PSYCHEDELIC RENAISSANCE

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LEARNING OBJECTIVES

- Upon completion of this CE activity, pharmacists should be able to:

1. Identify and define what makes a drug psychoanaleptic or psychomimetic
2. Understand how psychedelics have been used throughout history
3. Compare prescription psychotropics to illicit drugs for safety and efficacy
4. Describe the mechanism of action of psychedelics
5. Recognize the common side effects of current psychoactive substances

WHAT IS A PSYCHEDELIC?[1,2] (AK/CF)

- From Greek: *Psyche = Mind Delos = Manifest*
  - Alter perception of reality, mood, and consciousness
  - Can cause hallucinations, changes in thought patterns, and a sense of altered reality
- Novelist Aldous Huxley, who wrote "Brave New World" and "Doors of Perception"
  - "*To fathom Hell or soar angelic, just take a pinch of psychedelic*"
- In 1956, Huxley and Dr. Humphry Osmond (Canadian psychiatrist) coined the term "psychedelic" at a conference

PSYCHEDELIC DRUGS

- Used in almost every culture around the world for thousands of years
  - Cave paintings of psilocybin-containing mushrooms found in Algeria & Spain date back to 4000 to 7000 BCE[3]A)
- Called by many different names
  - Psychotogens, Psychotomimetics, Hallucinogens, Illusionogens
- "*Classic psychedelics are defined as drugs known for their ability to alter perception, cognition, and mood*"[2]CF)
- Primary effect is to produce perceptual changes & hallucinations
  - Can influence several sensory systems, perception of time, & space

PSYCHOACTIVE SUBSTANCE / PSYCHOTROPIC[4-12] (Z3-Z11)

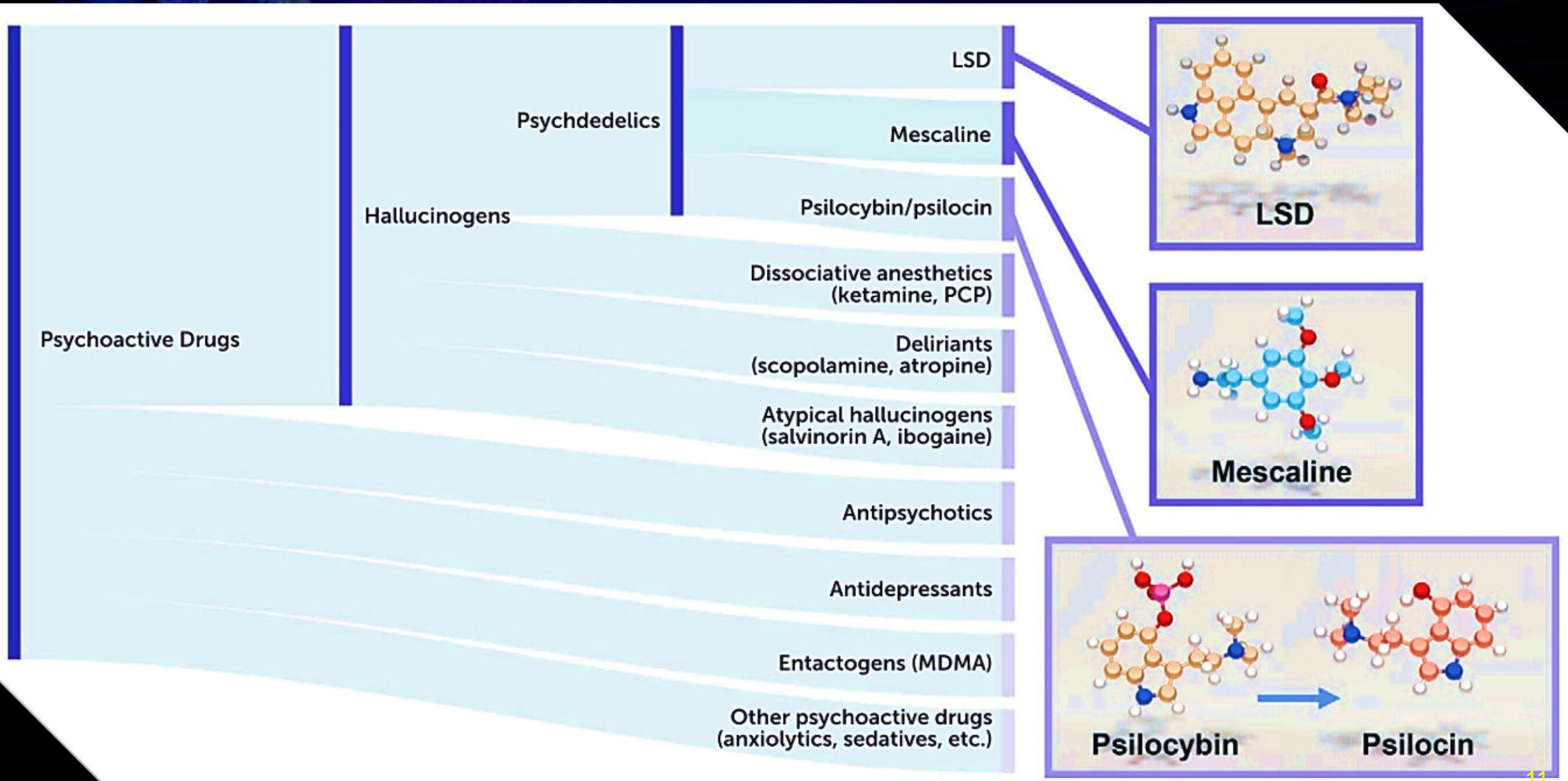
- Substance that affects the central nervous system
  - E.g., antidepressants, antipsychotics, caffeine, chocolate, alcohol

COMMONLY MISUSED PSYCHOACTIVE SUBSTANCES

SUBSTANCE	EFFECTS
Alcohol (liquor, beer, wine)	euphoria, stimulation, relaxation, lower inhibitions, drowsiness
Cannabinoids (marijuana, hashish)	euphoria, relaxations, slowed reaction time, distorted perception
Opioids (heroin, opium, pain meds)	euphoria, drowsiness, sedation
Stimulants (cocaine, methamphetamine)	euphoria, exhilaration, energy
Club Drugs (MDMA/Ecstasy, GHB)	hallucinations, tactile sensitivity, lowered inhibition
Dissociative Drugs (Ketamine, PCP, DXM)	feel separated from body, delirium, impaired motor function
Hallucinogens (LSD, mushrooms, Mescaline)	hallucinations, altered perception

SOURCE: National Institute on Drug Abuse

PSYCHOACTIVE SUBSTANCES[13] (CE)



WHICH PSYCHEDELIC DRUGS WILL WE REVIEW?

1. MDMA (Ecstasy)
2. DMT / Ayahuasca (dimethyltryptamines) / 5-Meo-DMT
3. Psilocybin (psilocin) / Mushrooms

WHICH PSYCHEDELIC DRUGS WON'T WE REVIEW?

1. Ibogaine
2. Ketamine
3. Kratom (mitragynine)
4. LSD (lysergic acid diethylamide)
5. Marijuana / Cannabis
6. Mescaline

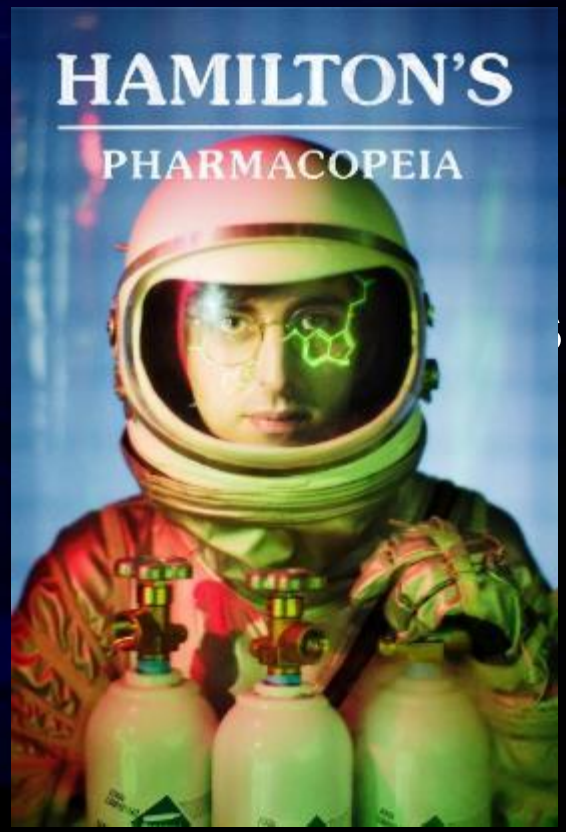
PSYCHOTROPIC TERMINOLOGY[1,14-15]

(DA=AH, CDAK=Erowid)

- **Entheogen** (theo = God)
  - To awaken the divine within or bring on a spiritual experience
  - "Pharmacotheon" = entheogenic drugs[16] (X)
- **Oneirogen**[17] (DO)
  - A drug that allows for dreaming or lucid dreaming
    - E.g., African Dream Root (Silene Undulata), Calea Zacatechichi, Mugwork (Artemisia vulgaris), Damiana (for erotic dreams)
- **Psychoanaleptic**
  - A psychotropic studied and used for therapeutic reasons
  - Psychoanalepsis is a twofer with therapy
- **Psychotomimetic**
  - To mimic the conditions of schizophrenia
    - Synthetic cannabinoids, cathinones, herbs

PSYCHOTROPIC TERMINOLOGY[1,14-15]
(DA/AH,AK,Erowid)

- **Entactogen**
  - To generate touch or increase touch sensations
- **Empathogen**
  - To generate empathy, connections, and feelings
- **Dissociative**
  - Parts of personality become separated from main
    - Out of body experience
- **Ego dissolution**
  - To have the boundaries between the self and the outside world dissolved
    - Become one with everything
- **Psychonaut / ePsychonaut**[18] Y
  - A person who uses or experiments with psychedelics



Hamilton's Pharmacopeia
(Hamilton Morris)

WHERE DO PEOPLE GET INFORMATION ON PSYCHEDELIC DRUGS?[19] (AO)

- *Journal of Psychoactive Drugs* conducted online survey
  - *N* = 1221

2021 NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH) (Past year use in ≥ 12 y.o.)[20] (DB)

- 61.2 million Americans were illicit drug users (21.9% of population)
  - ▲Marijuana - most commonly used drug in 2021
    - 52.5 million (18.7% of population)
  - ▲8.7 million prescription pain reliever drug users (3.1% of population)
  - ▲7.4 million hallucinogen users (2.6% of population)
  - ▲4.9 million sedative / tranquilizer users (1.7% of population)
    - 3.9 million benzodiazepine users (1.4% of population)
  - ▲4.8 million cocaine users (1.7% of population)
  - ▲3.7 million stimulant users (1.3% of population)
  - ▲2.5 million methamphetamine users (0.9% of population)
  - ▲2.2 million inhalant users (0.8% of population)
  - ▲1.1 million heroin users (0.4% of population)

http://www.samhsa.gov

PSYCHEDELICS IN THE 1950s to 1970s[21-26] (Aday/DC22-25Das to Yaden)

- Used by artists, writers, hippies, and psychotherapists
  - Salvadore Dali
  - Ken Kesey (One Flew Over the Cuckoo's Nest)
  - Ann Shulgrin (wife of Alexander "Sasha" Shulgin)
    - Godfather of Ecstasy
- Given to people unknowingly by the CIA (*MK-Ultra*)
- Used by mathemeticians to solve complex math theorems
- Recreational use mostly by Middle/Upper-Middle Class Whites
  - Negative press and misuse tainted the therapeutic potential
- Made illegal by the Comprehensive Drug Abuse Prevention and Control Act of 1970

"DESIGNER" PSYCHOACTIVE SUBSTANCES[18]

Psychedelics

5'-substituted tryptamines
Related to: bufotenin

5-MeO-DMT, 5-MeO-DALT, 5-MeO-MIPT, 5-MeO-MET, 5-MeO-DIPT, 5-MeO-DPT, 5-MeO-AMT, 5-MeO-AET

AMT, AET, MIPT, DIPT, DALT, NMT, DET, DPT

NBOMe series
Related to: 2C-x series

25C-NBOMe, 25I-NBOMe, 25D-NBOMe

2C-x series
Related to: mescaline

2C-B, 2C-D, 2C-I, 2C-E, 2C-T-7, 2C-P, 2C-B-FLY

Ergolines
Related to: LSD, LSA

ALD-52, LA-SS-Az (LSZ), PRO-LAD, ETH-LAD

4'-substituted tryptamines
Related to: psilocin

4-AcO-DMT, 4-HO-DPT, 4-AcO-DET, 4-HO-DALT, 4-HO-MIPT, 4-HO-DIPT, 4-MES-DMT

Psychedelic amphetamines
Related to: 2C-x, amphetamine

DOB, DOM, DOC, DOET, DOI, TMA-2, Bromo-dragonFLY

Cannabinoids

Functionally related to naturally occurring cannabinoids including THC

Naphthoylindoles
JWH-018, JWH-019, JWH-073, JWH-081, JWH-122, JWH-200, AM-1221, AM-2201

WIN-55,212-2

AB-001

Phenylacetylindoles
JWH-250, JWH-251, JWH-203, RCS-8

CP-47,497, CP-47,497, C8 homologue, CP-55,940

JWH-133, JWH-161

CB25, CB52

Benzoylindoles
AM-694, AM-1241, AM-2233, RCS-4

JWH-175

Cyclopropanoyl-indoles
UR-144, 5F-UR-144, A-834,735, A-796,260

Naphthoylpyrroles
JWH-307, JWH-147, JWH-030

HU-210, HU-211, HU-331

O-1812

Stimulants

Cathinones
Related to: methcathinone, cathinone, amphetamine, MDMA

Mephedrone, Pentedrone, Methylone, Flephedrone, Butylone, bk-PMMA, Benzedrone, 4-MEC

Piperazines
Related to: piperazine

BZP, mCPP, MBZP, pFPP, DBZP, MeOPP, MDBZP, TFMPP

5-APB, 6-APB, 6-ADPB

Desoxypipradrol

4-methylaminorex, 4-ethylaminorex

MDAI, MDAT, 2-AI, 5-IAI

Phenylalkyl-pyrrolidines
Related to: Pyrovalerone, Prolintane

MDPV, α-PPP, α-PVP, MDPVP, α-PBP, MOPVP

Dimethocaine

Substituted amphetamines
Related to: amphetamine, methamphetamine

4-FA, 3-FMA, 4-FMA, PMA, 3-FA, PMMA

Methiopropamine

Ethylphenidate

Camfetamine

Dissociatives

Related to: ketamine, PCP

Methoxetamine, 3-MeO-PCP, 4-MeO-PCP, 3-MeO-PCE, 2-MeO-ketamine

Sedatives

Opioids
Related to: morphine, fentanyl, heroin

α-methylfentanyl, 3-methylfentanyl, MPPP, O-desmethyltramadol, 7-acetoxymitragynine, Metonitazene, AH-7921

Phenazepam

SOURCE:
https://www.psychoactif.org

JULY 2016 FLORIDA DESIGNER DRUGS ENFORCEMENT ACT[28] (DD)

- F.S. 893.035
- Bans synthetic drugs by their pharmaceutical action in the brain
  - Not by their chemical molecular structure
  - Makes substances illegal before they appear
- Designer drugs:
  - Synthetic cannabinoids
  - Substituted cathinones
  - Substituted phenethylamines
  - N-Benzyl phenethylamines
  - Substituted tryptamines
  - Substituted phenylcyclohexylamines

LEGAL STATUS OF PSYCHEDELICS

- Medical Marijuana (only) -- (as of 7/13/23)[29] XX)
  - ▲Legal in 16 states, 2 territories (P.R. & US Virgin Islands)
  - ▲Recreational and Medical Marijuana legal in 20 more states, 2 territories (Northern Mariana Islands and Guam), and D.C.
    - ●Fully illegal in 6 of 51 states (as of 7/13/23)
- Delta-8 and Delta-10 THC legal in 29 states + 1 district (D.C.)[30] AL-1
- Mushrooms fully decriminalized in D.C. and Oregon
  - ▲Selectively decriminalized in CA, CO, MI, MA, and WA
  - ▲Spores are legal in all states
- Australia allows physicians to prescribe Psilocybin & MDMA[31] (G)
- Kratom – banned in 6 states, Sarasota Co., and < 21 y.o. in FL[32] (DE)

- *Just because something is illegal doesn't mean you can't get it![33]* *Z14*

https://www.ncsl.org/health/state-medical-cannabis-laws https://abdarasle.com/news/policy/delta-8-the-legal/

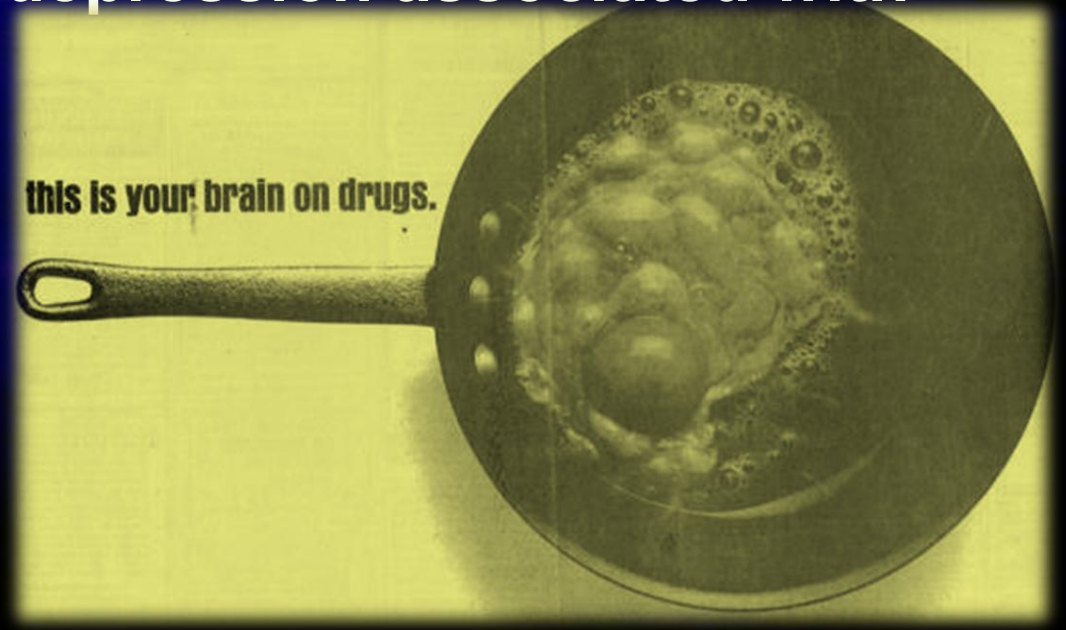
ABUSE POTENTIAL[2,3,34] (A/CF/AQ)

- **Schedule I:** Drugs with high abuse potential, no currently accepted medical use in the USA, and a lack of safety under medical supervision
- Analysis of abuse potential at Johns Hopkins contradicts legal scheduling -- **Recommend CIV status**
  - People and animals do not self-administer
  - Tolerance/Dependence can occur, but not overly significant
    - LSD and Psilocybin have cross-tolerance
  - May see withdrawal with some drugs (e.g., Kratom, MDMA)
  - Low risk of problems related to being under the influence
    - Accidents
    - Suicide
    - Aggression/violence
    - Toxic reactions or overdose (Kratom-related deaths are increasing, though)[35-40]

BG,Z15,AD,AF,AG,AT

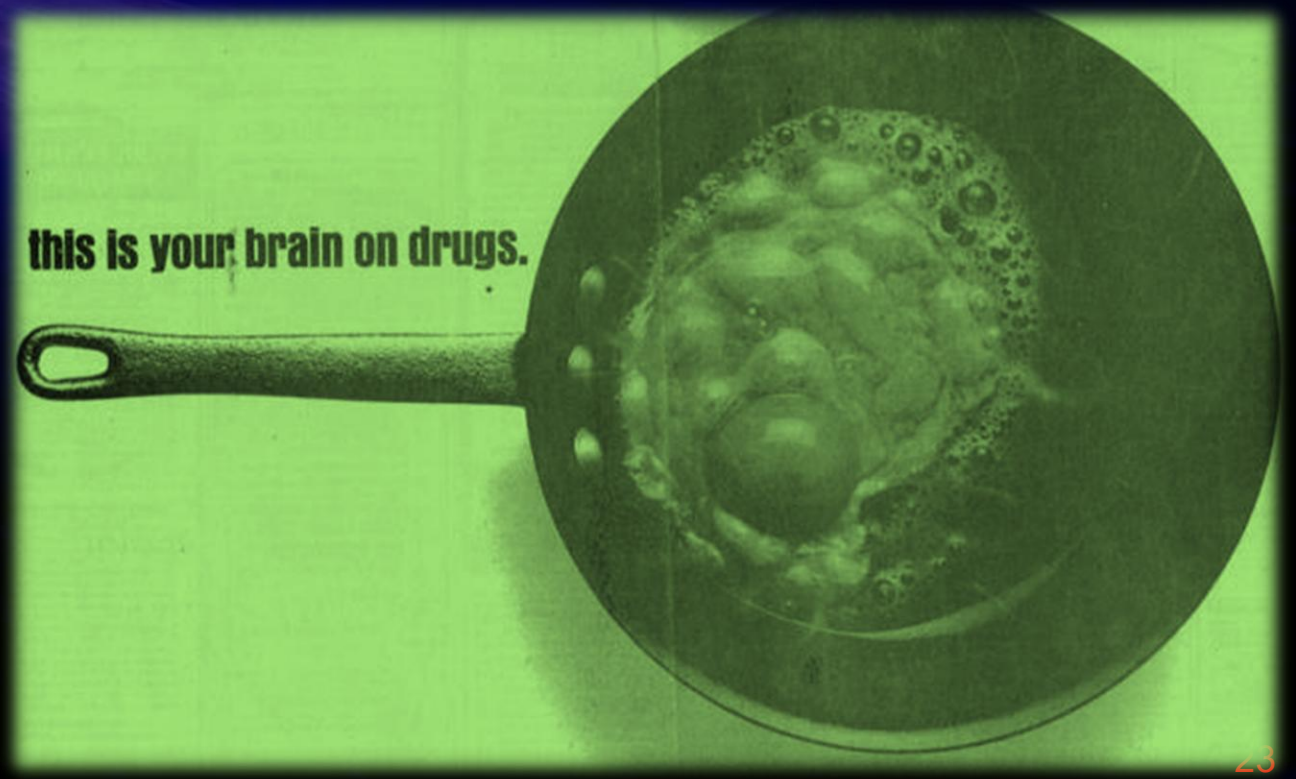
LONG-TERM EFFECTS OF PSYCHEDELIC USE

- Systematic review of 34 studies[41-44] (BL/DF/CK/DG)
  - Psychedelics cause a lasting, long-term positive change in attitudes, mental well-being, mindfulness, and substance misuse
  - Also, sustained decrease in anxiety & depression associated with life-threatening illnesses and cancer
- Ketamine – renally toxic[45] (K)
- LSD not mutagenic, but may be neurotoxic
  - Flashbacks common (5-64%)[46] (AU)
    - 16% have recurring (>10) flashbacks
    - DMT and 5-MeO-DMT too
  - Hallucinogen Persisting Perceptual Disorder (HPPD)



LONG-TERM EFFECTS OF PSYCHEDELIC USE

- MDMA may cause neurodegeneration of serotonergic system[47] (AE)
  - Longer-term studies of chronic recreational users[45] (K)
    - Worse sleep, poor mood, anxiety disturbances, memory deficits, and attention problems[48] (CH)
- MDMA found to have moderate potential for abuse[49] (CI)



WHY DO PEOPLE USE PSYCHEDELICS?

- Spiritual purposes
  - Psychedelics open the gates of awareness to the real or unreal world around us[2] (CF)
- Recreation
- Experimentation[50] Z13
- Self-medication
- Understand life and death
- Communicate with aliens

The title alien from the movie ‘E.T. the Extra-Terrestrial,’ 1982. Photo: Universal/Everett Collection

A BIT OF PHILOSOPHY

How does our brain interpret reality?

What is consciousness?

What is the meaning of life?

What happens after we die?

Do we have a soul?

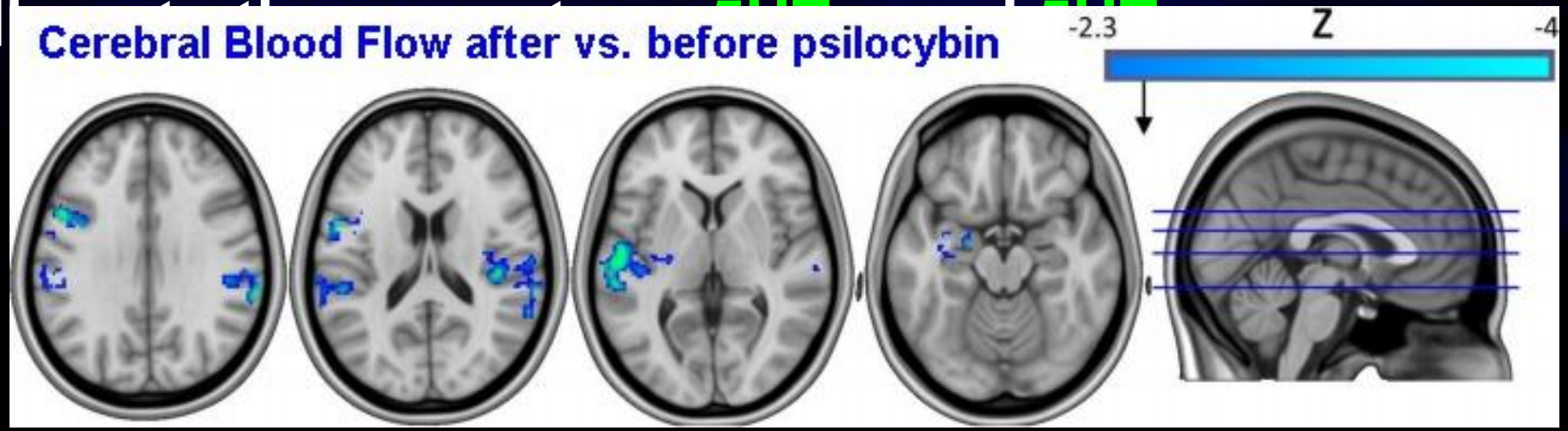
Nothing is impossible!!!

HOW DO PSYCHEDELICS WORK?[51-52] (CO/L)

1. Presumed to agonize $5HT_{2A}$ receptors[53-54] (C/D)
   - ▲Anxiogenic if too strongly agonized
   - ▲Next day headaches are common side effect
   - ▲Cortical receptors that regulate cognitive flexibility & creative thinking
   - ▲Ketanserin (antihypertensive drug)
     - Blocks 5HT2A / psychedelic effects
   - ▲$5HT2_A$ agonism[55] (Q)
     - Associated with disintegration of normally highly organized activity within resting-state networks (RSN)[56] AJ
     - "A simultaneous widening of dynamic repertoires of connectivity states"
     - Increased coupling of RSNs that are usually anti-correlated

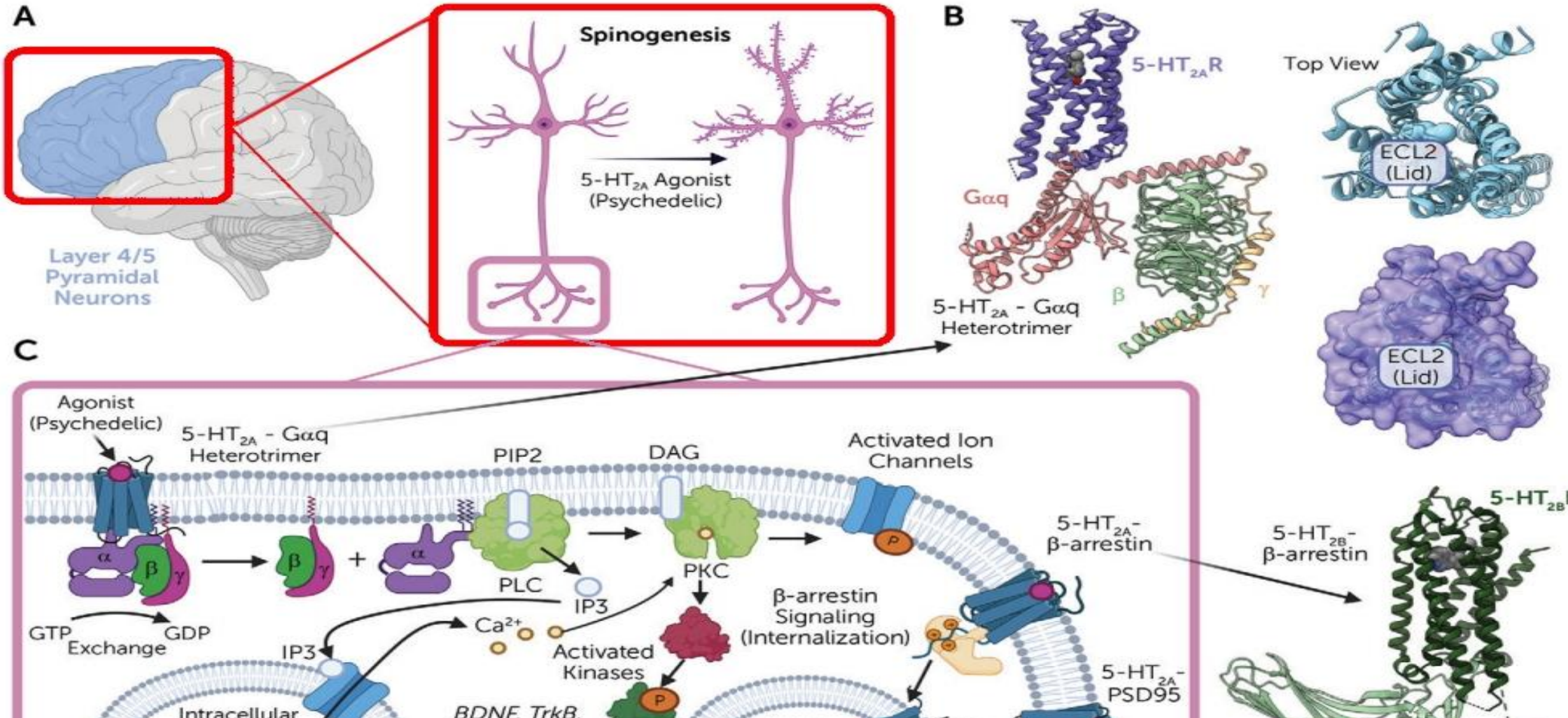
HOW DO PSYCHEDELICS WORK?

2. May also be due to $5HT_{1A}$ (an inhibitory auto-receptor)[51-52,57](CN/CO/L)
   - Agonists are anti-aggressive & anti-impulsive
     - Eltoprazine (↓ aggression – a "serenic" agent)
   - Promotes neurogenesis of hippocampus = ↑ memory encoding
     - Limbic area & hippocampus -- ↑ brain flexibility
   - Produces "cognitive bias" in the amygdala by protecting against stressful images and negative thinking
   - Bind

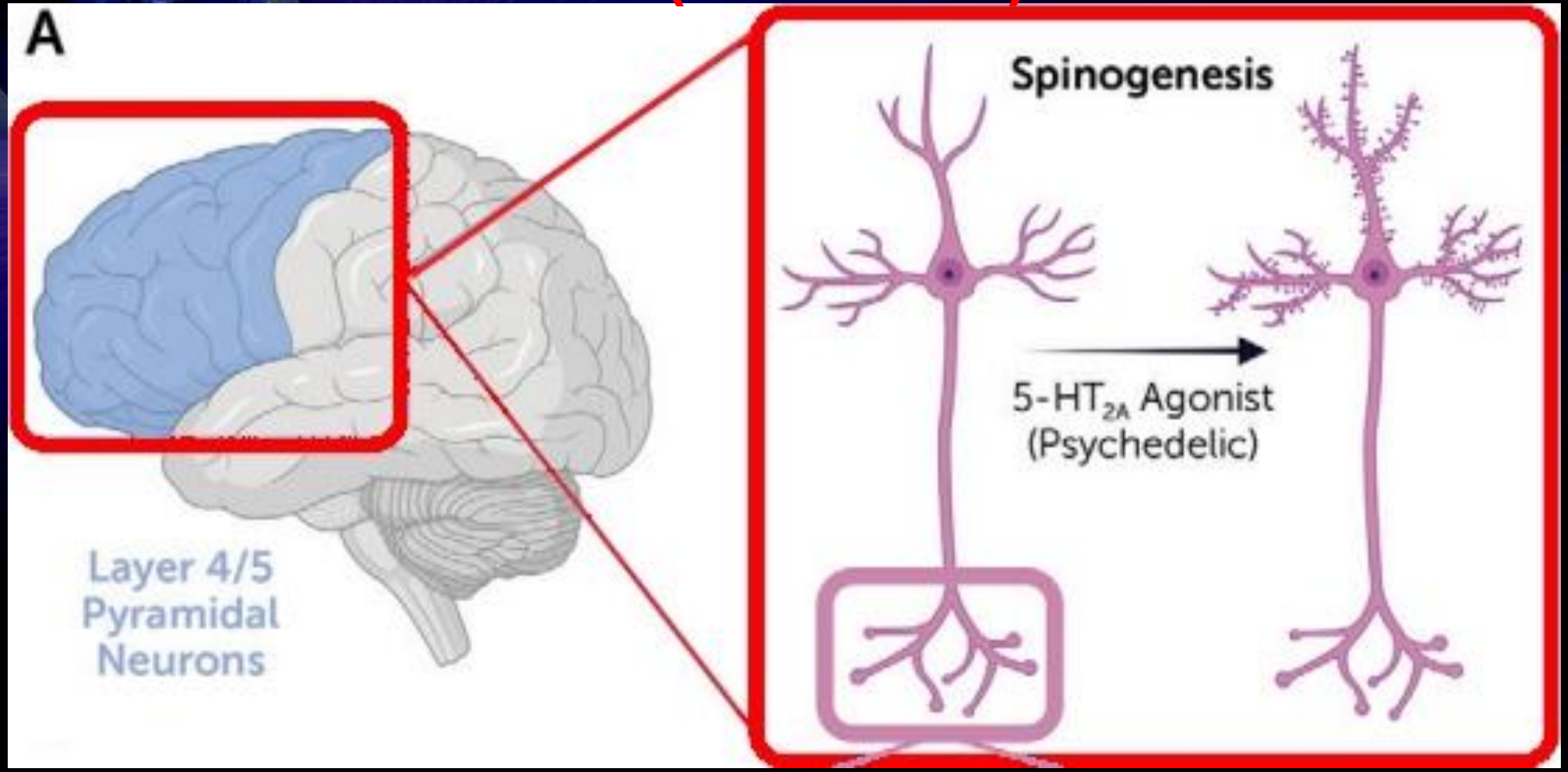


58 (CG)

Overall schematic showing the protein structure of and the location, downstream signaling, and scaffolding protein for 5-HT$_{2A}$ receptor

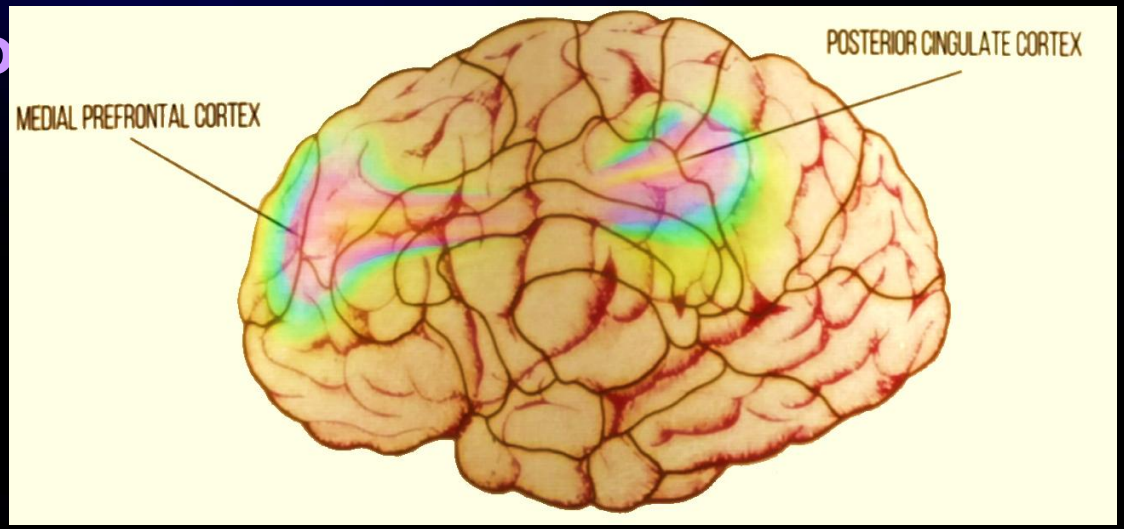


[58,76] (CG/Shao)


A
Layer 4/5
Pyramidal
Neurons
Spinogenesis
5-HT2A Agonist
(Psychedelic)

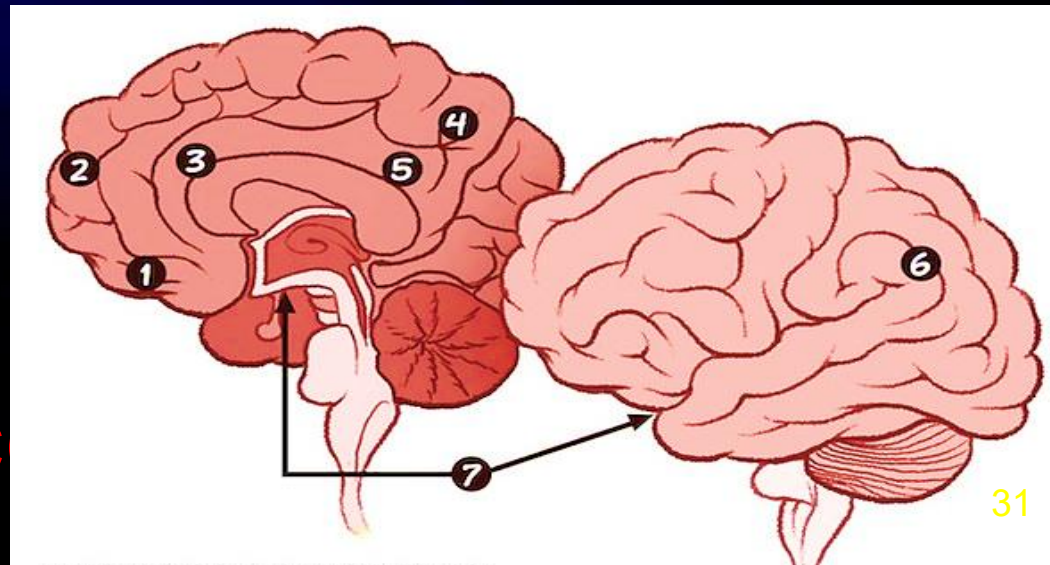
HOW DO PSYCHEDELICS WORK?

3. Decrease connectivity in the DMN (Default Mode Network)[51-52,59]
   (CO/CP /L)
   - ▲Network of brain regions that are more active when a person is not focused on the outside world
   - ▲Functions: Daydreaming, introspective, self-reflection, or "default" mental processes
   - ▲Perceptual stimuli is filtered to construct a reality
   - ▲Opposite of the task-positive netwo



HOW DO PSYCHEDELICS WORK?

- DMN is critical for self-reflection, self-awareness, and rumination
  - Overactive in PTSD
- *Decrease cerebral blood flow* to "key connector hub regions"[59](CP)
  - The thalamus, anterior (ACC) and posterior cingulate cortex (PCC), and the medial prefrontal cortex (mPFC)
  - Causes a significant ↓ in the coupling between the mPFC and PCC
  - The magnitude of this decrease predicts the intensity of the subjective psychedelic effects
- Psychedelics ↓ activity to ↓ filtered information resulting in a state of unconstrained cognition[59-61]Z1/Z2/picC



CRITICAL PERIODS OF LEARNING

- During brain development[65] (F)
  - During specific periods of brain development, we have a heightened sensitivity to relevant stimuli
    - Stage of neurogenesis for motor learning, languages, vision/auditiory, music
  - Psychedelics may drive the brain to reinterpret the world, updating past beliefs and desires
  - Also "reopen" the brain to new social learning, like in children
    - May help with recovery from stroke, TBI, paralysis[66-67] (AA/H)
      - Psychedelic drugs in mice reopened critical period for 2-4 weeks post-dose
- New class of drugs: Neuroplastogens[63] (U)
  - Causes rapidly-induced and enduring neuroplasticity
- *Psychoplastogens*[55] (Q) / *Meta-plastogens*[68] (I)
  - Result in meta-plasticity, not hyper-plasticity

RECREATIONAL VS. STUDY EXPECTATIONS

- A review of 20 studies by Romeo *et al*. supports and concluded that the main predictive factor of a response to a psychedelic is the intensity of the acute psychedelic experience[55,62] (Q1)(Q)
  - ▲Also shown with antidepressant effects of Ketamine[69] (BOTT)

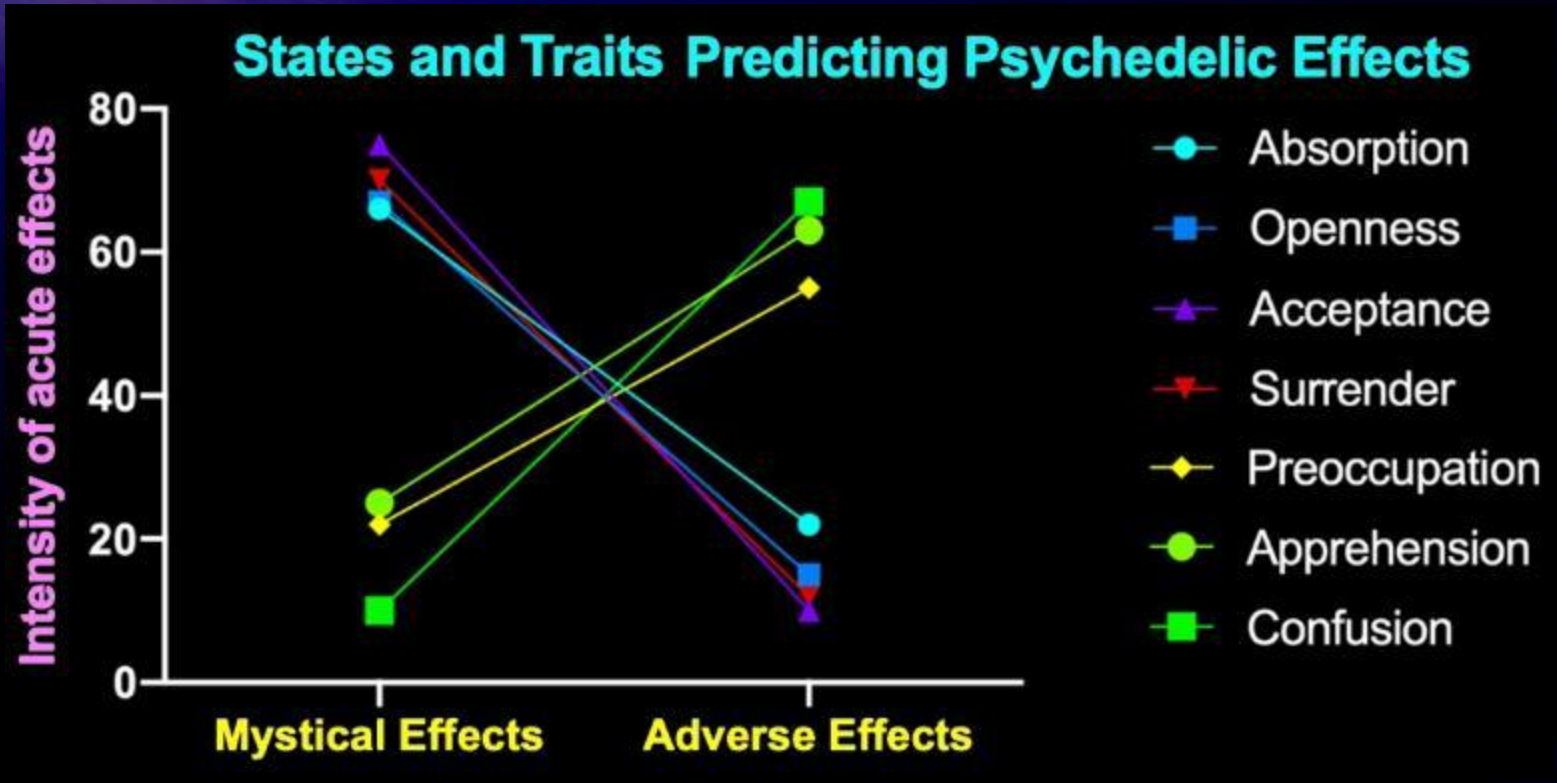
- Typical study procedures[21,70-73] Colloca1,2,3/Muth / Aday

1. Preparatory sessions
   - ▲Outcome expectancy
2. Drug exposure
   - ▲Dosage is a factor
   - ▲Metaplasticity/psychedelic experience
3. Integrative sessions
   - ▲Analytical reinterpretation of expected efects

INTENSIONS AND OUTCOMES

- Good trip vs. Bad trip?[74] Haijen
  - ▲Having clear intention and positive mindset ↑ odds of a "good trip"
    - ●Better mystical-type experiences and visual effects
  - ▲Recreational intention more likely to result in a "bad trip"
  - ▲Oregon "clients" can be refused psilocybin therapy by clinician[75] #

- Analysis of 14 studies[21]
- Aday



IMPORTANT RESEARCH QUESTIONS[58,64] (CG/BJ)

- Are the subjective experiences intrinsic to, or separable from, their therapeutic effects?
- Is it the biological effects or experience itself that creates a permanent change?
- New experiments with non-hallucinogenic analogs disagree with that[63] (U)

CURRENT STATE OF RESEARCH[77-78] (CS/CU)

- Almost all clinical trials are Phase 1 and 2 (a & b)
- Only a few Phase 3 human trials for MDMA
- Research is clustered around major psychedelic research institutes or pharmaceutical companies
  - MAPS (Multidisciplinary Association for Psychedelic Studies)
  - Johns Hopkins Center for Psychedelic and Consciousness Research
  - UC Berkeley Center for the Science of Psychedelics
  - Usona Institute
  - Imperial College London - Centre for Psychedelic Research (UK)
  - Mind Medicine Australia (Australia)
  - Canadian Centre for Psychedelic Science (Canada)
  - Compass Pathways (compasspathways.com)

MDMA ONGOING TRIALS[78-79] (CT/CU)

- Amphetamine Use Disorder
- Anxiety disorders
- Borderline Personality Disorder
- Eating disorders
- Co-occurring PTSD and OUD after childbirth
- Social anxiety in adults with autism
- Sustance Use Disorders (SUD)

DMT AND 5-MeO-DMT ONGOING TRIALS[78-79] (CT/CU)

- No current Phase 3 trials
  - Bipolar II Disorder
  - Chronic Lower Back Pain
  - Major Depressive Disorder
  - Postpartum Depression
  - Stroke
  - Treatment Resistant Depression (TRD)
  - With or without SSRIs in participants with MDD

ONGOING TRIALS WITH PSILOCYBIN[77-79] (CT/CU/CS)

- Alzheimer's Disease
- Burnout by professionals/caregivers
- Chronic Suicidal Ideation
- Cocaine Use
- COVID 19
- Depression in Bipolar II Disorder
- Eating disorders
- Depression with alcohol use
- End of life & palliative care
- Fragile X Syndrome behaviors
- Major Depressive Disorder (MDD)
- Methamphetamine Use Disorder
- Migraine Headache
- Moral Injury
- Obsessive-Compulsive Disorder (OCD)
- Palliative Care
- Parkinson's Disease
- Phantom Limb Pain
- Post-treatment Lyme Disease
- PTSD with alcohol misuse
- Smoking Cessation
- Treatment-Resistant Depression (TRD)
- Use with SSRI/SNRIs for TRD

ONGOING TRIALS WITH KETAMINE[78-79] (CT/CU)

- Adolescent depression
- Alcohol Use Disorder / relapse
- Analgesia for spinal stenosis
- Cancer pain (intranasal)
- Chronic daily headaches
- Chronic pain conditions
- Cluster headaches
- Cocaine Use Disorder
- Depression in Parkinson's
- Fatigue
- Genital pain (topical)
- MS fatigue
- OCD
- Opioid Use Disorder with depression
- Peripheral Neuropathy
- Post-comatose Disorders
- Post-operative pain
- PTSD
- Rett Syndrome
- Sepsis
- Sickle cell pain
- Suicidal ideation
- Tinnitus
- Tobacco Use Disorder
- Trauma
- TRD
- Treatment-refractory status epilepticus
- Treatment-resistant Bipolar/ Bipolar Depression

ONGOING TRIALS WITH OTHER PSYCHEDELICS[78-79] (CT/CU)

- Ibogaine
  - Veterans with repeated blast exposures and head injuries
  - Alcohol Use Disorder
  - PTSD
  - Alcoholism
  - Opioid Withdrawal
  - Methadone Detoxification
  - Norwegian Addiction, Pain and Trauma Study
    - Mescaline too
- Kratom
  - Drug interaction studies
  - Chronic fatigue
  - Pain
  - Substance Use Disorders
- LSD
  - Major Depressive Disorder
  - Anxiety disorders
  - Cluster Headache
  - Effects on Neuroplasticity
  - Alcohol Use Disorder

LIMITATIONS ON CONDUCTING STUDIES[13,80-82] (B80/AI81/CE13/DH82/DP83)

- Legal status (Schedule I)
  - ▲Permission to obtain & use drug
- Small sample sizes / Not generalizable
- Lack of control groups or Limited blinding
- Expectations given from concurrent therapy[71] (Muth)
- Exact drug of study
  - ▲E.g., ayahuasca & medical marijuana are multiple drugs
- Takeaways from FDA published guidelines[83] (June 2023)
  - ▲2 monitors must always be present with subject
  - ▲Must re-evaluate patient after 12 weeks
  - ▲Drugs that are $5HT_{2B}$ agonists have to report on heart valvulopathy
    - ●E.g., Ergotamines (LSD or for migraine) / fenfluramine / MDMA

PSYCHEDELIC GOLD RUSH

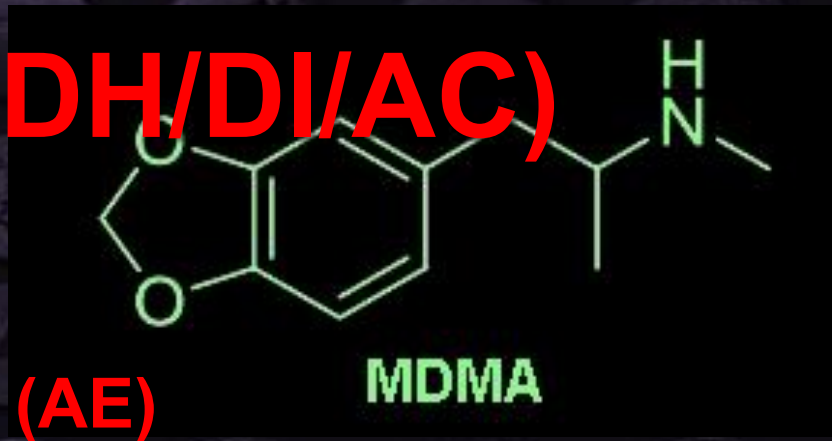
- Next big "get rich" scheme for some
- Investors are pouring big $$$ into promotion, research, and sales (not always legitimate)[84] (AM-7)
  - Hemp extracts, CBD, Kratom, Delta-8 THC, mushroom grow kits, microdosing, etc. [85-94] (AL,AM-2 to 5, J, BN, M, CB, CC)
- *Unregulated Ketamine clinics*[95 (AN)], *Ayahuasca retreats*[96 (AM8)]
- Nascent analogue drug development and patents by chemists and pharmaceutical companies[97-98 (AM6/delix)]

MDMA

Ecstasy / Molly /

Adam / Beans / Biscuit / Clarity / Disco Biscuit / E / Ebombs / Empathy / Eve / Go / Hug Drug / Lover's Speed / Peace / STP / X / XTC

MDMA (ECSTASY)[82,99-100] (DH/DI/AC)



- 3,4-methylenedioxy-methamphetamine
  - Similar to methamphetamine and mescaline[47] (AE)
- Synthesized in 1912 – patented in Germany by Merck in 1914
  - Looking for a blood clotting agent
- Reverses transport direction of SERT = ↑ efflux (output) of 5HT[69] (O)
  - Releases 5HT, DA, and NE
- In the 1950s - briefly researched by U.S. Government as part of the CIA's and the Army's chemical warfare investigations
- Alexander Shulgin "*Godfather of Ecstasy*"[54] (D)
  - Authored the books PiHKAL and TiHKAL
    - *Phenethylamines / Tryptamines I Have Known And Loved*[100] (AC)

MDMA (ECSTASY / MOLLY)[101-102] (DJ/DK)

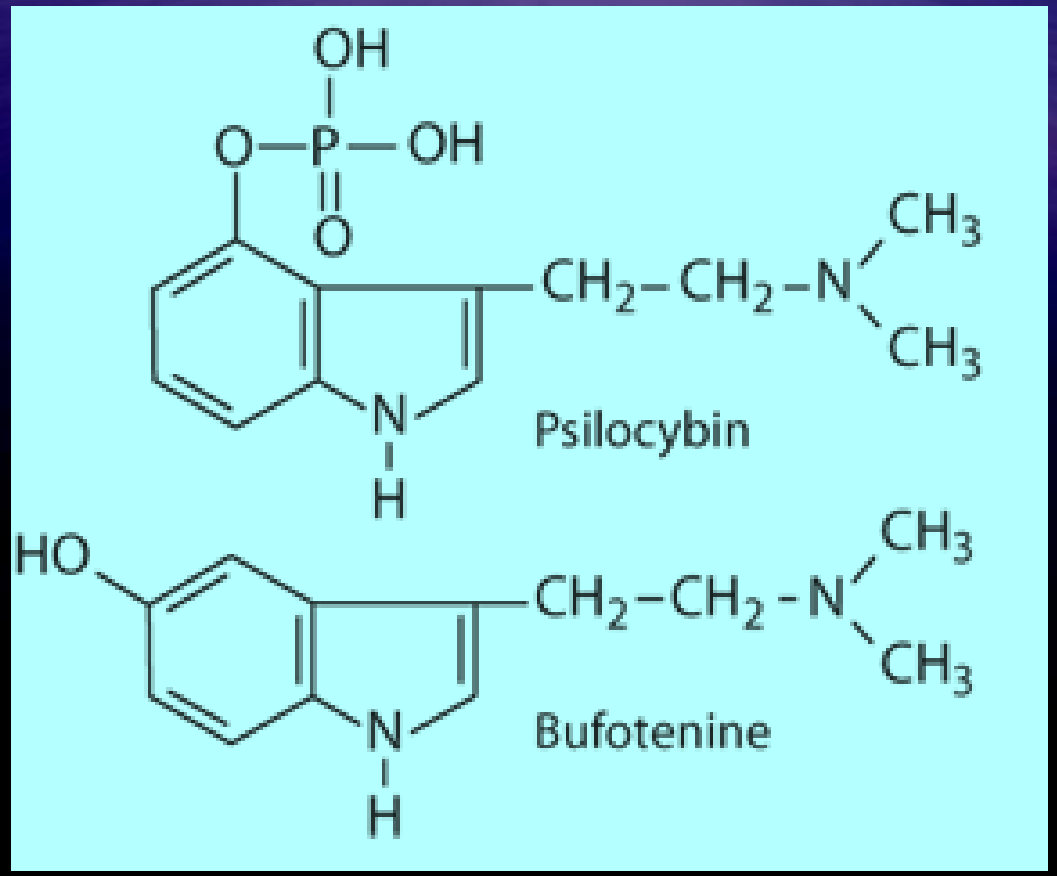
- Made from sassafras oil (80% safrole)
  - Steam distilled from dried root bark of Cambodia's *Cinnamomum parthenoxylon* tree (now endangered)
  - FDA banned sassafras and safrole for human consumption in 1960[103] FDA
    - Known carcinogen, once used in making root beer
  - Recent studies: 55-60% of Ecstasy contained MDMA[101-102]
    - Often is diButylone, methylone (*β-ketone MDMA*), ethylone, mephedrone, Para-methoxyamphetamine/methamphetamine (PMA/PMMA) or methamphetamine[104] (Y1)
- Reverses transport direction of SERT = ↑ efflux (output) of 5HT[105] (O)
  - Releases 5HT, DA, and NE
  - Also a weak 5HT1 and 5HT2 receptor agonist, targeting $5HT_{2A}$, $5HT_{2B}$,

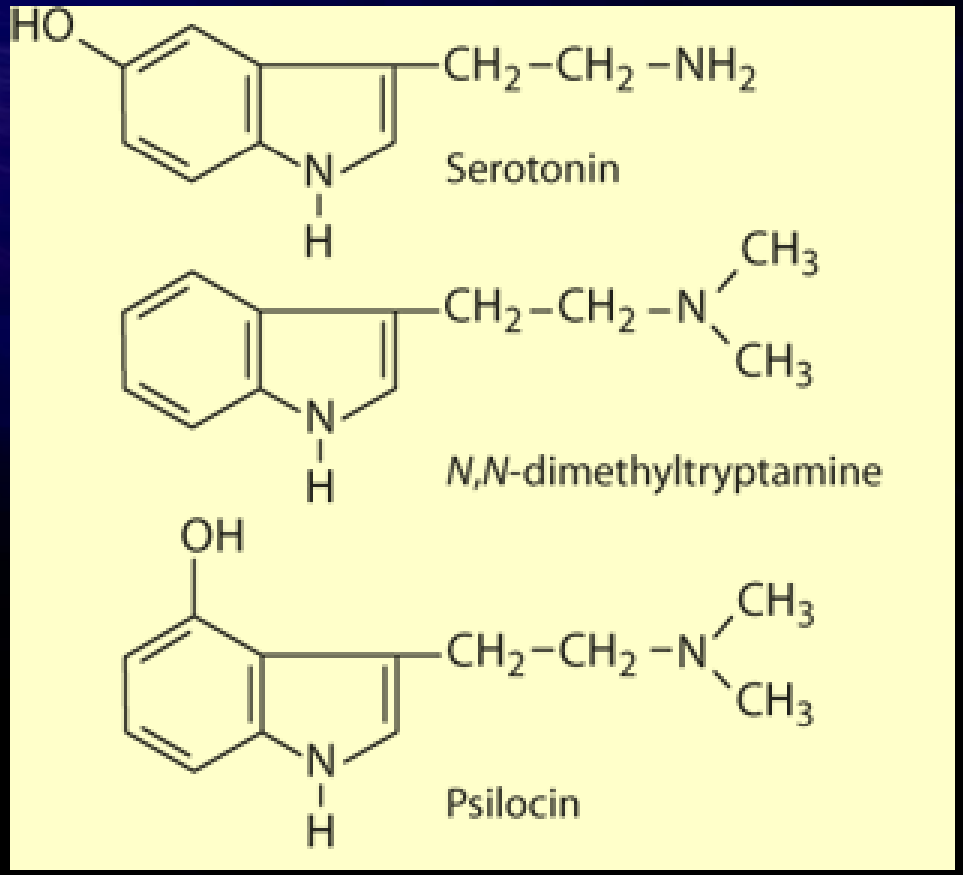
MDMA (ECSTASY / MOLLY)

- Increases the release of oxytocin and prolactin[45,99] (K/DI)
- Decreases brain activity and ↓ blood flow to lower brain regions
  - Left amygdala & hippocampus[54] (D)
- Drug of choice at raves, clubs, festivals, parties
  - Entactogen / empathogen
  - Causes hyperthermia, bruxism, stimulant effects, enhanced perception, dehydration, anxiety, insomnia, loss of appetite, and fever
    - Serious side effects can include uncontrollable seizures, high blood pressure, elevated body temperature and depression
  - Usual dose is 100-140 mg of MDMA
  - Onset: 30-45 minutes / duration of 6 hours

TRYPTAMINES[100] (AC)

N,N-dimethyltriptamine (DMT) / Ayahuasca / 5-MEO-DMT / Diethyltryptamine / Dipropyltryptamine / Diisopropyltryptamine





TRYPTAMINES

- Naturally occurring in living animals & plants
  - ▲e.g., *Psychotria viridis*
  - ▲Virola trees inner bark contain N,N-DMT resin
  - ▲S. America ("Yopo") from seeds (*Anandenanthera peregrina*)[107] (Z)
- Most are not orally bioavailable due to rapid metabolism by MAO-A and MAO-B
- Substituted tryptamines from chemical structure[100] (AC)
  - ▲e.g. LSD, serotonin, psilocin, psilocybin, melatonin, sumatriptan, tryptophan, DMT (N,N-dimethyltryptamine), many others
  - ▲Bufotenine = N,N-dimethylserotonin (metabolite of 5-MeO-DMT)
    - ●Does not cross the BBB, causes HTN
  - ▲Oral 5-MeO-DiPT (5-methoxy-diisopropyltryptamine) "foxy methoxy"[49]

N,N-DIMETHYLTRYPTAMINE (DMT)

- Called the "God Agent" because it naturally occurs within us
- Also called the "spirit molecule"[16,108] (X/X1)
  - Rick Strassman wrote a book ("The DMT Gland") after federally funded study at the Univ. of NM Hospital's Clinical Research Center
    - From 1990-1995, 60 healthy volunteers received > 400 IV doses of DMT
  - Believed to be released from pineal gland at when dying
    - Disproved by thorough analysis and animal studies[105] (O)
- Immunomodulatory activity and tissue regeneration effects
- Decreases pro-inflammatory cytokines
- Increases BDNF
- Reduces amygdala and insula reactivity
- Modulates brain regions associated with interoception, emotional processing, and volition

N,N-DIMETHYLTRYPTAMINE (DMT)[55,66,107] (AA66/Q55/Z107)

- Substrate for the Serotonin Reuptake Transporter (SERT) and Vesicular Monoamine Transporter (VMAT)
  - ▲Binds to 5HT 1A, 2A, 1B, 1D, 2B, 2C (agonist – gets desensitized), 5A, 6, & 7A
- Act as a non-selective 5HT agonist and 5HT/DA/NE releasing agent (SNDRA)
- The only endogenous agonist ligand of sigma-receptors[109] (DL)
  - ▲May be responsible for neuroplasticity
- DMT found in bark of the Yakee plant (virola calophylla)
- ↑ DBP & HR (sympathomimetic)
- Smoked, injected, or snorted (not DMT base – nasally inactive)
  - ▲Has a very short half-life
  - ▲Nasally and GI irritating (lungs, throat, mouth)

N,N-DIMETHYLTRYPTAMINE (DMT)

- "DMT Space" (minimally effective CNS concentration)[105] (O)
  - ~ 60ng/ml (318nM of base)
    - 25mg bolus infusion in 75kg person with 4.2mg/min IV
- Inhaled – 40-100mg DMT[66] (AA)
- IV – 0.05, 0.1, 0.2, and 0.4mg/kg studied
  - 0.2mg/kg is minimally effective dose
- Low dose DMT (1mg/kg) is anxiolytic / high dose (10mg/kg) is anxiogenic
  - Low dose doesn't cause 5HT2 receptor down-regulation
    - Good for depression & anxiety
- Effects peak in 1 min. / lasts for 10 min.

AYAHUASCA "TEA"[45,105,110-111] (K45/O103/P/DQ)

- Crushed vine + leaves from the Amazon Jungle boiled in to a liquid
  - "Vine of the soul / dead" entheogen used by *Amazon natives*
  - DMT also found in teas of the Cashinahua and Aguaruna Indians
- 2 plants interacting for oral administration
  - DMT from "Chacruna" (*psychotria viridis*)
  - *Banisteriopsis caapi* vine
    - Harmine, Harmaline, & THH (tetrahydroharmaline)
- Lasts > 4 hrs with nausea (71%) & vomiting (57%) (
- Intense visuals and hallucinations
  - Allows exploration of "other realms", resulting in a peaceful connectedness
- "Sold" as a weekend treatment for
  - Drug and alcohol addiction (SUDs), PTSD, childhood abuse trauma, depression, & anxiety

HARMINE, HARMALINE, & THH (TETRAHYDROHARMALINE)[45,110] (K/P)

- Beta-carboline alkaloids with highly active reversible monoamine oxidase-A inhibitor (RIMA)
- Harmine also called "Telepathine" or "Banisterine"
- Harmaline is also mildly psychoactive
  - ▲Acts as an acetylcholinesterase inhibitor & releases DA
  - ▲Inhibits histamine N-methyltransferase = causes insomnia
  - ▲Also found in the Syrian Rue (*Peganum harmala*) plant
- Harmine shown to induce neurogenesis in adult cells (in vitro)
- Harmala alkaloids degrade over time (not DMT)[66] (AA)

PHARMAHUASCA[55,66,112,113] (AA/Q/Cameron/Peters)

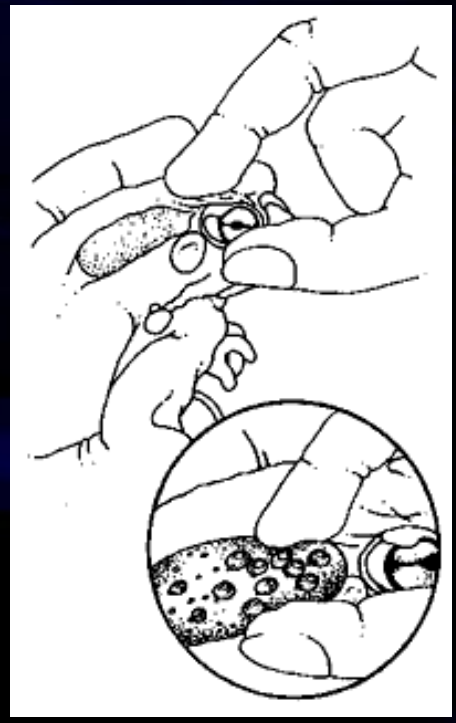
- Combo of MAO_A inhibitor & tryptamine (DMT)
  - Pargyline (Eutonyl) – MAO_B inhibitor
    - An antihypertensive discontinued in 2007
    - Structurally related to selegiline and rasagiline (Azilect)
  - Moclobemide also used (available in Europe)
- Change α and β side-chain hydrogens make it MAOI-resistant
- Tabernanthalog NEW DRUG
  - Non-hallucinogenic 5-MeO-DMT & ibogaine analog by Delix Therapeutics[62,98] (Q1/Delix)
  - Effective in rodent models of EtOH/Heroin use disorders & depression
- Deuterhuasca - deuterating a hydrogen on DMT[66] (AA)
  - Patented by Small Pharma[97]

5-MeO-DIMETHYLTRYPTAMINE (5-MeO-DMT)[114-115] (DM/DN)

- Methoxy group increases lipid solubility
  - ▲10X more potent than DMT
- Not orally active
- Inhibits SERT (like an SSRI)
  - ▲5HT1$_A$ agonist that is 300-1000x higher than 5HT2$_A$ agonist
- 2019 prospective observational study showed a single dose found to ↓ anxiety, depression, & stress up to 4 weeks after[55] (Q)
  - ▲People with greater ego dissolution, the more effective ("one-ness with the universe")
  - ▲Users surveyed said they tried it for PTSD, depression, anxiety, SUDs, OCD
    - ●~80% reported positive effects / only 2-10% said it worsened them

5-MeO-DIMETHYLTRYPTAMINE (5-MeO-DMT)[55] (Q)

- Bufo alvarius[100,104,114,115] (AC/Y1/DM/DN)
  - Sonoran Desert & Colorado River Toads
  - Glandular venom = 6-16% 5-MeO-DMT
  - Skin contains 50-160mg/g of 5-MeO-DMT
    - 50mg of toad bufotoxin = 5-7mg of 5-MeO-DMT
  - 3-5mg = psychoactive effect
  - Discovered in 1959 to be the predominant alkaloid in the hallucinogenic snuffs of several tribes in South America



- Phalaris aruninacea plant = DMT + 5-MeO-DMT [104] (Y1)
  - "Businessman's Trip" – rapid onset, short duration (<60min)

COMPARING DMT TO 5-MeO-DMT[107,114] (DM/Z)

- DMT: other worldly encounters, very visual, out of body
- 5-MeO-DMT: Ego dissolution, spiritual experiences, one with universe, transcendental
  - Acts as a somatic amplifier (Interoception)
    - Zoom in on things going on with one's body
  - Causes more vivid, complex visual imagery

PSILOCYBIN / PSILOCIN

MUSHROOMS

PSILOCYBINS[45,100] (K/AC

- Use dates back over 6000 years
- Used by the Mayans and Aztecs
  - Called them "God's flesh"
- Biosynthesized in 1957 by Albert Hoffman at Sandoz Labs
  - Discovered LSD in 1938, but later exposed by touch in 1943
- Psilocybin is biologically inactive
  - Rapidly metabolized to bioactive psilocin
- Onset: 20 minutes / Duration: 2-6 hours
- Half-life of Psilocin is 1-3 hours

MUSHROOMS[45,93-94,100,116,117] (K/AC/CC/CB/BA/BB/BD)

- From *Psilocybe genus* mushrooms
  - Grow on cow manure
  - Contain Psilocin (α-methyltryptamine (AMT)), Baeocystin, and Norbaeocystin
- Dried mushrooms = 0.2%-1% psilocybin, only trace psilocin
  - Psilocin less stable, oxidizes upon drying
- 10-30 mg typically ingested
  - ~2 grams of fresh mushrooms
  - 1-2 mg = low dose (microdose)
  - LD_{50} ≈ 6000 mg
- "Magic Mushrooms" used in the 1960's led to legal reforms
- Mushroom spores are still legal to buy in the US

EFFECTS OF MUSHROOMS[43,100,118-121] (AC/CR/CK/E/BI/BI-2)

- Physical effects
  - ▲*Nausea* and vomiting
  - ▲Muscle weakness
  - ▲Lack of coordination
  - ▲Facial flushing
  - ▲Sweating
  - ▲Enlarged pupils
  - ▲Drowsiness
  - ▲Salivation
  - ▲Restlessness
  - ▲Diarrhea
  - ▲Tearing
  - ▲Makes limbs heavy
  - ▲↑ BP/P (not safe in cardiovascular/cerebrovascular diseases)[45] (K)

- Psychological Effects
  - ▲Crossing of senses
    - ●Synesthesia
  - ▲Euphoria
  - ▲Hallucinations
    - ●Earthy visual hallucinations
  - ▲Enmeshment with surroundings
  - ▲Panic / Psychosis
  - ▲Detachment from reality
  - ▲Introspective and self-revealing (like Ayahuasca)
  - ▲Dwelling thoughts

PSILOCYBIN

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THERAPEUTIC PSILOCYBIN

- "REBUS" – Relaxed beliefs under psychedelics[80] (B)
- May be effective for personality disorders and political fanaticism
  - Can alter, reshape, and relax rigid beliefs & personality traits
  - Completely transforms a patient's view of themselves, others, & meaning of life
  - Increase belief in universal interconnectedness & ego dissolution

- Treatment-resistant Depression
  - COMP360 trial (Phase 2b study)
  - Single dose of psilocybin 25 mg effective on TRD at 12 weeks
    - But 10 mg not[119] (BI-2)

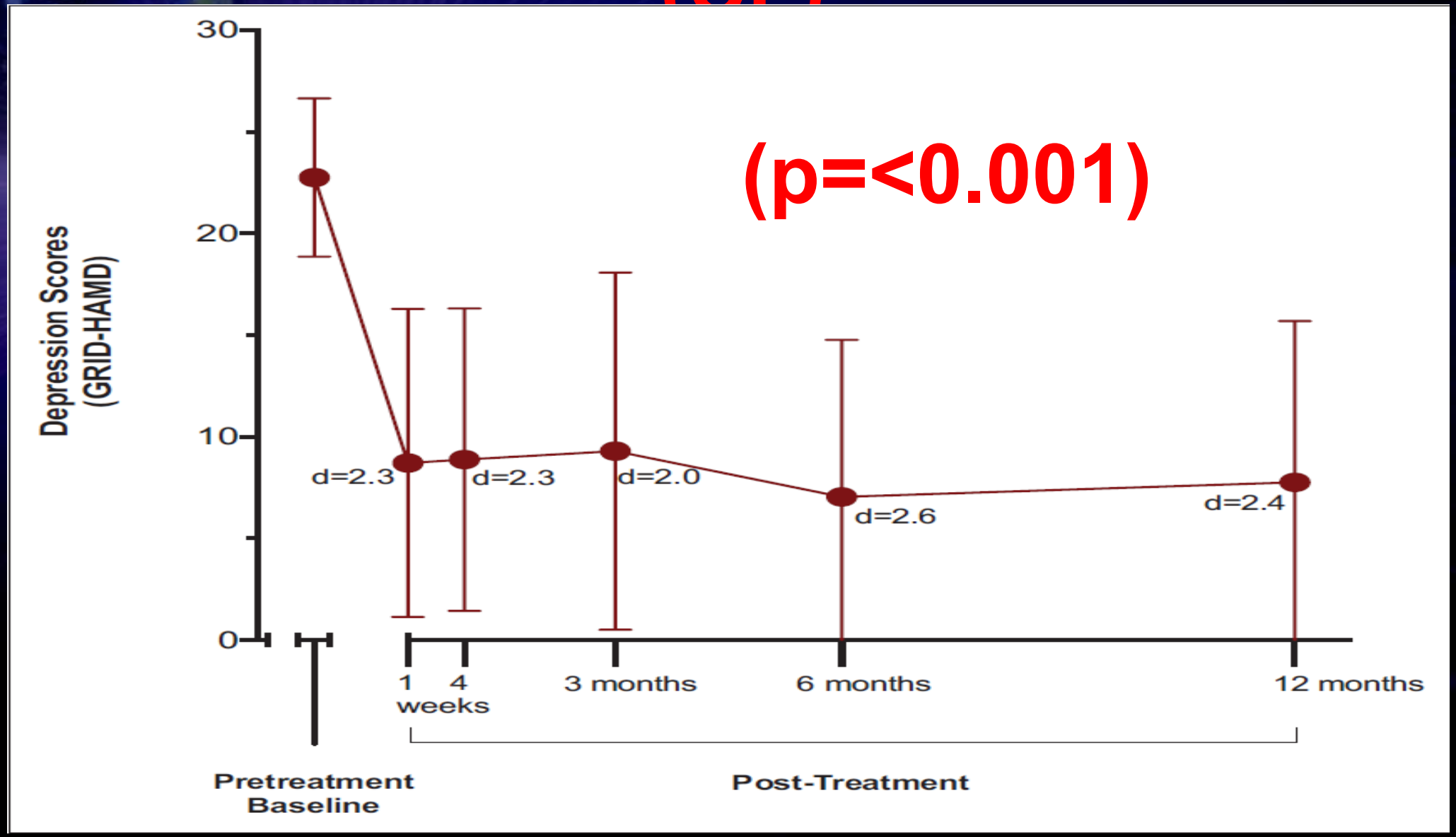
DEPRESSION TREATMENT

- Phase 2 trial compared 2 doses of psilocybin 1 or 25 mg vs. 20 mg of escitalopram for 6 weeks (n=59)[118] (BI)
  - Two 25 mg psilocybin doses given 3 weeks apart[45,122] (K / BI-1)
  - Headache and nausea most common ADRs reported
  - QIDS-SR-16 response for psilocybin vs. escitalopram (70% vs. 48%)
  - QIDS-SR-16 remission for psilocybin vs. escitalopram (57% vs. 28%)
  - Trial not powered to show statistical significance
    - Statistical re-analysis by Nayak *et al*. showed non-inferiority and even some superiority to escitalopram[118] (BI)
- On-line retrospective survey by Nayak *et al.* of 611 individuals
  - Concomitant use of SSRI/SNRIs may reduce overall psilocybin effects + up to 3 months after d/c[123] (BH)

PSILOCYBIN IN DEPRESSION[54,57,118,122,124,-126] (D/CN/BI/BI-1/CL/AR/CM)

DEPRESSION						
Author/Title	**n=**	**Study Design**	**Dose**	**Timing**	**Measurement**	**Symptom Improvement**
Carhart-Harris | Psilocybin... treatment-resistant depression	12	open-label feasibility trial	10 mg and 25 mg	7days	MDD	Yes
Robin Carhart-Harris | Trial of Psilocybin versus Escitalopram for Depression	59	double-blind, randomized, controlled trial	25 mg	3 weeks	Depression symptoms vs. Escitalopram	Yes, but not significant over Escitalopram
Carhart-Harris | Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms	19	Open label clinical trial	10 mg and 25 mg	1 week	Treatment resistant derpression	Yes
Davis | Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder	27	randomized,waiting list–controlled clinical trial	session 1: 20mg/70 kg; session 2: 30mg/70 kg	1.6 weeks	MDD	Yes
Gukasyan | Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up	24	Randomized, waiting-list controlled, 12 month	20 mg/70 kg and 30 mg/70 kg	2 weeks	MDD	Yes
Zeifman | Decreases in suicidality following psychedelic therapy	"	Meta Analysis	"	"	Suicidality	Yes

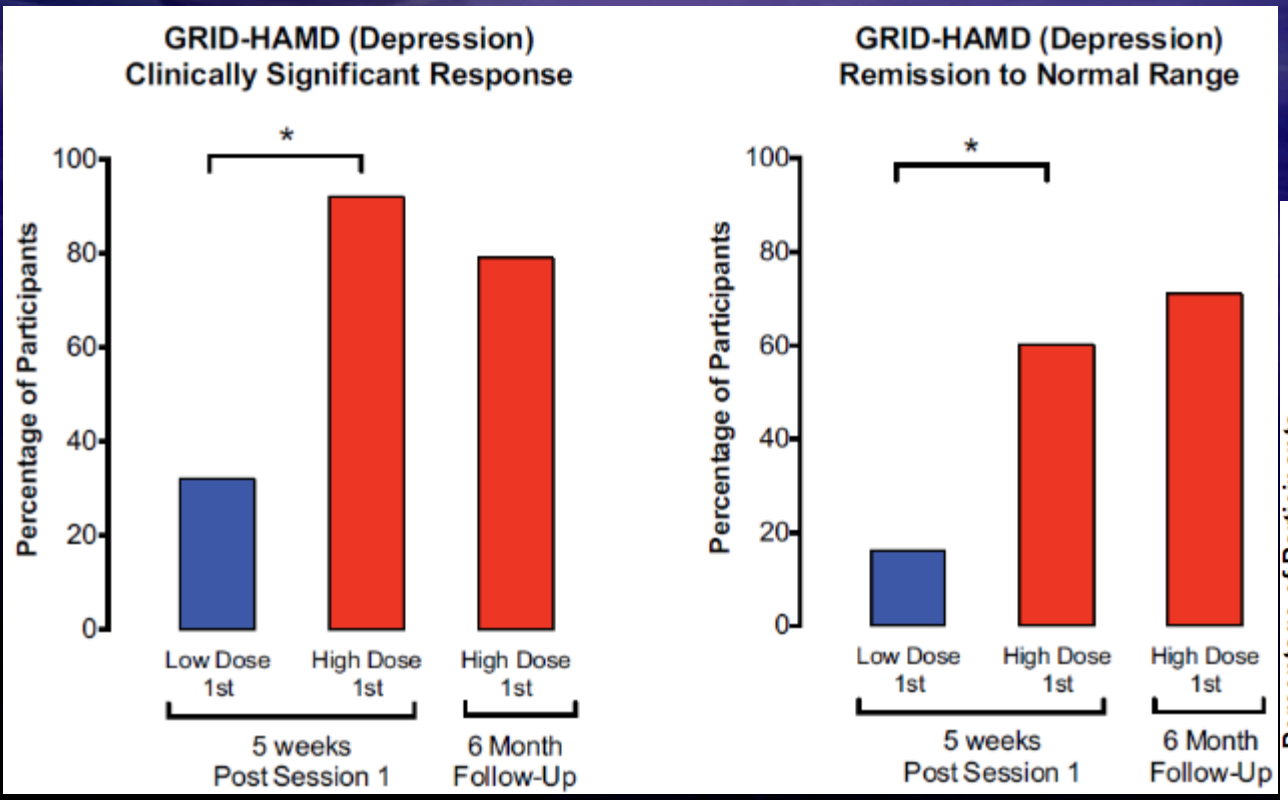
GUKASYN'S RESULTS IN DEPRESSION[124] (CI)

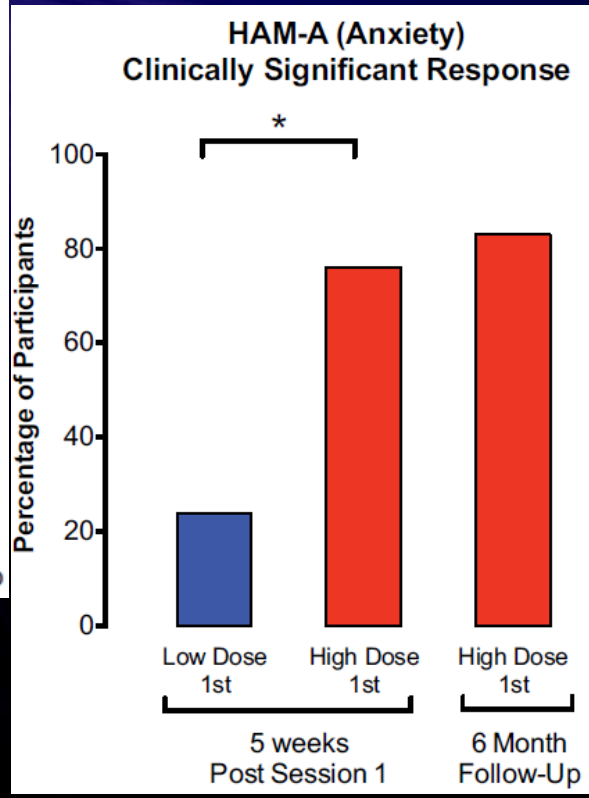


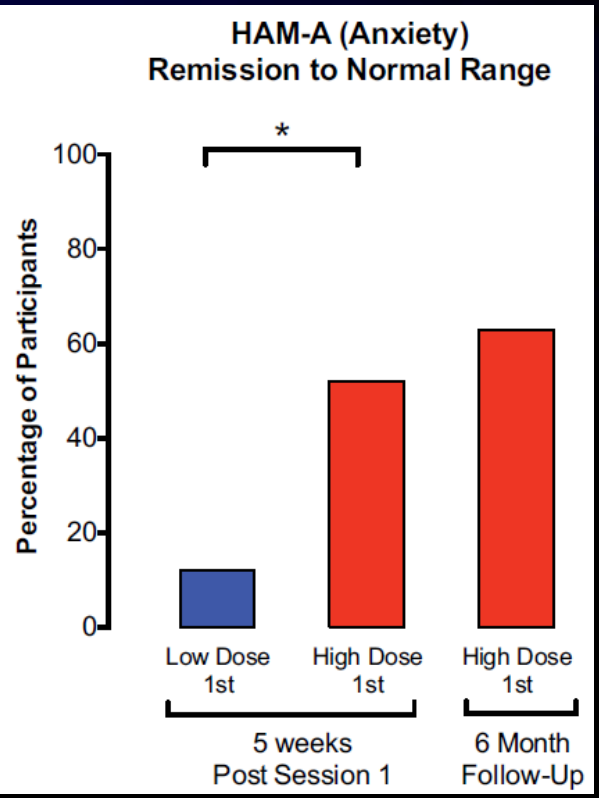
PSILOCYBIN FOR TERMINAL(?) CANCER[43] (CK)

- 51 patients with potentially life-threatening cancer diagnoses and symptoms of depression and/or anxiety
- Low dose = 1-3 mg **vs.** High dose = 22-30 mg
- At 6-month follow-up, changes were sustained
  - ▲80% showed clinically significant ↓ in depression & anxiety
- High-dose improved attitudes about life/self, mood, relationships, and spirituality to the experience
- >80% endorsed overall increased well-being and life satisfaction
  - ▲Mystical-type experiences correlated to positive therapeutic effects
- No serious adverse events occurred
  - ▲↑ BP/P, nausea, emotional lability, and yawning seen

PSILOCYBIN FOR TERMINAL(?) CANCER[43] (CK)





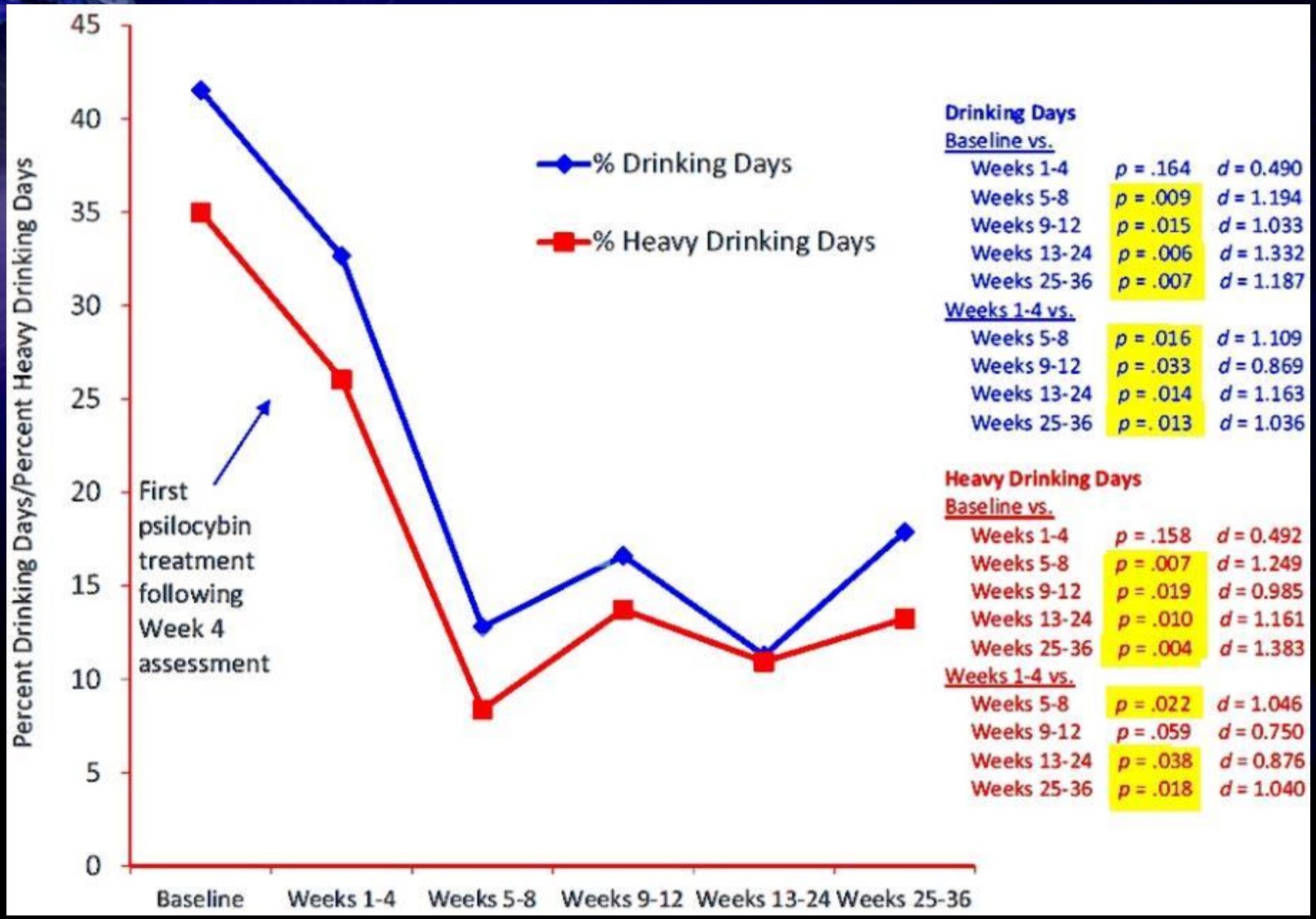


ALCOHOL (EtOH) USE DISORDER (AUD)[127] (DT)

- Psilocybin given to alcoholics helped them process painful emotions from past traumas and promoted a state of self-compassion, awareness, and interconnectedness[68] (I)
  - ↓ shame and self-critical thoughts, ↓ cravings, ↑ affect regulation

- Psilocybin on heavy alcohol (EtOH) drinking[128] (S)
  - Used high doses (25-40mg per 70kg) at weeks 4 & 8, vs. diphenhydramine 50-100mg
  - Patients received 12 psychotherapy sessions
  - Open-label extension at 38 weeks
  - At 32 weeks, 9.7% vs. 23.6% drank heavily
    - > 5 drinks/d men / > 4 drinks/d women

PSILOCYBIN ON HEAVY ETOH DRINKING[128]



Bogenschutz *et al.*[128] (S)

MDMA

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MDMA FOR PTSD

- In 2017 for PTSD – breakthrough therapy designation by the FDA[34,54] (D/AQ)
  - "Serenic" agent used to get "cognitive control" over emotionally charged memories
    - It dampens down emotions enough to reprocess trauma
    - Allows for memory reconsolidation and fear extinction[45] (K)

- 2020 Systematic review and meta-analysis[129] (BE)
  - 5 trials reviewed (n=106) / only 2 used placebo
  - All studies showed 1 to 3 sessions of MDMA was better than placebo (for up to 74 months)
  - 75 and 125 mg superior to 30mg doses

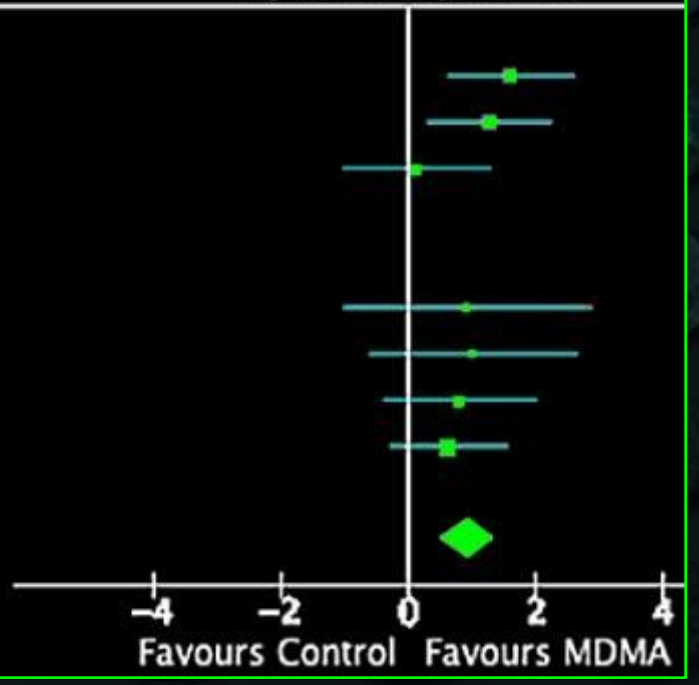
2021 meta-analysis of MDMA for PTSD[130] (CJ)

- 10 studies / 168 patients who all received psychotherapy
- MDMA doses from 25 to 187.5 mg with an average of 2.4 sessions
- **Conclusion:** MDMA + psychotherapy = better clinically significant responses compared to controls (psychotherapy + placebo)

	Control			MDMA				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bouso et al, 2008	40	1.41	2	32	2.01	4		Not estimable
Mithoefer et al, 2011	39.3	13.3	8	17.2	13.2	16	18.5%	1.61 [0.63, 2.60]
Mithoefer et al, 2018	44.7	14	7	22.3	18.1	19	20.2%	1.26 [0.32, 2.21]
Monson et al, 2019	21.54	19.67	6	19.37	13.71	6	14.0%	0.12 [-1.01, 1.25]
MP-16, 2020	0	0	32	20.25	9.98	32		Not estimable
MP-17, 2020	0	0	4	14.84	10.76	4		Not estimable
MP-4, 2017	46	7.1	2	37.2	7.7	4	4.9%	0.93 [-0.99, 2.85]
MP-9, 2020	42	9.2	3	31	9.5	5	7.1%	1.02 [-0.58, 2.61]
Oehen et al, 2013	39.1	4.5	4	30	12	12	13.0%	0.79 [-0.38, 1.97]
Ot, alora et all, 2018	47.4	11	6	36	18.7	28	22.4%	0.63 [-0.27, 1.52]
Total (95% CI)			36			90	100.0%	0.93 [0.51, 1.36]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.80$, $df = 6$ ($P = 0.57$); $I^2 = 0\%$

Test for overall effect: $Z = 4.31$ ($P < 0.0001$)



Forest plot of Standardized Mean Difference (SMD) of effect of MDMA (versus control) on PTSD symptoms score

MDMA FOR PTSD

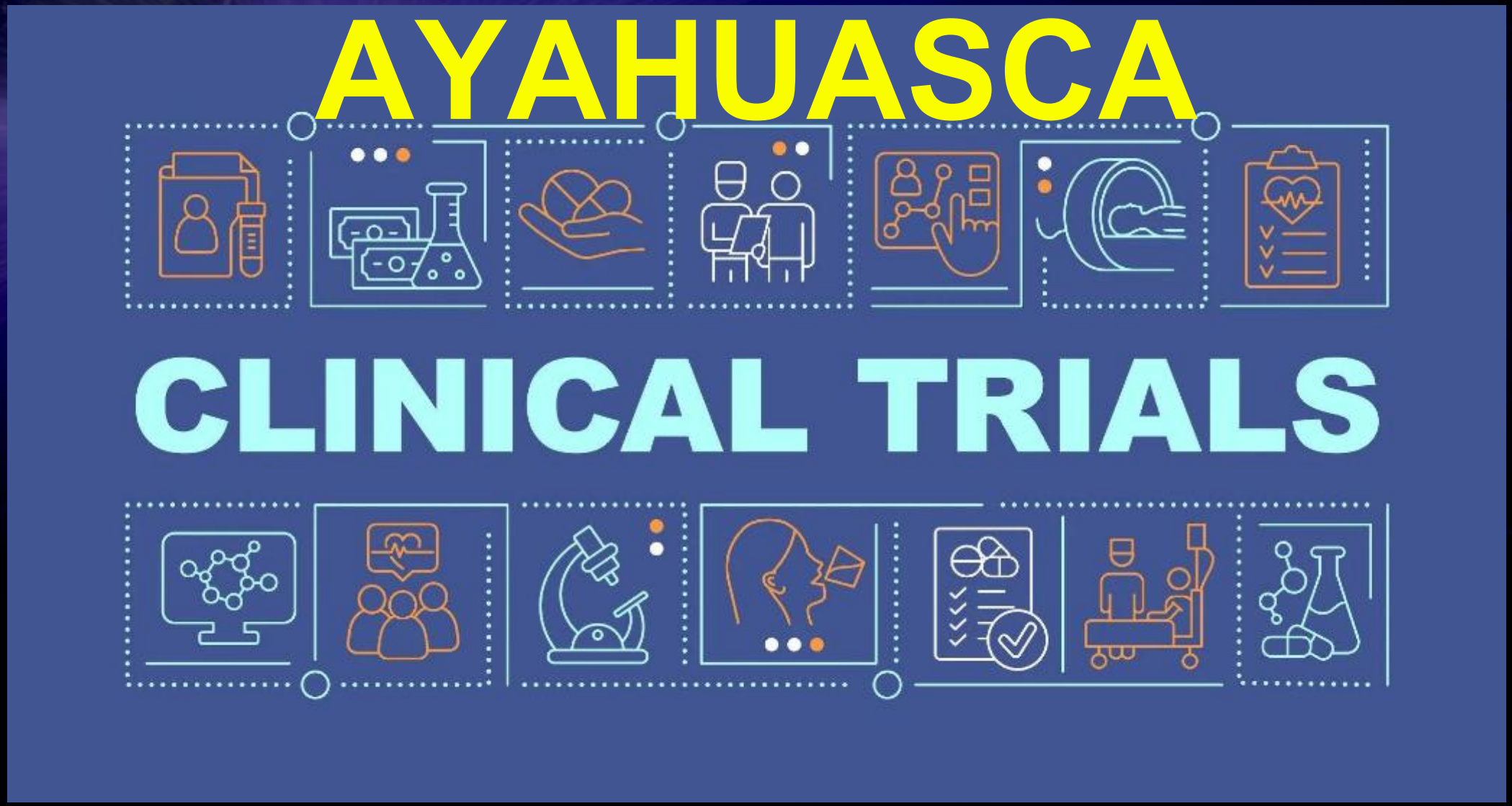
- MAPP1 Phase 3 study[131] (AB) (n=46 vs n=44 placebo)
  - https://maps.org/mdma/ptsd/mapp1/
  - 80mg – 120mg – 180mg doses used
  - 3 preparatory sessions, then randomized
    - 3 exposure sessions – 4 weeks apart
    - 9 integration sessions between exposures (total of 15 sessions)
    - Assessed between sessions and 2 mo later (week 18)
  - Significantly ↓ PTSD severity scores and disability scores
  - 88% of participants with severe PTSD experienced a clinically significant reduction in PTSD diagnostic scores at endpoint
    - Compared to 60% of placebo participants
  - No significant suicidality, abuse, or QT-prolongation
  - 67% at endpoint no longer met Dx of PTSD
  - ADRs: muscle tightness, ↓ appetite, nausea, sweating, feeling cold

MDMA FOR PTSD

- MAPP2 Phase 3 study[132] (n=100)
  - https://maps.org/mdma/ptsd/mapp2/
- Randomized, double-blind, placebo-controlled, multi-site
  - A flexible dose of MDMA or placebo
    - Initially 80 mg or 120 mg, then a supplemental half-dose 2 hours later
  - Each monthly experimental session followed by 3 integrative sessions of non-drug therapy
  - Total time of 12 weeks
  - *Results are not yet published*

99 Ecstasy (MDMA) Tablets
Image © 2000 Erowid.org

DIMETHYLTRYPTAMINE / AYAHUASCA



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AYAHUASCA STUDIES[133-135] (BC/BF/DS)

- Ayahuasca (n=14) vs. placebo (n=15) in TRD (DBPCT)
  - Single DMT dose of 0.36 mg/kg
  - MADRS & HAMD at Day 7 showed significant response (64% vs. 27%; p=0.04) and almost significant remission rates (36% vs. 7%; p=0.054)
- Ayahuasca on SUDs (systematic review)
  - 9 studies (4 in rodents)
  - All rodent studies reported mostly positive results with changes in substance use disorder cFos protein expressions
  - Most human trial results were positive (↓ drug use, anxiety, & depression) - Also increases in QoL and well-being
  - No trials were placebo-controlled

GLOBAL AYAHUASCA PROJECT (GAP)[136,137] (W)

- Has data on 10,836 people from over 50 countries
- Large on-line survey of adults' use

# of times used	1	2-3	4-10	11-20	21-50	51-200	200-499	> 500
% of respondents	8	12	19	8	11	15	13	13

- Ongoing non-clinical and clinical studies
  - Depression, addiction, anxiety, PTSD, suicidality, grief, Eating disorders, Borderline Personality Disorder, Parkinson's Disease

5-MeO-DIMETHYLTRYPTAMINE (5-MeO-DMT)[114,115,138] (DM/DN/DR)

- Currently in several phase I & II trials (safety only)[55] (Q)
  - Inhaled/intranasal/Intramuscular (2, 6, 12, & 18mg doses)
- ADRs: acute fear, sadness, anxiety, confusion, fatigue, crying, paranoia, trembling, vomiting, nausea, headache, pressure on the chest or abdomen and loss of body perception and subacute flashbacks for a few weeks after
  - Smoking more likely to cause brief flashbacks vs. IM (mostly pleasant or neutral rxn)
- IM – peaks in seconds / lasts 15-20 min
- Intranasal onset in 5-7 min & lasts 45-60 min

TO LEARN MORE

- Bluelight Forum - https://bluelight.org/xf/forums/
- Erowid -- https://www.erowid.org/
- Johns Hopkins Center for Psychedelic and Consciousness Research
  - https://hopkinspsychedelic.org/
- MAPS (Multidisciplinary Association for Psychedelic Studies)
  - www.maps.org
- Psychedelic Drug Development Tracker - Psychedelic Alpha
  - https://psychedelicalpha.com/data/psychedelic-drug-development-tracker
- Psychonaut Wiki -- https://psychonautwiki.org/wiki/Main_Page
- UC Berkeley Center for the Science of Psychedelics
  - https://psychedelics.berkeley.edu

CONCLUSION

- Psychedelics can be useful therapeutic tools
  - Psychoanaleptic
- Psychotherapy will likely be a mandated component for use
- The risk of misuse of psychedelics is minimal, but likely to occur in the light of profiteers
- Invest in companies that make psychedelics


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REFERENCES