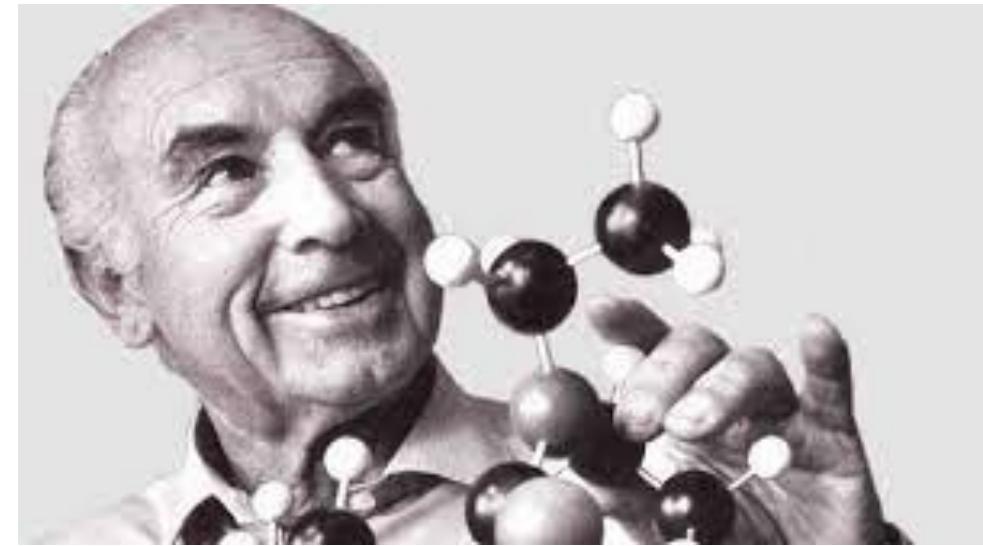
A series of natural and synthetic chemicals compounds that include the semisynthetic compound & classic hallucinogen LSD, the prolactin inhibitor Cabergoline, the Parkinson's drug Pergolide, Methylergometrine used post birth to induce Uterine contractions, natural morning glory alkaloids

## Tryptamines

Plant, Mushroom, and Synthetic compounds that include chemicals such as Melatonin, Serotonin, DMT, Psilocybin, & Psilocin, 5-HTP, all potentially derived from the amino acid Tryptophan

## Phenethylamines

Compounds such as Mescaline, Amphetamines, MDMA, and 2C-B



# History

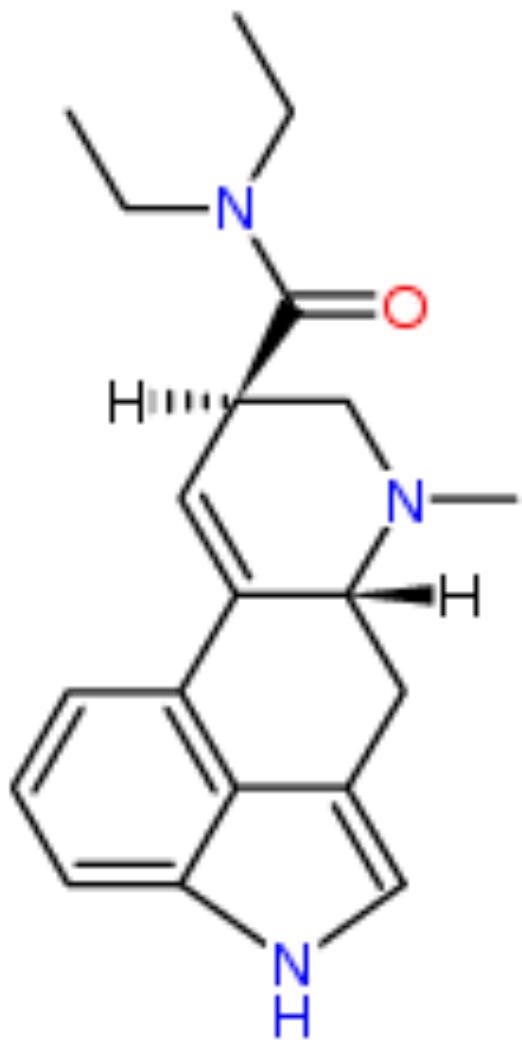
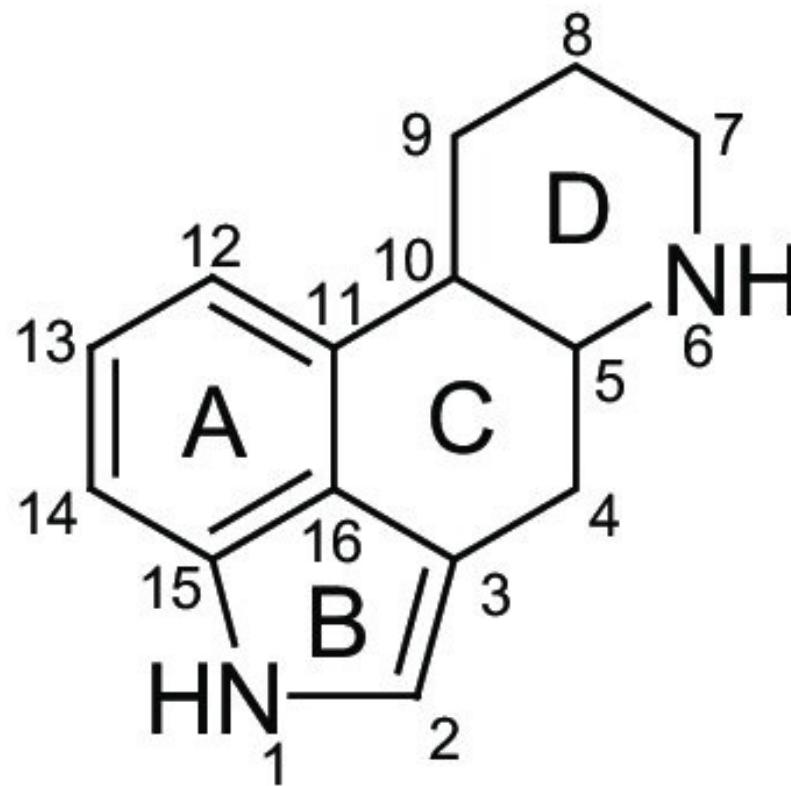
PiHKAL - 179 phenethylamines, 1990  
TiHKAL - 55 tryptamines, 1997

Ergolines – Nichols Lab  
LSD – Albert Hoffman, Sandoz; first synthesized in 1938

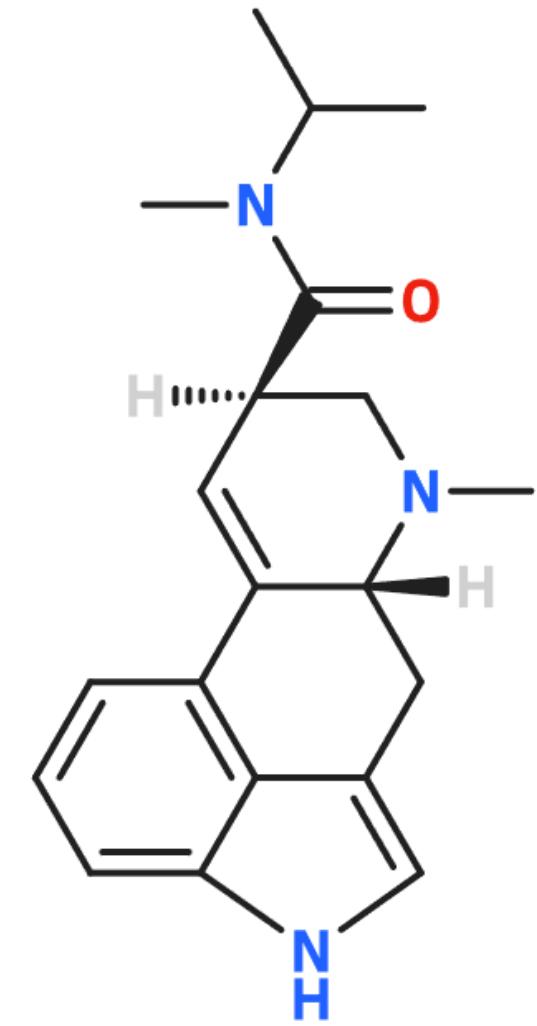
# Drug Nomenclature

Ergolines

IUPAC numbering system:



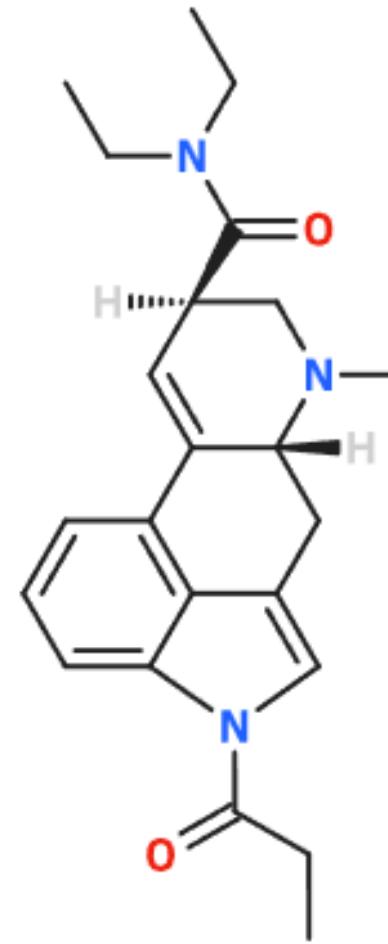
Lysergic Acid Diethylamide  
LSD



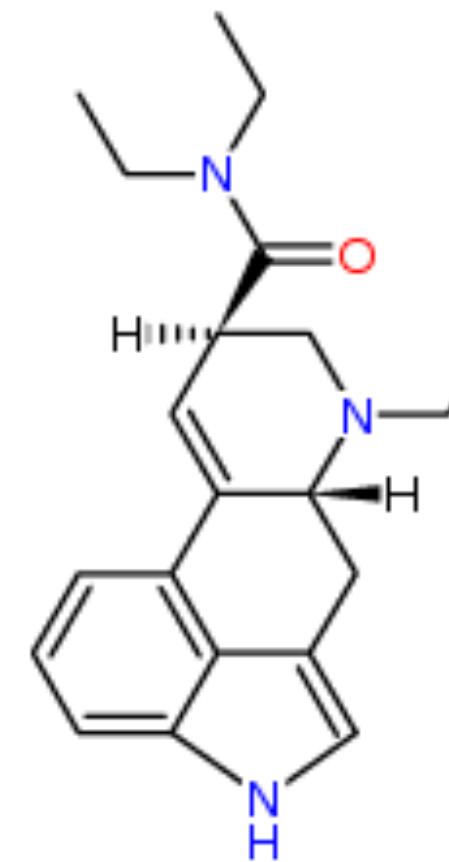
Lysergic Acid Methylisopropylamide  
MIPLA or LAMID

# Drug Nomenclature

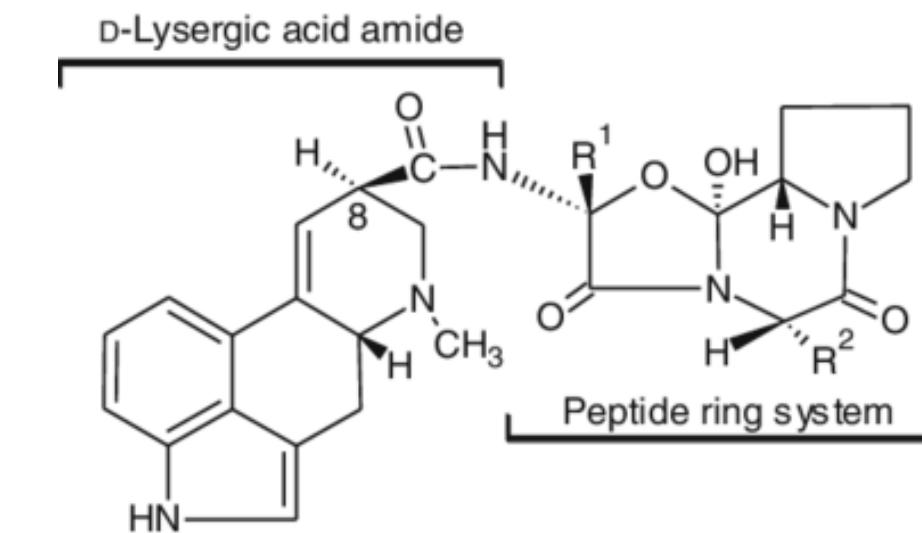
## Ergolines



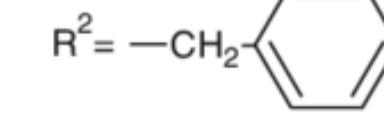
Propionic Acid in  
position 1 of LSD  
1P-LSD



Ethyl side chain in  
position 6 of LSD  
ETH-LAD

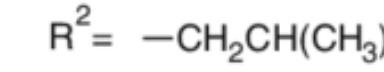


$R^1 = -CH_3$



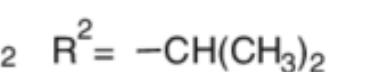
Ergotamine

$R^1 = -CH_3$



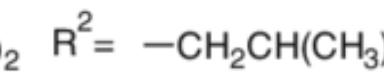
Ergosine

$R^1 = -CH(CH_3)_2$



Ergocornine

$R^1 = -CH(CH_3)_2$



$\alpha$ -Ergocryptine

$R^1 = -CH(CH_3)_2$

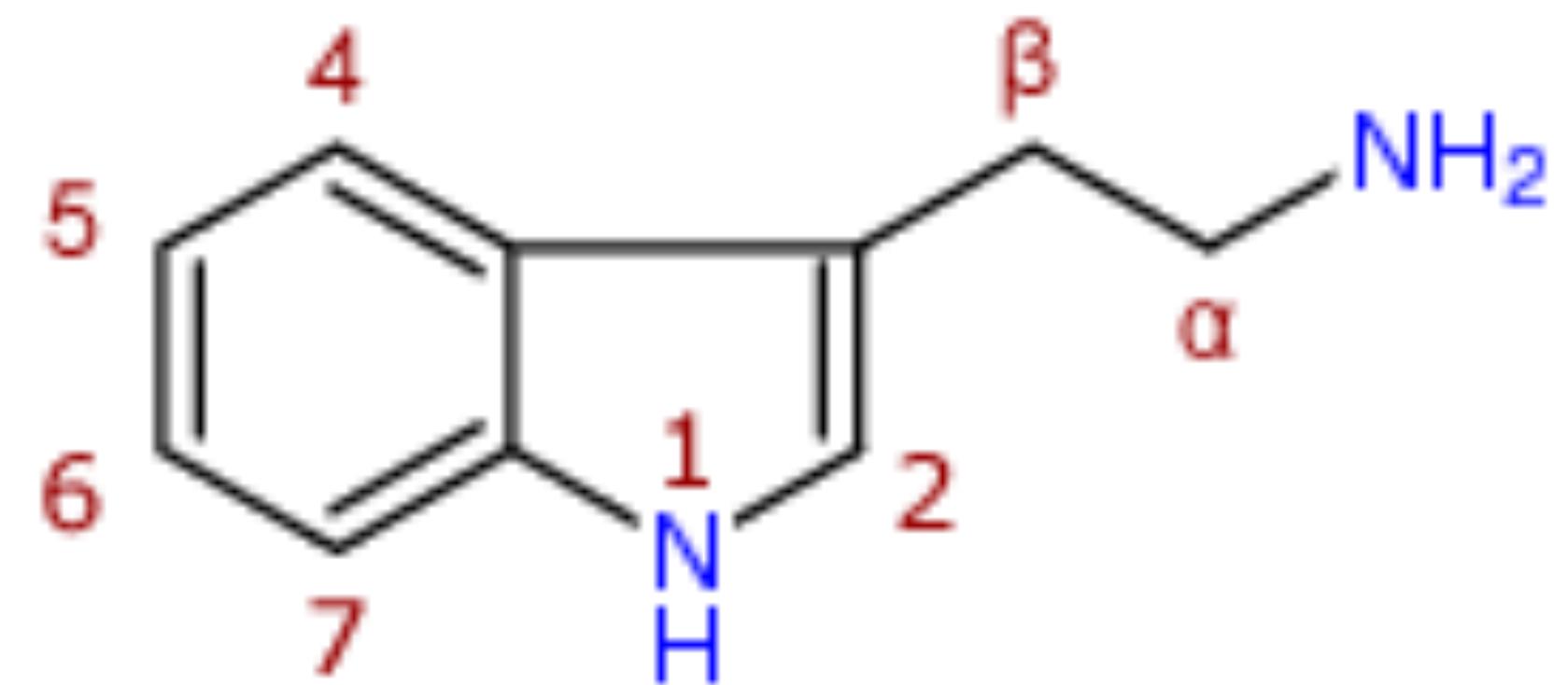


Ergocristine

# Drug Nomenclature

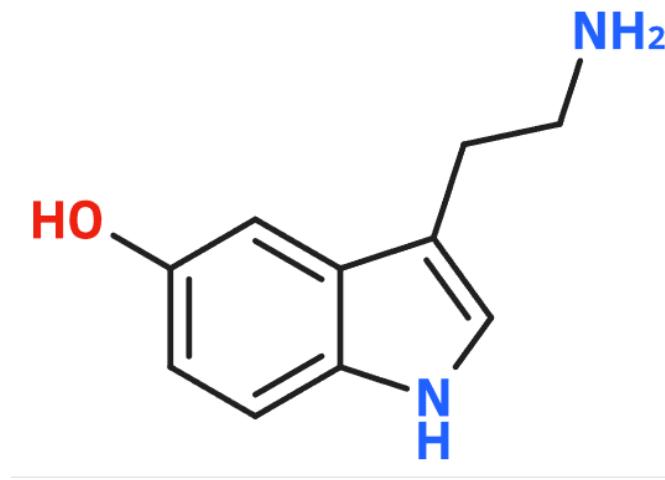
Tryptamines

IUPAC numbering system:

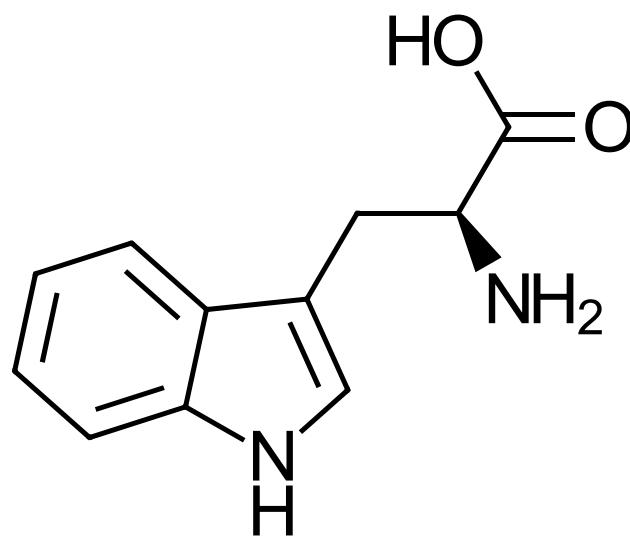


# Drug Nomenclature

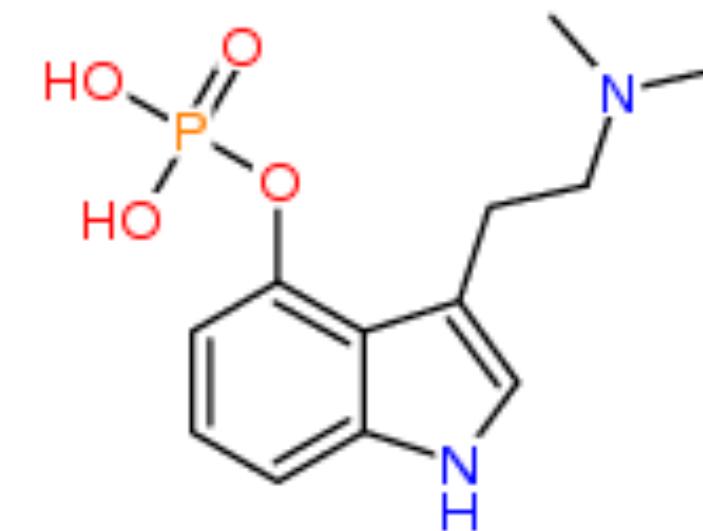
Tryptamines



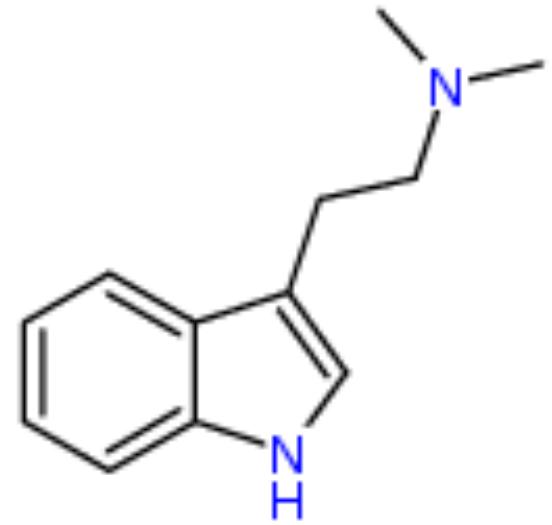
Serotonin



Tryptophan



Psilocybin

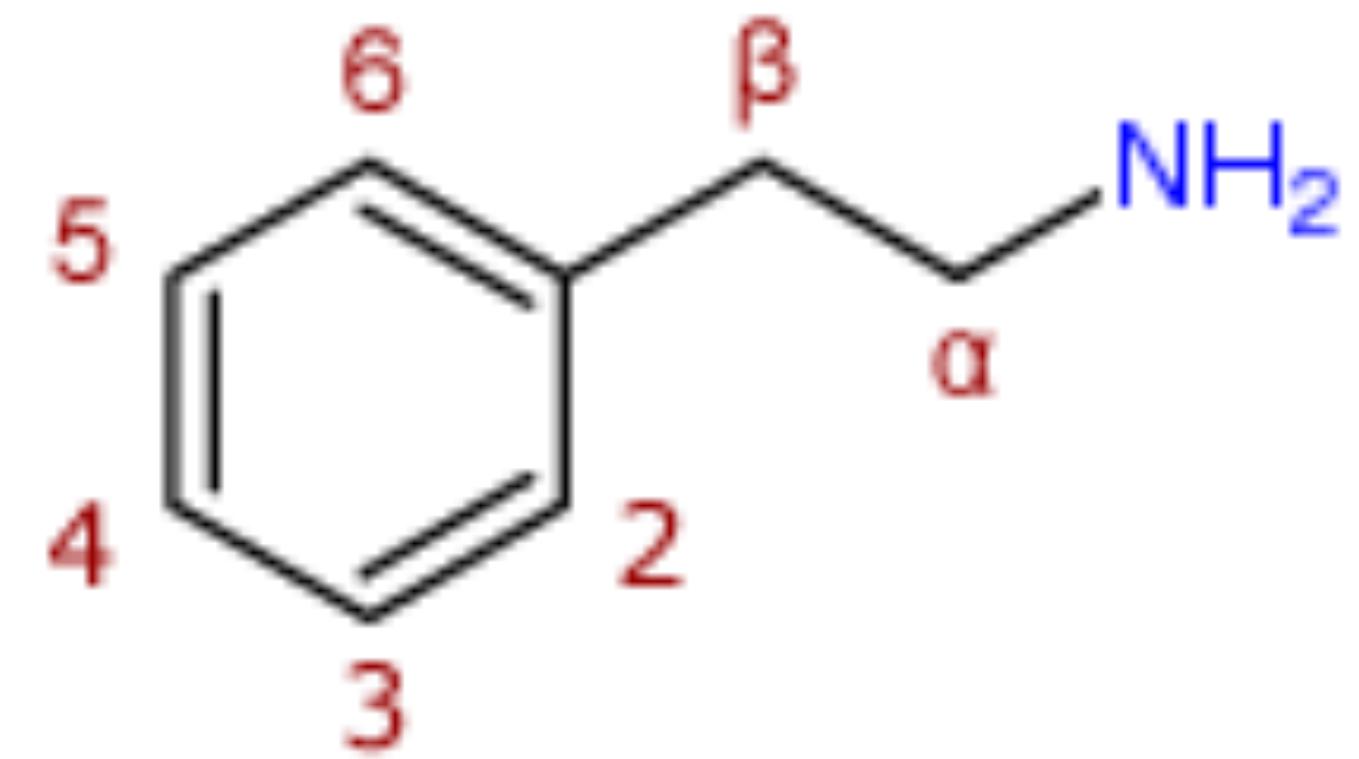


Psilocin

# Drug Nomenclature

Phenethylamines

IUPAC numbering system



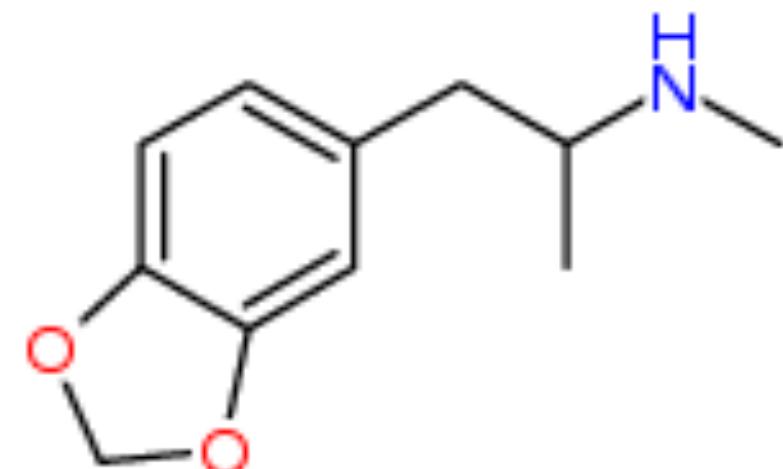
Phenyl

ethyl

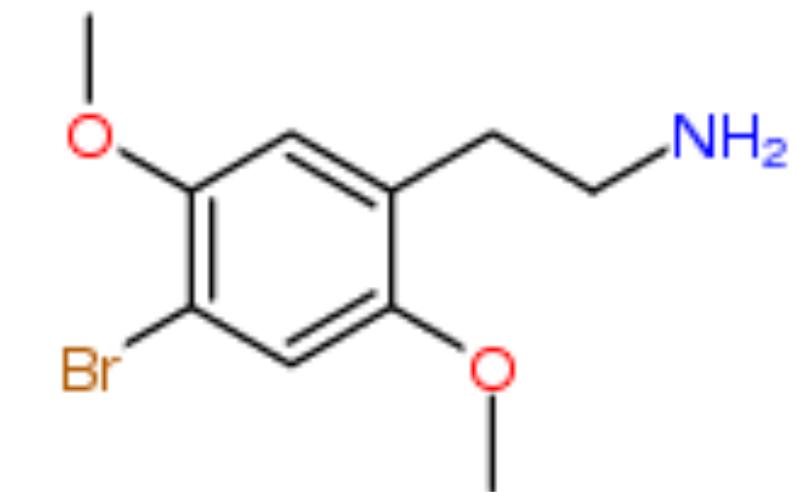
amine

# Drug Nomenclature

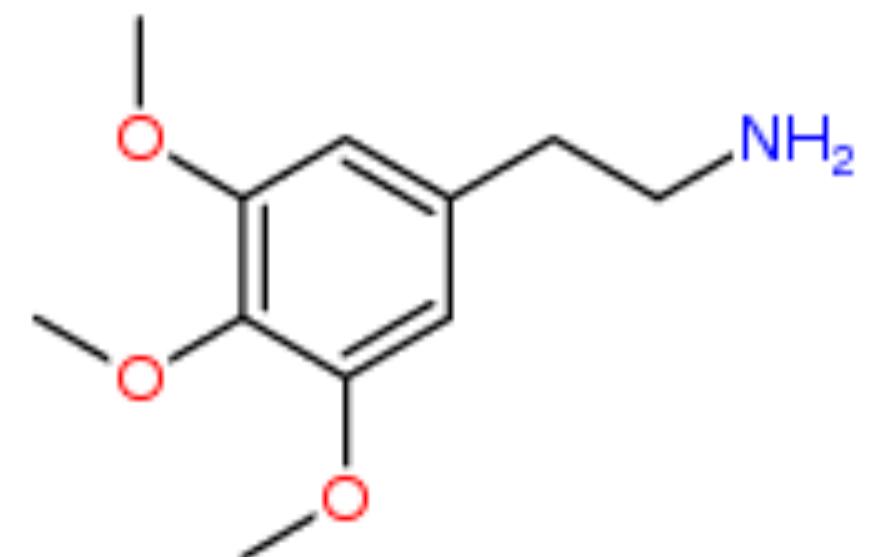
Phenethylamine Examples



MDMA



2C-B



Mescaline

# Microdosing 101

Now commonly referred to as a microdose, which can be described as the consumption of an active psychedelic compound that does not initiate psychedelic effects.



## Fadiman Protocol

James Fadiman includes microdosing in his **2011** book, *The Psychedelic Explorer's Guide*.

LSD 5-10 ug  
LSD Analogues 7-12 ug

1 day on  
2 days off

Follow for 4-6 weeks  
Then 2-4 week washout period

# Microdosing 101

Now commonly referred to as a microdose, which can be described as the consumption of an active psychedelic compound that does not initiate psychedelic effects.



## Stamets Stack

Paul Stamets, mycologist and owner of Fungi Perfecti. In 2017 reveals his formulation:

100-200 mg Psilocybin containing mushroom biomass  
500 mg to grams Lion's Mane Mushroom (*Hericium erinaceus*)  
50 – 200 mg Niacin

4 days on  
3 days off

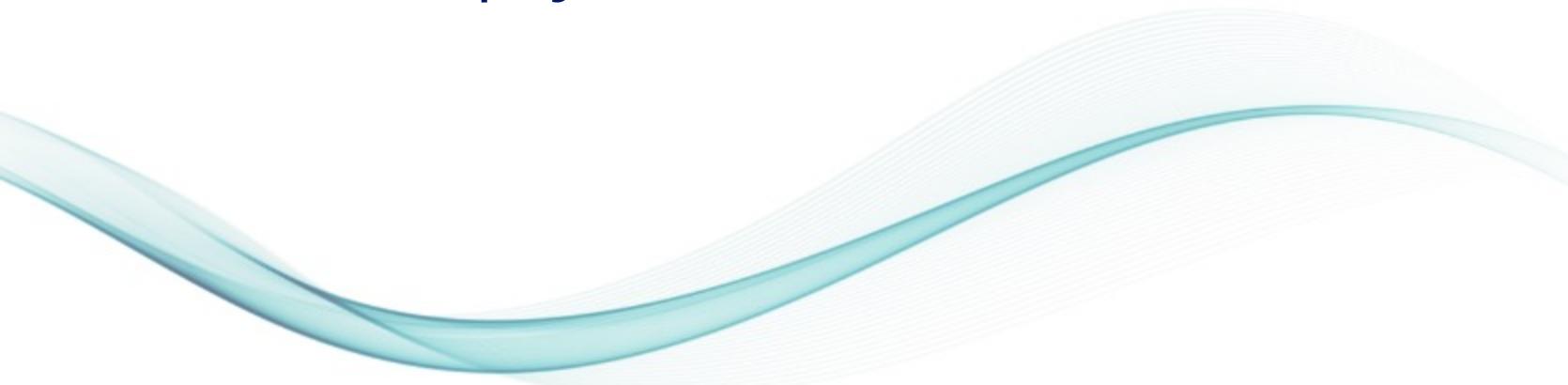
Follow for 4 weeks

Lion's Mane Mushrooms may be supplemented on off days



# Microdosing 101

Now commonly referred to as a microdose, which can be described as the consumption of an active psychedelic compound that does not initiate psychedelic effects.



## Apex Labs Protocol

Studying PTSD in clinical trials with Veterans

2.5 mg Psilocybin (synthetic) or Equivalent in mushroom biomass

5 days on  
2 days off

Currently in active clinical trials with Health Canada



## Optimi Health MELO trial

MOOD AND COGNITIVE EFFECTS OF LOW DOSES OF PSILOCYBIN  
OBSERVED IN HEALTHY SUBJECTS (“MELO”): A BLINDED,  
PLACEBO- CONTROLLED, DOSE-FINDING STUDY

# Microdosing 101

Now commonly referred to as a microdose, which can be described as the consumption of an active psychedelic compound that does not initiate psychedelic effects.

Phase 1 in conjunction with Health Canada

Double Blinded & Randomized Dosing:

0 mg  
1 mg  
2 mg  
5 mg  
8 mg  
10 mg

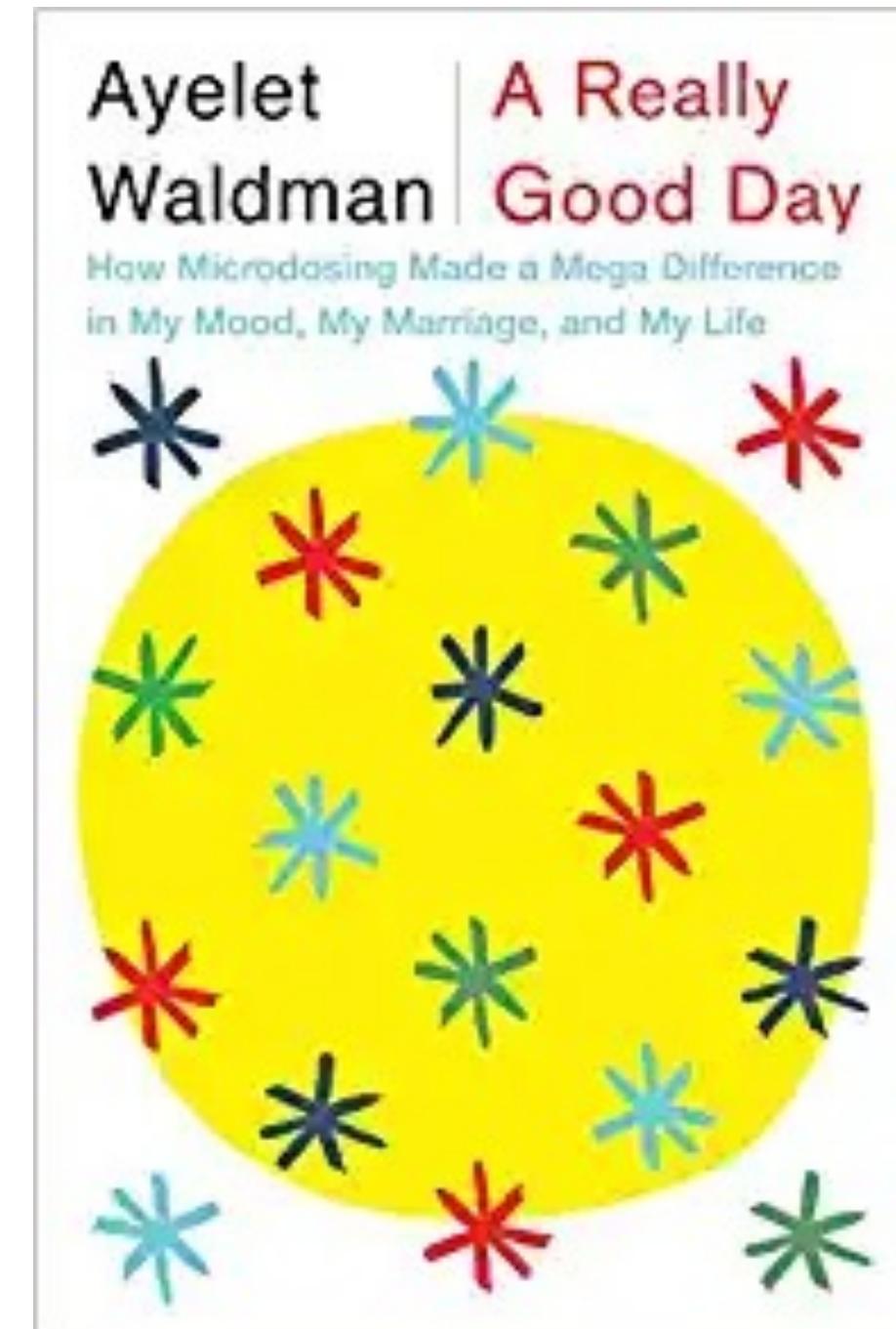
In the form of GMP grown and processed powdered and encapsulated Psilocybin containing mushroom biomass

Product named “Melocin”

# Benefits?

Potential benefits for:

- Mood
- PTSD
- Depression
- Concentration
- Improved Sleep
- Increased Energy
- Empathy
- Gratitude
- Placebo?

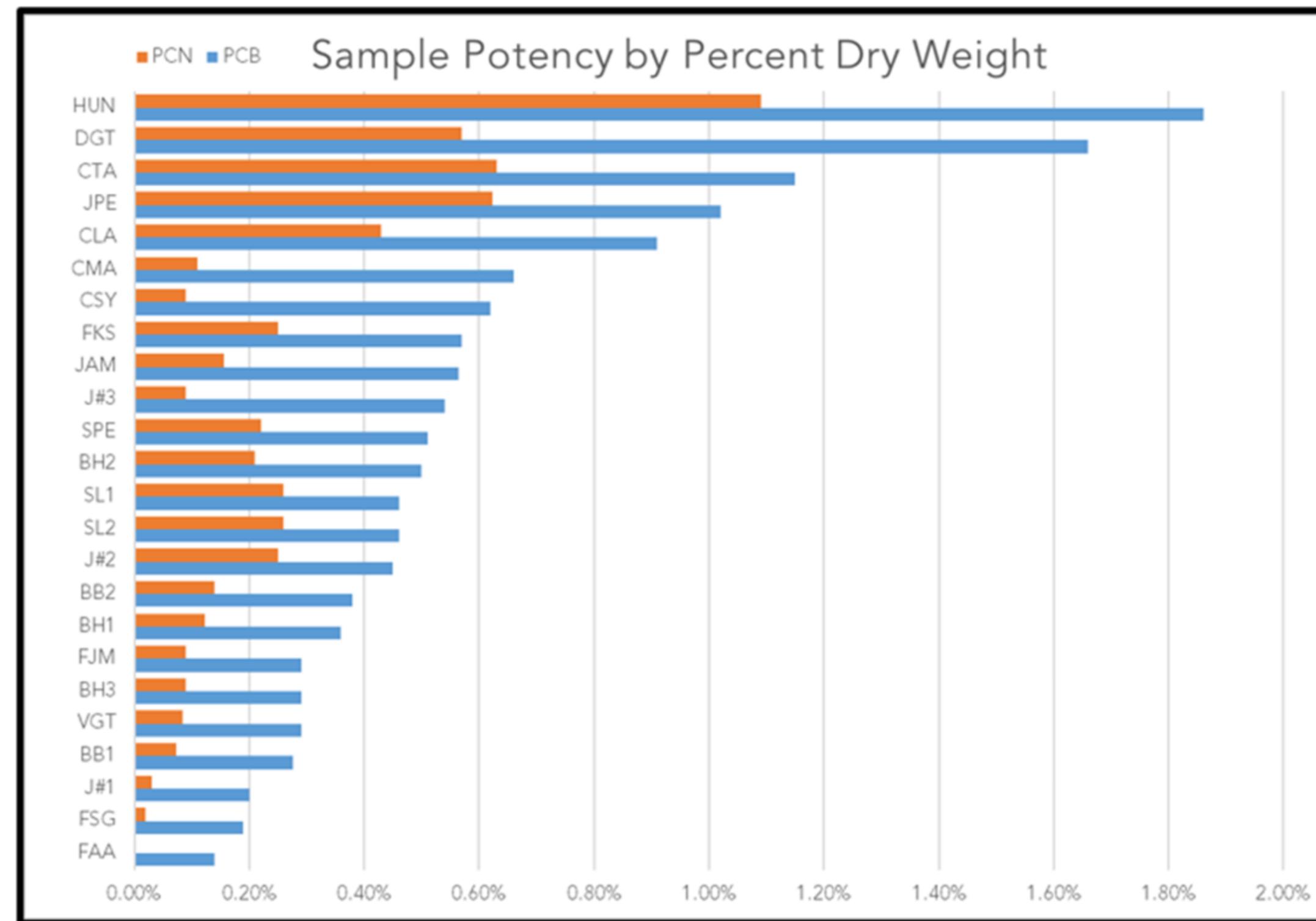


# Negatives?

Potential negatives:

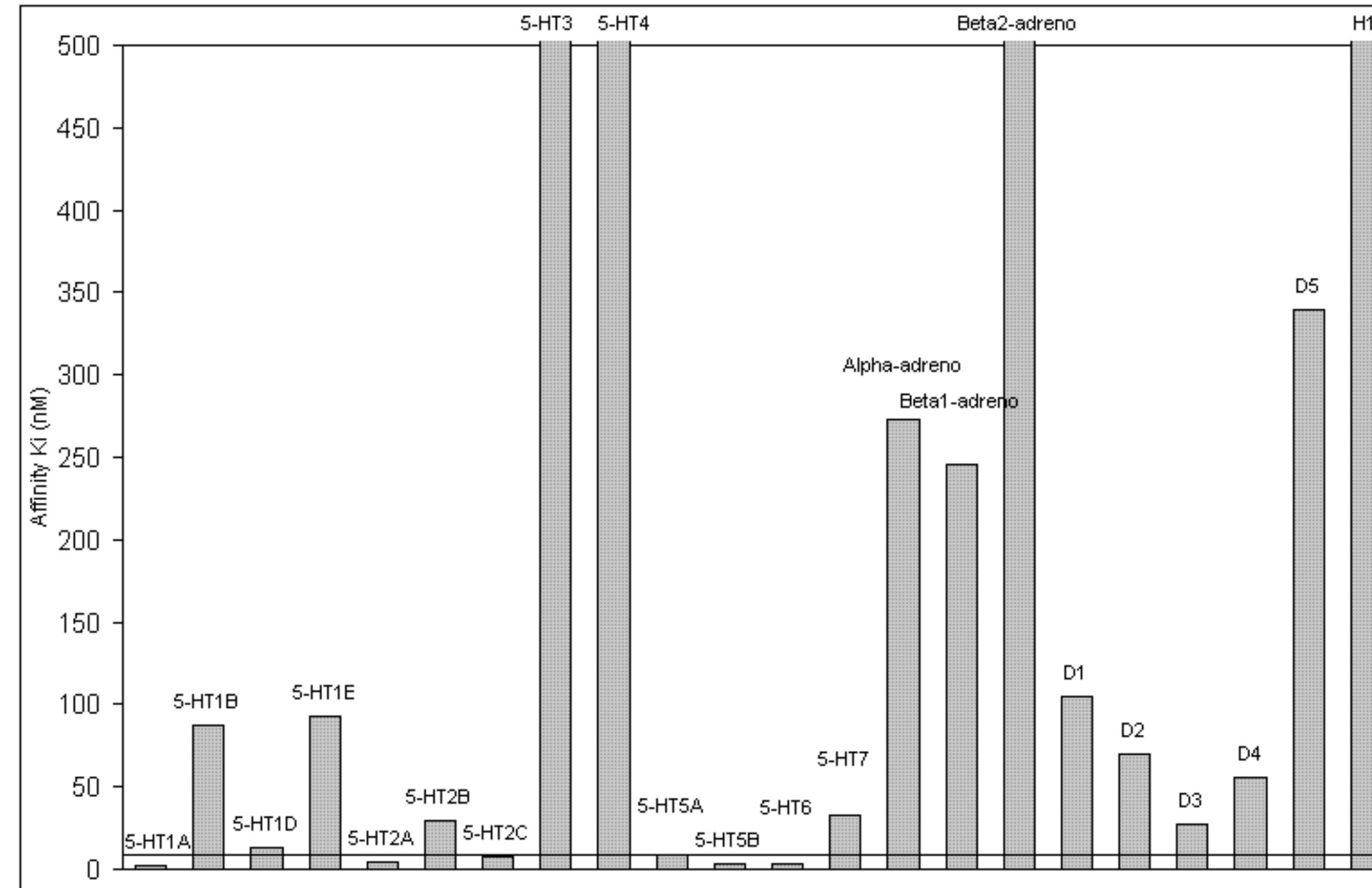
- Lack of standardization
  - Black market supply
  - Mushroom alkaloid content variability
- Fatigue
- Sleep Disruptions
- “Tripping” at work or while driving (inaccurate dose)
- Lack of Receptor Selectivity

# Negatives? Lack of Standardization



# Negatives? Lack of Receptor Selectivity

LSD



# Negatives? Lack of Receptor Selectivity

The American Journal of Cardiology

VALVULAR HEART DISEASE | VOLUME 100, ISSUE 9, P1442-1445, NOVEMBER 01, 2007

Possible Association Between 3,4-Methylenedioxymethamphetamine Abuse and Valvular Heart Disease

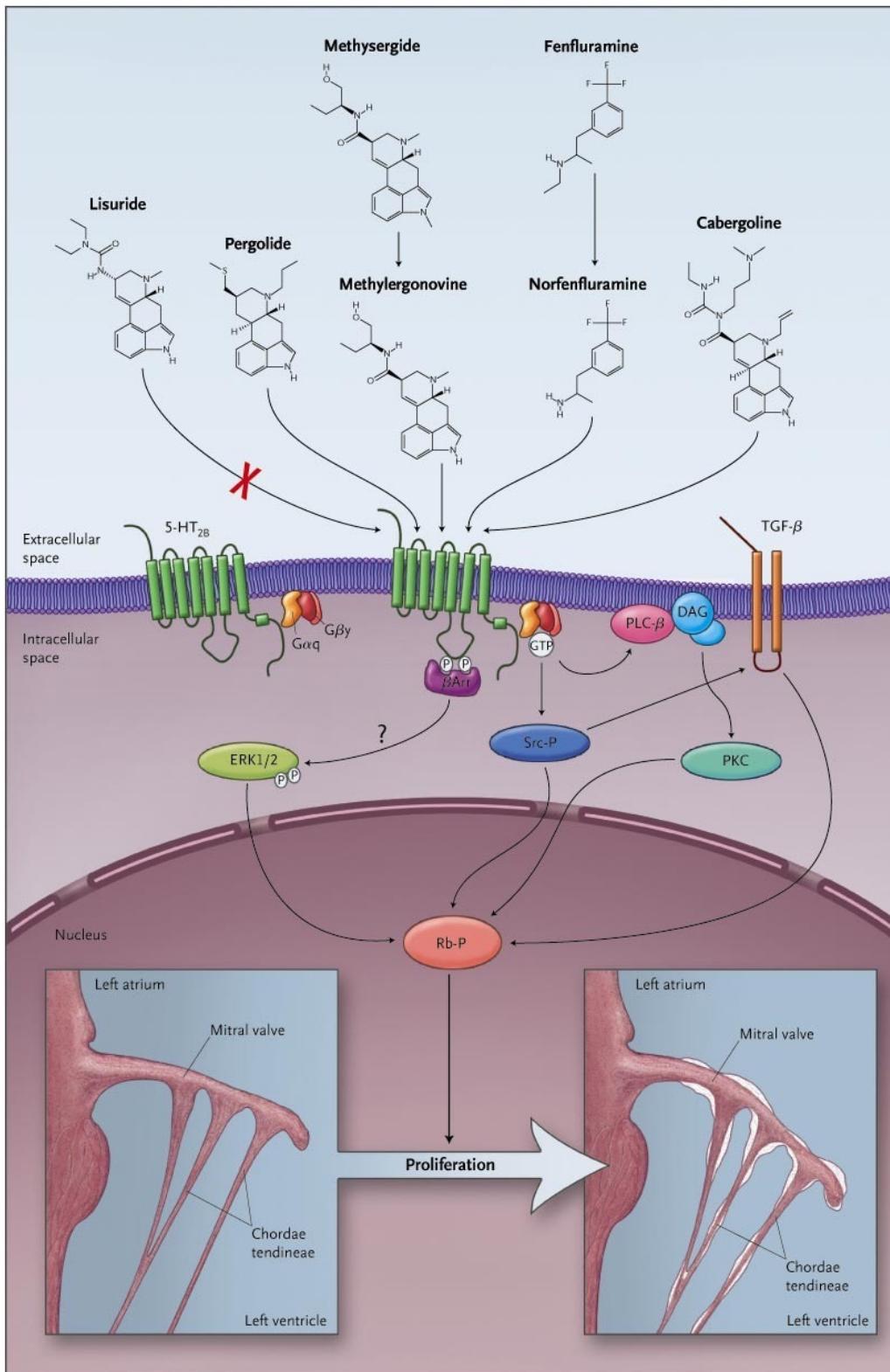
Steven Droogmans, MD <sup>1</sup> • Bernard Cosyns, MD • Hugo D'haenen, MD, PhD • ...  
Jean-Luc Vandenbossche, MD, PhD • Serge Bechet, MD, PhD • Guy Van Camp, MD, PhD • Show all authors •  
Show footnotes

DOI: <https://doi.org/10.1016/j.amjcard.2007.06.045>

In an epidemiologic case-control study of 29 MDMA users who averaged 3.6 tablets per week for 6.1 years, 28% had VHD confirmed by echocardiography versus none in the gender- and age-matched controls. This evidence demonstrates that chronically dosing another “psychedelic” with 5HT2B affinity, even when only taking a few doses per week, has also been associated with VHD.

LSD and psilocybin used for microdosing have even stronger binding affinity for 5HT2B receptor than MDMA and its active metabolite MDA (+LSD Ki = 30 nM, psilocin Ki= 3.6 nM; MDMA Ki = 500 nM, MDA Ki = 100 nM), in addition to their “psychedelic” 5HT2A receptor effects.

# Negatives? Lack of Receptor Selectivity



**N Engl J Med 2007; 356:6-9 Bryan Roth UNC-Chapel Hill**  
**DOI: 10.1056/NEJMp068265**

Psilocin has an EC<sub>50</sub> at 5-HT<sub>2B</sub> – 2.37 nM (Klein et al, 2021) – 58 nM (Sard et al, 2005)

Psilocin blood level with 6 mg dose reaches ~19 nM, 3 mg dose = ~10 nM; stays above ~5 nM for approximately 5 hours for both dosages

This suggests there will be significant activation of 5-HT<sub>2B</sub> receptors after a “microdose”

Pergolide EC<sub>50</sub> at 5-HT<sub>2B</sub> – 3.8 nM (Gornemann et al, 2005) – 53 nM (PDSP, Setola et al, 2003)

Pergolide clinical doses that were associated with valvulopathy  
 Notice the similar dosing and similar EC<sub>50</sub>

Risk increased linearly with pergolide cumulative dose – in other words, the higher the total amount of pergolide a person received (dose x time), the higher their risk of valvulopathy

# Study Results

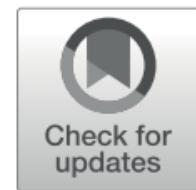
Psychopharmacology (2020) 237:1521–1532  
<https://doi.org/10.1007/s00213-020-05477-0>

ORIGINAL INVESTIGATION

## Perceived outcomes of psychedelic microdosing as self-managed therapies for mental and substance use disorders

Toby Lea<sup>1,2</sup>  · Nicole Amada<sup>3</sup> · Henrik Jungaberle<sup>4</sup> · Henrike Schecke<sup>5</sup> · Norbert Scherbaum<sup>5,6</sup> · Michael Klein<sup>1</sup>

Microdosing was perceived by most respondents (79%) as having a beneficial effect on mental health, and many respondents reported having ceased psychiatric medications since commencing microdosing.



## Addiction Biology

**SSA** SOCIETY FOR THE STUDY OF ADDICTION

ORIGINAL ARTICLE

## Repeated low doses of LSD in healthy adults: A placebo-controlled, dose-response study

Harriet de Wit , Hanna M. Molla, Anya Bershad, Michael Bremmer, Royce Lee

First published: 01 February 2022 | <https://doi.org/10.1111/adb.13143> | Citations: 1

“We removed any expectations that this was a psychedelic drug,” de Wit explained. “Because in the real world, people’s expectations can strongly influence their responses.” The drug did not improve mood or affect participants’ performance on cognitive tests, either during the drug sessions or at the follow-up session.



# Study Results

Journal of Psychopharmacology  
 Volume 36, Issue 1, January 2022, Pages 97-113  
 © The Author(s) 2021, Article Reuse Guidelines  
<https://doi.org.proxy2.library.illinois.edu/10.1177/02698811211050556>



[www.nature.com/scientificreports/](http://www.nature.com/scientificreports/)

## scientific reports

Check for updates

OPEN

### Psilocybin microdosers demonstrate greater observed improvements in mood and mental health at one month relative to non-microdosing controls

Joseph M. Rootman<sup>1</sup>, Maggie Kiraga<sup>2,5</sup>, Pamela Kryskow<sup>3</sup>, Kalin Harvey<sup>2</sup>, Paul Stamets<sup>4</sup>, Eesmyal Santos-Brault<sup>2</sup>, Kim P. C. Kuypers<sup>5</sup> & Zach Walsh<sup>1</sup>

Our findings of improved mood and reduced symptoms of depression, anxiety and stress are nonetheless generally similar in direction and size to the unadjusted small to medium positive effects reported in those investigations

Original Papers



### Psilocybin microdosing does not affect emotion-related symptoms and processing: A preregistered field and lab-based study

Josephine Marschall<sup>1</sup>, George Fejer<sup>1</sup>, Pascal Lempe<sup>1</sup>, Luisa Prochazkova<sup>1</sup>, Martin Kuchar<sup>1,3,4</sup>, Katerina Hajkova<sup>3,4</sup>, and Michiel van Elk<sup>1</sup>

Our confirmatory analyses revealed that psilocybin microdosing did not affect emotion processing or symptoms of anxiety and depression compared with placebo. Our exploratory analyses revealed that psilocybin microdosing did not affect self-reported interoceptive awareness, that symptoms of depression and stress were significantly reduced in the first block compared with baseline, that participants broke blind in the second block and that there was no effect of expectations.





#PeptideWC2022

# THANK YOU!

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