Tidbits of Toxicity: Exploring effects of ketamine, psilocybin, and other psychedelics

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ASAM 2024, Saturday April 6

Disclosure Information

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No Disclosures

Learning Objectives

- Review the pharmacology of therapeutic psychoactive agents: ketamine, ibogaine, MDMA (phenethylamines), psilocybin, and dimethyltryptamine and harmaline alkaloids
- Develop a better understanding of the potential beneficial clinical effects, adverse effects and management strategies for patients experiencing toxicity or adverse effects of therapeutic psychoactive agents.
- Address societal implications of using therapeutic psychoactive agents.

Hallucinogen chemical classification

- Phenethylamines
  - Mescaline
  - Cathinone
  - Ephedrine
  - Pseudoephedrine
  - Amphetamine
  - Methamphetamine
  - MDMA
- Arylcyclohexamines
  - Ketamine
  - Phencyclidine
- Phenylalkylamines
  - Mescaline (peyote cactus)
- Indolealkylamines
  - Ergolines
    - LSD
  - Tryptamines
    - DMT
    - Psilocybin/Psilocin
    - 5-MeO-DMT
    - Ibogaine
    - Bufotenine
- β-carboline alkaloids
  - Harmine, harmaline

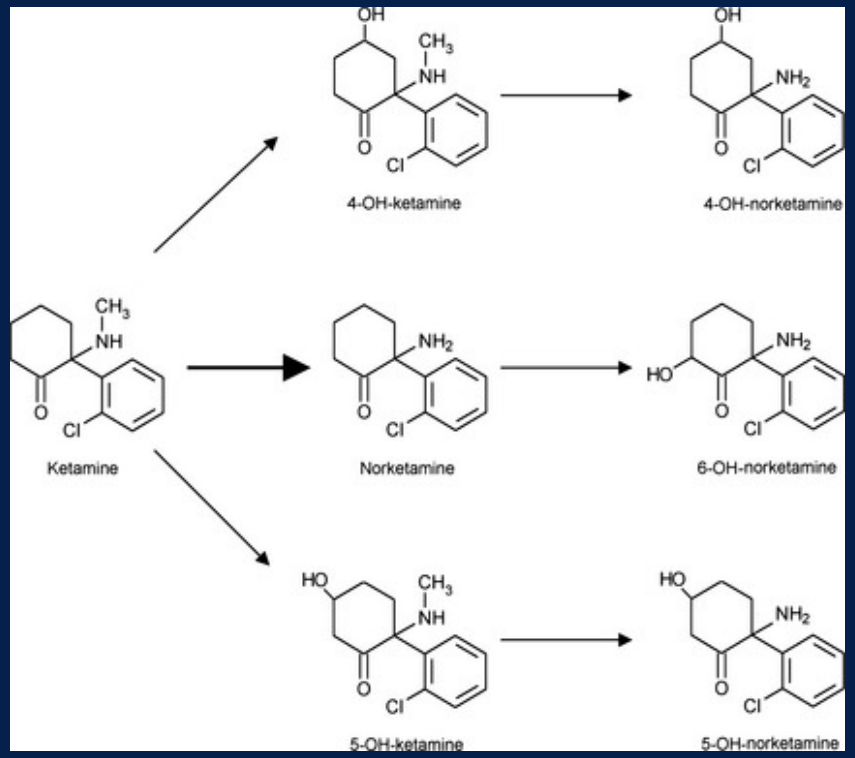
Brent et al., 2017

Ketamine Clinical Use

- Pain Relief
  - Dissociative anesthesia
  - Perioperative Pain
- Treatment Resistant Depression
  - Maximum efficacy 24 hrs. Lasts 1–2 weeks after infusion
- Addiction
  - Prolong abstinence
  - Reduced craving

Bell, RF, and Kalso, EA. 2018
Corriger, A, and Pickering, G 2019
Ivan Ezquerra-Romano,. (2018)

Ketamine Pharmacology

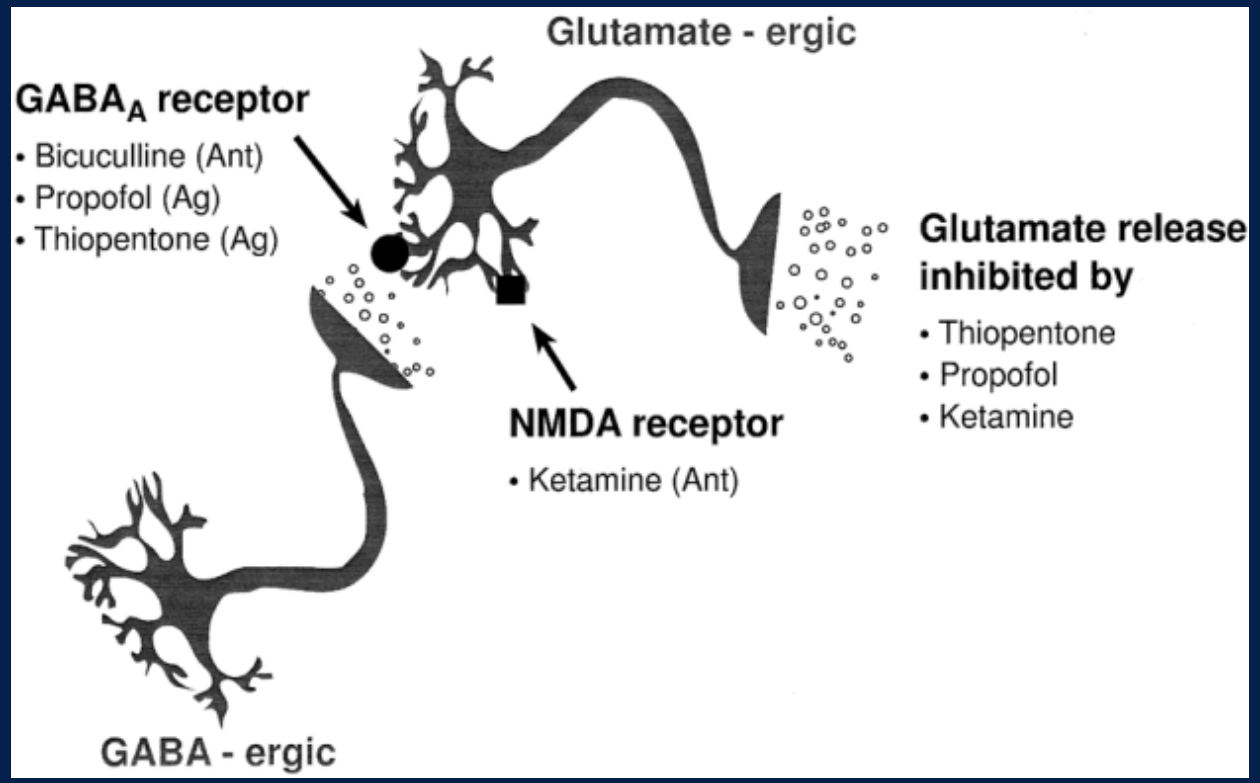


- Routes
  - mainly IV, IM
- Onset
  - Minutes
- Half Life 2-4 hours
- Metabolite Norketamine
  - 20-30% analgesia potency of ketamine
  - Peak 30 minutes
  - ? Elimination half life 5 hours
- Drug interactions
  - CYP enzyme inducers increase metabolism and clearance
- Active enantiomer
  - S-ketamine
    - >strength than racemic, R-enantiomer
    - FDA approved nasal spray for treatment resistant depression

Mion G, Villevieille T. 2013

Ketamine

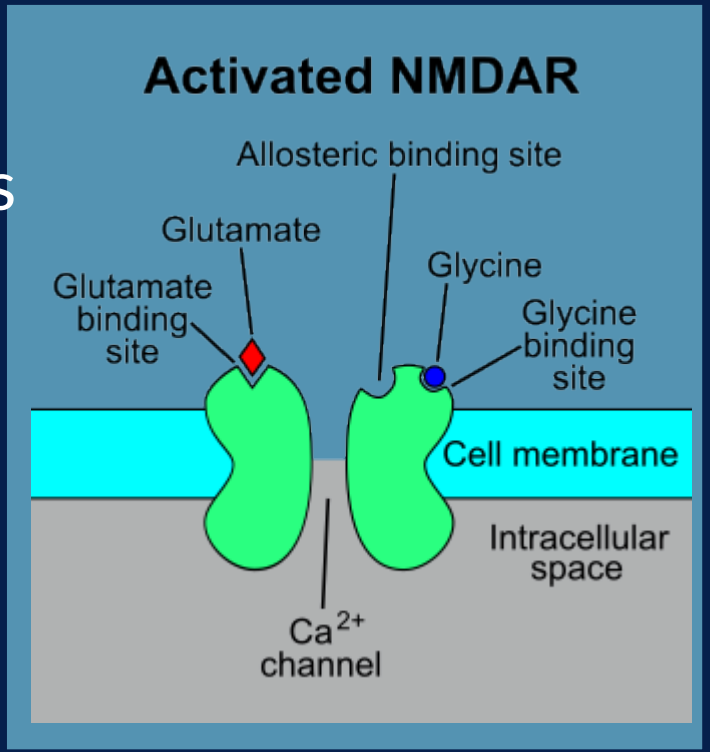
- The basics: NMDA antagonism



Slide courtesy of Dr. Jon Cole

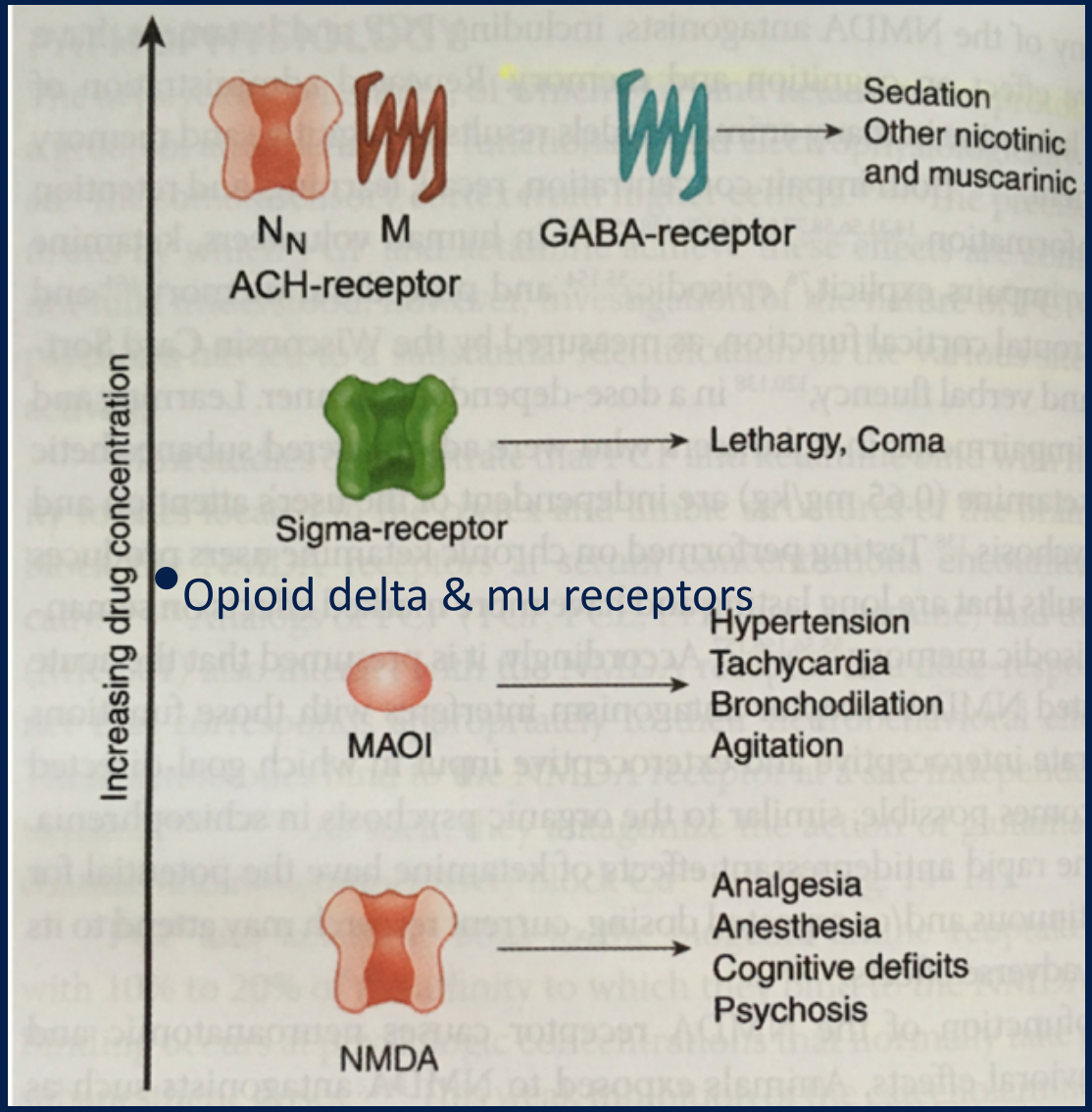
NMDA

- Glutamate
  - Excitotoxicity
    - Epilepsy, Alzheimer disease
  - Role in synaptic plasticity and neurogenesis
    - Memory formation
      - Block reconsolidation of drug-related memories
    - Disruption of relevant functional neural networks
      - Enhancing psychological therapy efficacy
      - Treats depression



Ivan Ezquerra-Romano et al. 2018

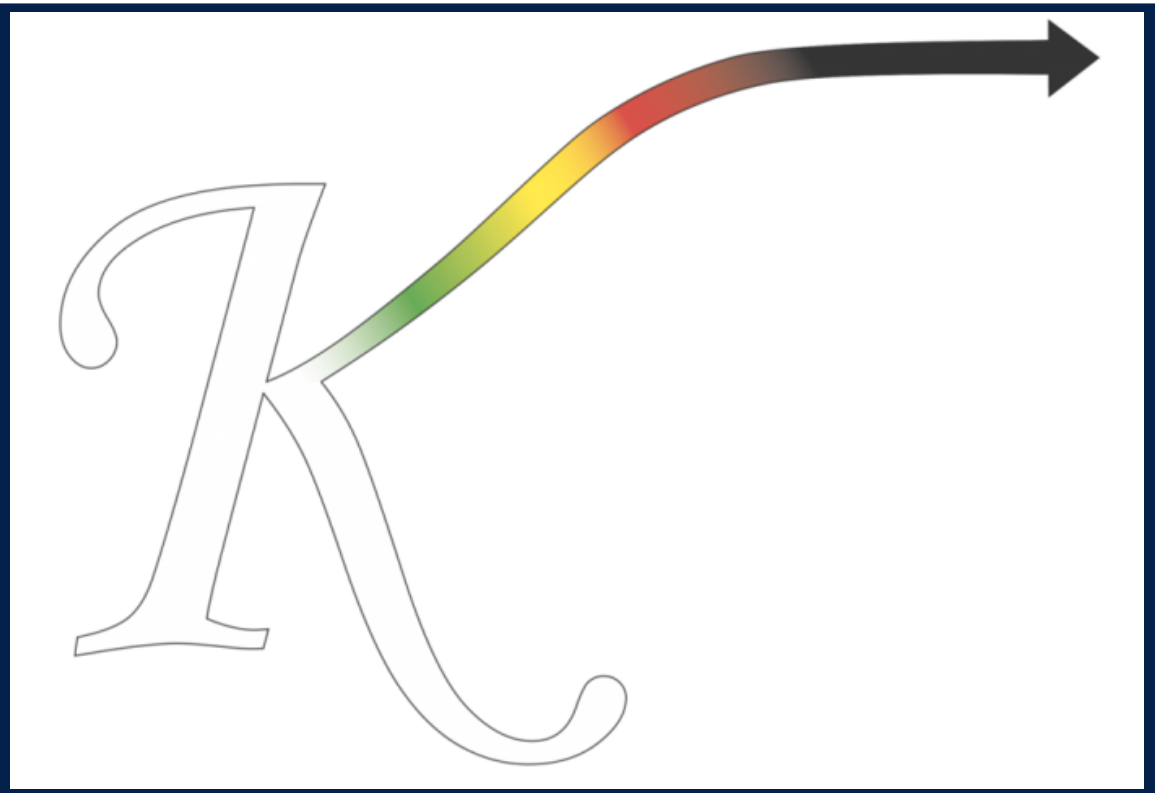
Pharmacology of Ketamine: More than NMDA



The (IV) Ketamine Dosing Continuum

0.1-0.3 mg/kg →0.4 – 0.8 mg/kg → 0.5mg/kg-1 mg/kg→ >0.7 mg/kg → 1-5 mg/kg

Analgesic → Partial Dissociation → Depression Tx →Dissociation →Anesthetic



Slide courtesy of Dr. Jon Cole

Acute Toxicity

Recreational

- Co-administration of other drugs
- Psychotomimetic properties
- ?Cardiovascular

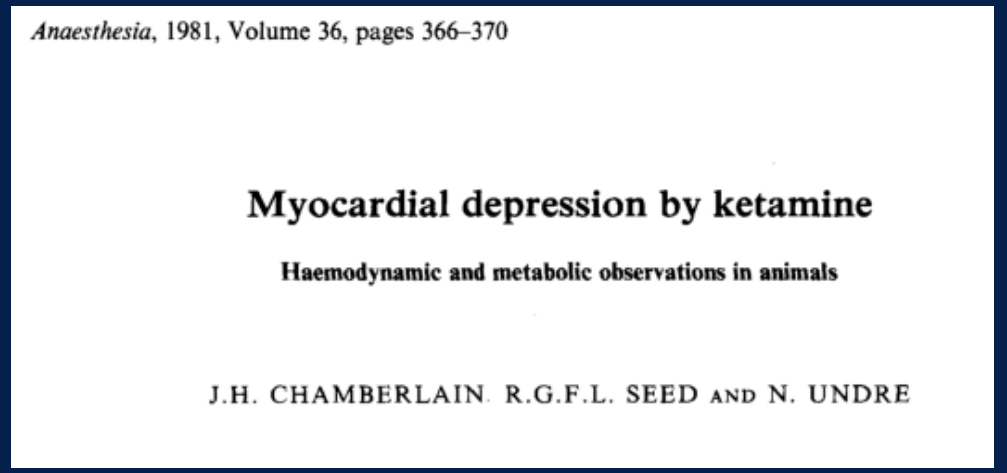
Management

- Supportive

Kalsi 2011

Ketamine Paradoxes: Cardiovascular

- Ketamine has MAOI effects
- May also cause release of biogenic amines (dopamine, serotonin, norepinephrine)
- Patients on ketamine generally are more tachycardic and hypertensive
- But…



Anaesthesia, 1981, Volume 36, pages 366–370

Myocardial depression by ketamine

Haemodynamic and metabolic observations in animals

J.H. CHAMBERLAIN. R.G.F.L. SEED AND N. UNDRE

Ketamine Complications 5 mg/kg

Table 4. Complications.

	Ketamine	Haloperidol
Hypersalivation[a]	38% (21/56)	0 (0/69)
Emergence Reaction	10% (5/52)	0 (0/69)
Vomiting	9% (5/57)	3% (2/71)
Dystonia	5% (3/56)	3% (2/69)
Laryngospasm	5% (3/55)	0 (0/69)
Akathisia	2% (1/53)	0 (0/69)
Deaths	0	1% (1/82)

[a]Treatments for hypersalivation: suctioning (4), atropine (6), intubation (11).

Cole JB, et al 2016

Time Out! Ketamine & ICP?

PAIN MANAGEMENT AND SEDATION/SYSTEMATIC REVIEW–META-ANALYSIS

The Effect of Ketamine on Intracranial and Cerebral Perfusion Pressure and Health Outcomes: A Systematic Review

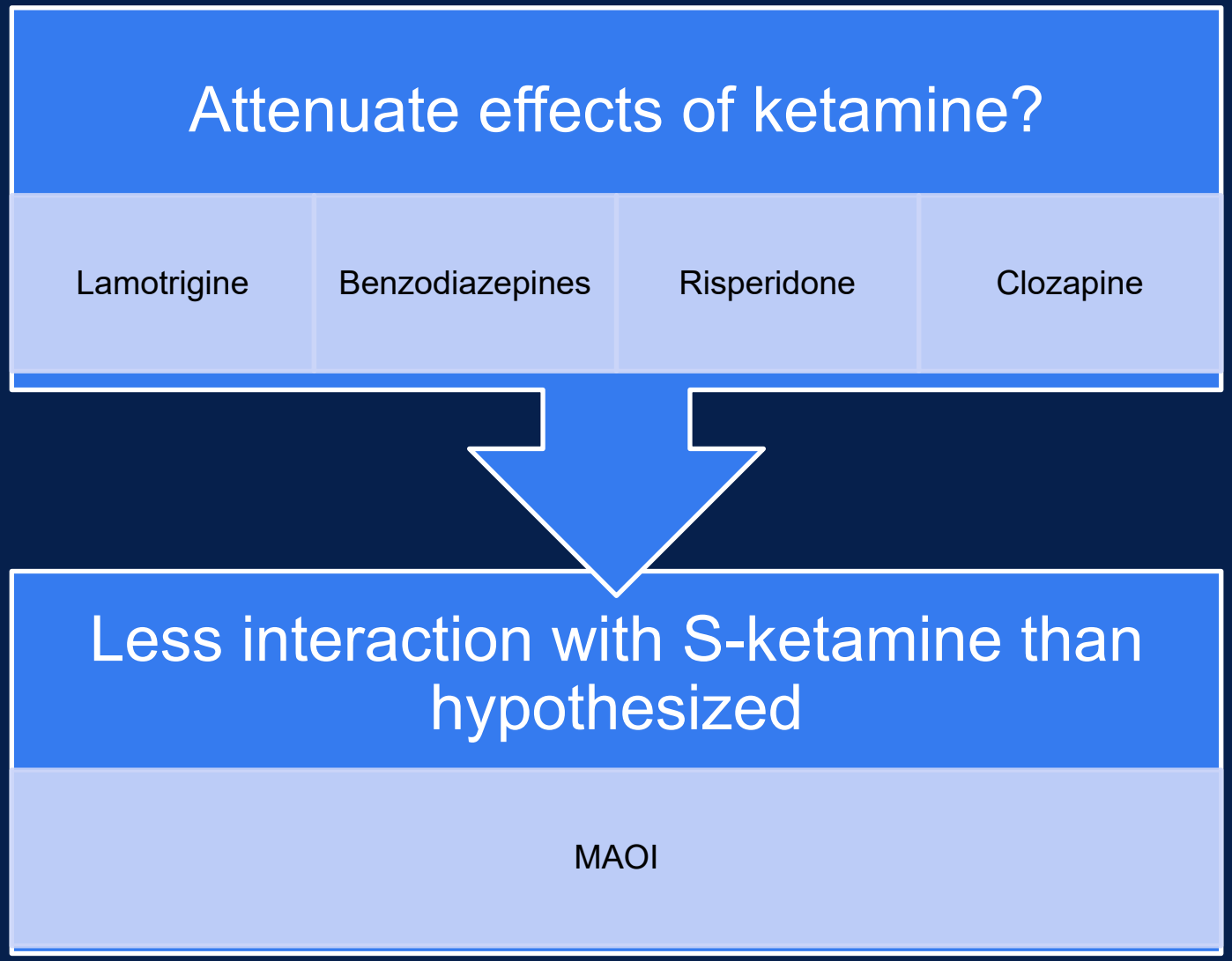
Lindsay Cohen, MD; Valerie Athaide, MD, FRCP(C); Maeve E. Wickham, MSc; Mary M. Doyle-Waters, MA, MLIS; Nicholas G. W. Rose, MD, FRCP(C); Corinne M. Hohl, MD, FRCP(C)*

*Corresponding Author. E-mail: chohl@mail.ubc.ca.

- 10 studies, 953 patients
- No significant differences in ICP, CPP, neurologic outcomes, ICU LOS, mortality

Slide courtesy of Dr. Jon Cole

Drug drug interactions



Veraart et al, 2022

Chronic Adverse Effects

- Recreational Use
  - More pronounced and persistent neuropsychiatric symptoms
    - Memory impairment
    - White matter degeneration MRI
  - Lower Urinary Tract Symptoms
  - Use Disorder

Kalsi 2011

Relative Contraindications

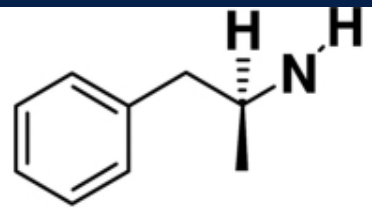
- Moderate to Severe HTN
- Heart Failure and/or CAD
- Pregnancy
- History of Psychosis
- Acute Alcohol Intoxication
- ?Risk of increase IOP/ICP
- ?Stroke
- Bladder

MDMA

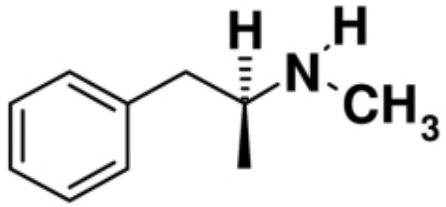
3,4-Methylenedioxymethamphetamine Pharmacology

- Ecstasy (tablet), Molly/Mandy (crystalline powder), gelcaps
- Empathogen
  - 5-HT1B (with some 5-HT2A)
- Increased synaptic concentration of 5-HT, Dopamine and Norepinephrine
  - Transporter protein (SERT, DAT and NET) inhibition/reversal
  - VMAT2 inhibition
  - 3-8 x as surge of 5-HT compared to dopamine
- Often dosed 1-1.5 mg/kg recreationally ***
  - 80-120 mg followed by 40-60 mg in phase 3 trials
  - Animal models doses greater than 3 mg/kg
- Metabolization
  - 80% hepatic
  - 20% renal
- Metabolism via CYP450 (CYP2D6, CYP3A4) and COMT

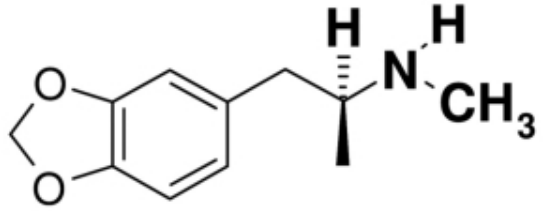
- Silins Eet al 2007
- Vuori E, Henry JA et al. “2003



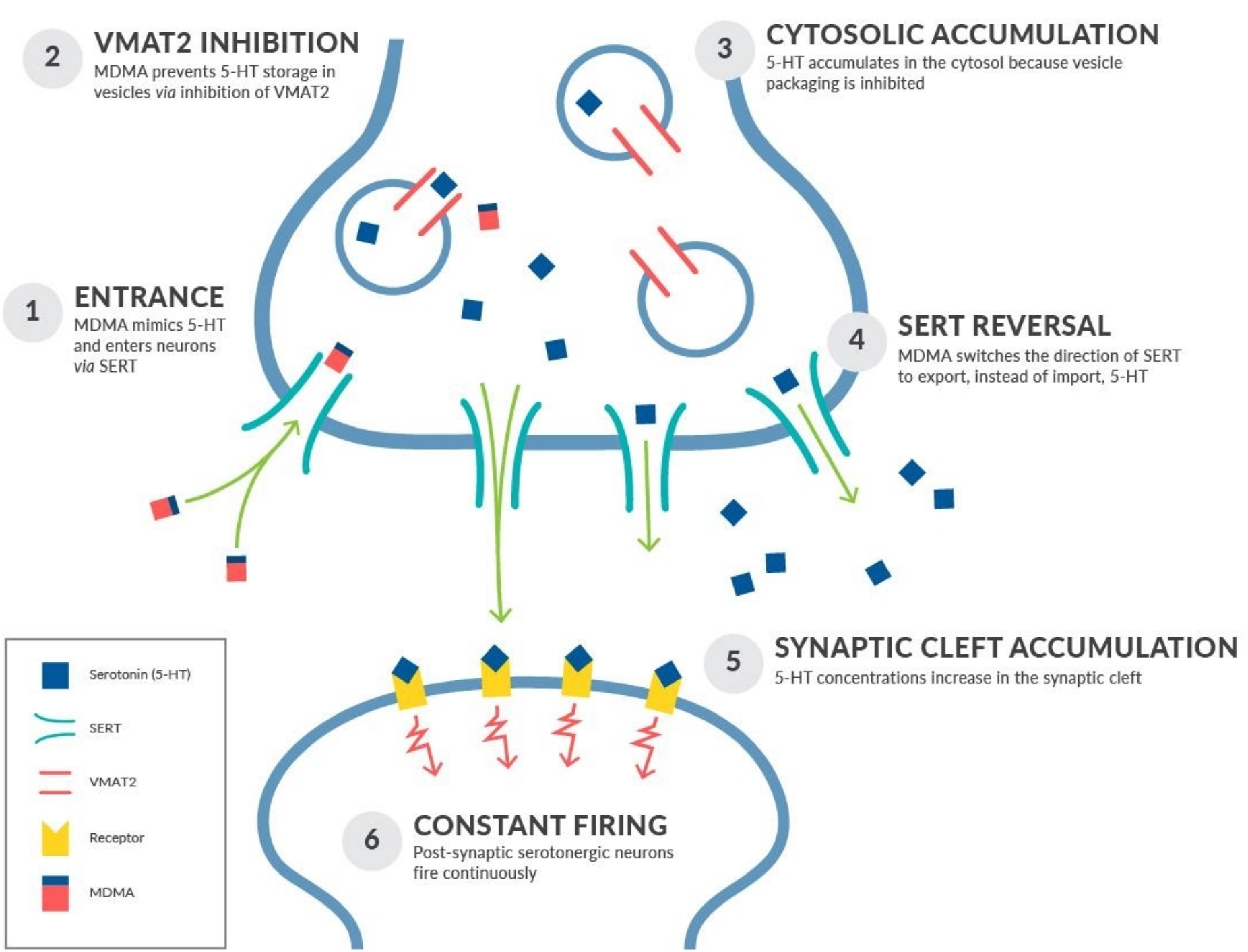
(+)-Amphetamine



(+)-Methamphetamine



(+)-3,4-Methylenedioxymethamphetamine


2
VMAT2 INHIBITION
MDMA prevents 5-HT storage in vesicles *via* inhibition of VMAT2
3
CYTOSOLIC ACCUMULATION
5-HT accumulates in the cytosol because vesicle packaging is inhibited
1
ENTRANCE
MDMA mimics 5-HT and enters neurons *via* SERT
4
SERT REVERSAL
MDMA switches the direction of SERT to export, instead of import, 5-HT
Serotonin (5-HT)
SERT
VMAT2
Receptor
MDMA
5
SYNAPTIC CLEFT ACCUMULATION
5-HT concentrations increase in the synaptic cleft
6
CONSTANT FIRING
Post-synaptic serotonergic neurons fire continuously

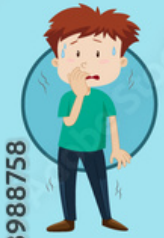
Rupp

EFFECTS OF MDMA

Psychological

- euphoria

- feeling energetic and confident



- heightened senses
- excessive sweating and skin tingles

- reduced appetite

Physical

- dehydration

- fast heartbeat
- increased blood pressure

- heat stroke

- drinking extreme amounts of water

- muscle aches and pains

- Liechti ME, et al 2001
- Meyer JS. 2013
- Carvalho M, et all 2012

Adverse Effects

- Minor
  - agitation, confusion, paranoia, psychosis
- Severe
  - DIC, convulsions, hallucinations, serotonin syndrome, rhabdomyolysis, AKI, hyponatremia
- Adulterants including methamphetamine, caffeine, fentanyl, and others complicate this
- Paramethoxyamphetamine (PMA)
  - “Dr. Death”, “Death”, “Mitsubishi Double Stack”, “Killer”, “Red Mitsubishi”
  - Cheaper than MDMA
  - Slower onset and longer effects
  - Much more narrow therapeutic effect than MDMA

Greene SL, Kerr F, Braitberg G. 2008
Betzler F, Viohl L, Romanczuk-Seiferth N. 2017

MDMA Drug Interactions

Adrenergic Agents (clonidine, pindolol, etc)

- No significant interaction (benefit?)

Antipsychotics (haloperidol)

- Dysphoria, higher anxiety

Bupropion

- Mild increase in heart rate, euphoria prolongation

Memantine

- No significant effect

Psychostimulants (methylphenidate)

- Delayed time to max concentration, increased HR/BP

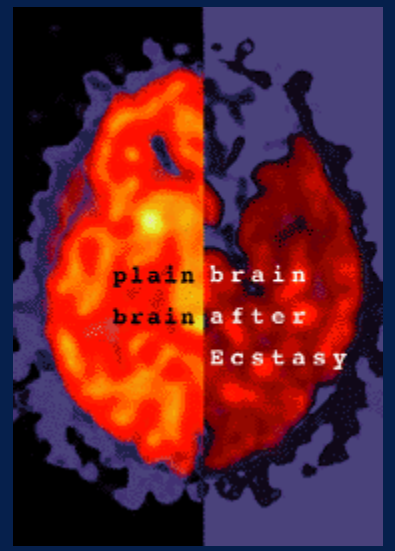
SSRIs/SNRIs (citalopram, fluoxetine, paroxetine, duloxetine)

- Increased euphoria, reduced empathogenic effect (duloxetine)

Sarparast 2022

Neurotoxicity of MDMA

- Surges in neurotransmitters/neuromodulators
- Methamphetamine causes neurotoxicity
  - Primarily Dopaminergic
- Some rodent models: loss of serotonergic tone
  - Not neurotoxicity of serotonergic neurons
  - In nonhuman primates seems to be less profound
  - 2002 study published in *Science*
- Hyperthermia can cause neurotoxicity
  - Need for temperature regulation



Long Term Adverse Effects of MDMA

- Difficult to know
  - Polysubstance use
  - Rave culture (dehydration, hyperthermia, etc)
  - Conflicting data
- Few rodent studies with mixed results
- Humans
  - LDS study
  - ? cognitive impairment/memory loss
  - Increased impulsivity (correlation?)

PTSD: MDMA-Assisted Psychotherapy

2017: FDA designated with breakthrough therapy designation
2020: Expanded access for clinical trials approved
Several phase III trials published with others ongoing
- USA, Canada and Israel
- Results generally favorable compared to placebo
- Few negative outcomes from MDMA compared to placebo

Proposed Mechanism
- Reduction in connectivity between amygdala and insula
- Dopamine reinforced empathy for themselves

Submitted for approval to FDA December 2023
- Who can administer?
- Off label use?
- DEA rescheduling?
- Cost?

Ongoing studies for
- SUD
- Anxiety
- Eating Disorders

MAPS
MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES

Mitchell JM, Ot'alora GM et al 2023

Psilocybin

- Psilocybin (4-phospho-N, N-dimethylamine) is a toxic alkaloid produced by hundreds of mushroom species, most notably those in the *Psilocybe* genus
- Most common route is oral ingestion of fresh or dried fruiting bodies of mushrooms
  - Sometimes cut into small pieces, brewed into tea, and/or ingested with food to offset taste
  - Variable amount of psilocybin, some species contain 1% psilocybin by weight or higher
- Can lead to co-ingestion of other toxic compounds such as muscarine, baeocystin, or aeruginascin

Hillebrand 2006
Patocka 2021
Image credit in references

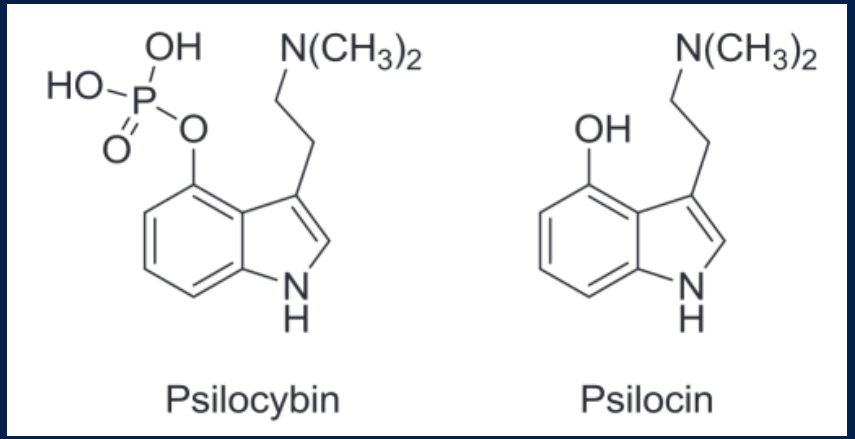
Psilocybin – History and Context

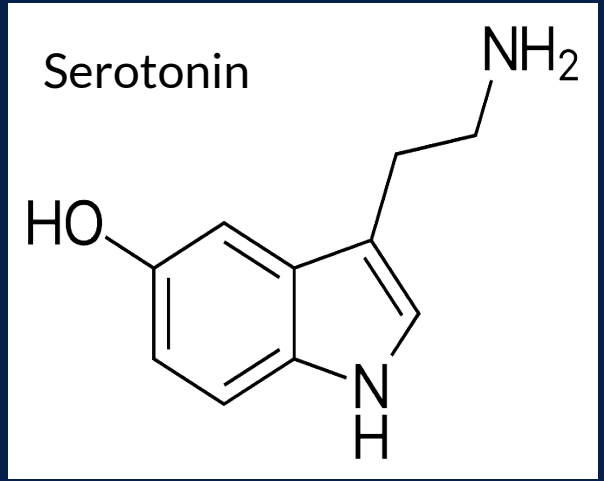
- Hallucinogenic mushrooms used in cultural and religious ceremonies for thousands of years
- First extracted and reported 1958
- US: psilocybin first banned in 1968, Schedule I controlled substance in 1970
- First human subject trials with psilocybin 1950s and 1960s,
  - Decreased after Schedule I classification
  - In 2000s clinical trials with psilocybin re-emerge

Carhart-Harris 2017
Sharma 2023

Psilocybin – Pharmacology

- Rapidly dephosphorylated to active form: psilocin
- Partial agonist at the serotonin 5-HT_{2A} receptor
- Shows agonist activity at other serotonin receptors*
- Degraded in liver by monoamine oxidase and/or aldehyde dehydrogenase, similar to serotonin
- Onset of action 10-40 minutes (oral), peak effects at 60-90 minutes, usual duration 4-6 hours
- Half-life ~3 hours, <5% renal clearance
- Effect can be increased by MAOIs and other serotonin-modulating drugs, theoretically may also be affected by UGT inducers/inhibitors





*includes 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2B}, 5-HT_{5A}, and 5-HT_7

Wojtas 2024
Brown 2017
Nichols 2020
Hasler 2004

Psilocybin – Effects and Toxicity

- Intense hallucinatory experiences (characterized as a dream-like state), visual effects, altered perception of space and time, intense mood changes, and other effects (auditory, gustatory, tactile, etc)
- Low doses (3-5mg): subjective sympathomimetic effects
- Higher doses (8-25mg): more prominent hallucinogenic effect
- Relatively low lethality with LD50 ~280mg/kg
- Acute intoxication: lethargy, anxiety/agitation, altered sensorium, acute psychosis, and sympathomimetic symptoms (mydriasis, tachycardia, hypertension)
  - minimal ongoing effects after clearance
- Effects can be reduced with risperidone (mixed 5-$HT_{2A/C}$ antagonist and D2 antagonist) or ketanserin (5-$HT_{2A/C}$ receptor antagonist, not available in US)

Sharma 2023
Gable 2004

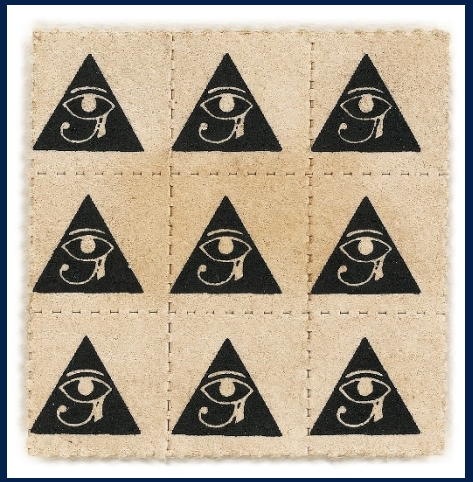
Psilocybin Microdosing

- Not well-defined
  - Some use to mean a dose that is 1% of the pharmacologically active dose
  - Others use to mean sub-hallucinogenic doses
- Purported benefits include: improvements in mood, creativity, memory, focus, and general well-being
  - Very little scientific evidence to support this
- Numerous online resources provide regimens which vary in dosing, timing, route of administration, and claimed benefits
  - Taking doses every 3 days relatively common, many other approaches exist
- Observational studies have **not shown high prevalence of adverse effects**, but currently **no well-accepted "safe" regimen** or amount of use

Polito 2019
Sharma 2023

LSD

- LSD (lysergic acid diethylamide) is a semisynthetic derivative of lysergic acid, a compound produced by the rye fungus *Claviceps purpurea*
- Categorized as a tryptamine, shares properties with other substituted tryptamines (25I-NBOMe, 2C-I, many others)
- Generally ingested orally or sublingually
- Schedule I controlled substance
- Often distributed on “blotter paper”



Passie 2008, image available in public domain via Wikimedia Foundation

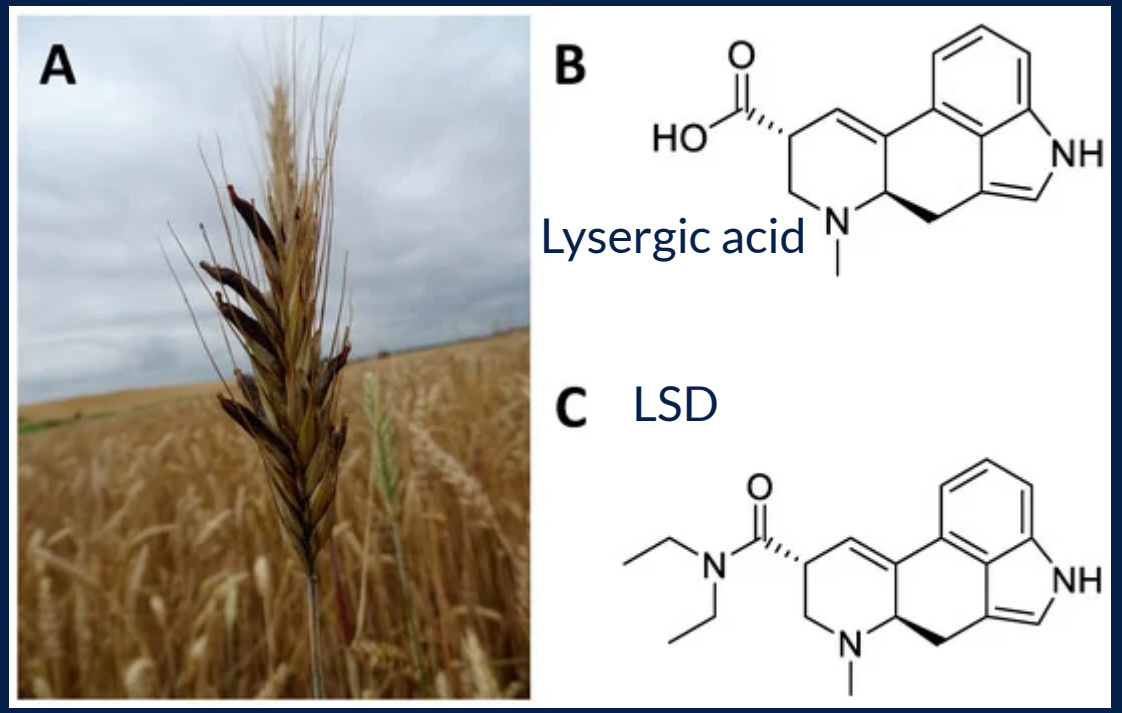
LSD – History and Context

- First synthesized in 1938, hallucinogenic effect discovered in 1943
- Studied extensively from 1940s-1960s as a tool in psychiatry
  - Studied for treatment of schizophrenia, anxiety, depression, and pain
- Recreational use popularized in 1960s
- In 1970, LSD was categorized as a Schedule I controlled substance
  - Subsequent decrease in research
- Recent resurgence in LSD research, particularly in Europe
- Categorized as an indolealkylamine

Nichols 2018
Passie 2008

LSD – Pharmacology

- Strong agonist at 5-HT_{1A}, partial agonist at 5-HT_{2A}, also shows non-selective affinity for numerous other serotonin receptors
- Metabolized in the liver into inactive metabolites, minimal renal clearance
- Onset of action 30-45 minutes (oral), peak effects at 1-2.5 hours, duration of action 9-12 hours
- Half life ~3 hours



Passie 2008
Nichols 2018
Mastinu 2023; image adapted from Mastinu 2023

LSD – Effects and Toxicity

- Minimal effects from doses less than 25 micrograms
- Moderate doses (75-150 µg): altered state of consciousness, including euphoria, hallucinations, synesthesia, and altered cognition
  - Doses greater than 100 µg have been shown to impair tests of attention, concentration, memory, psychomotor functions, and time perception
- Overdose can be associated with psychosis, comatose state, hypertension
- Several published cases of death in overdose exist, seem to be rare
- Minimal evidence of long-term physiologic effects, though psychiatric complications (both acute and chronic) have been noted

Schlag 2022,
Passie 2008

Hallucinogen Persisting Perception Disorder (HPPD)

- Rare and poorly-understood condition linked to use of hallucinogens
- Refers to recurrence of perceptual disturbances experienced during hallucinogen use in the absence of drug **in a way that is persistent, prolonged, and distressing**
- Prevalence not well understood – some estimates as high as 4% of those who use hallucinogens, other studies suggest much more rare
- Has been reported in association with LSD, cannabis, synthetic cannabis, MDMA, PCP, psilocybin, and NPS drug use
  - Most commonly associated with LSD and PCP
- Risk factors and dose dependence not well established

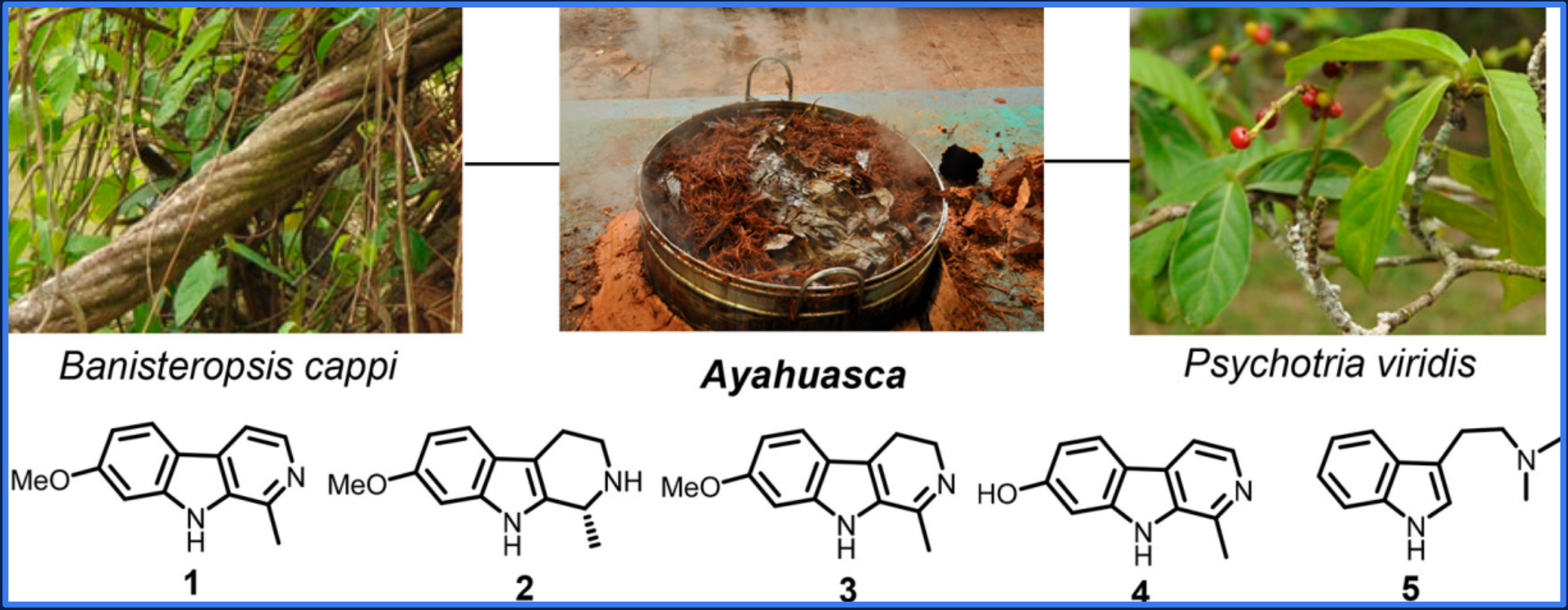
Martinotti 2018
Schlag 2022

Ayahuasca

- Hallucinogenic herbal preparation
  - Used by indigenous Amazonian tribes in religious ceremonies and as a healing tool
- Typical mixture
  - *Psychotria viridis* **leaves**
    - N,N-dimethyltryptamine (DMT)
  - *Banisteriopsis caapi* **stem/bark**
    - Harmaline alkaloids (β-carboline alkaloids)

Brent et al., 2017; Images from National Tropical Botanical Garden

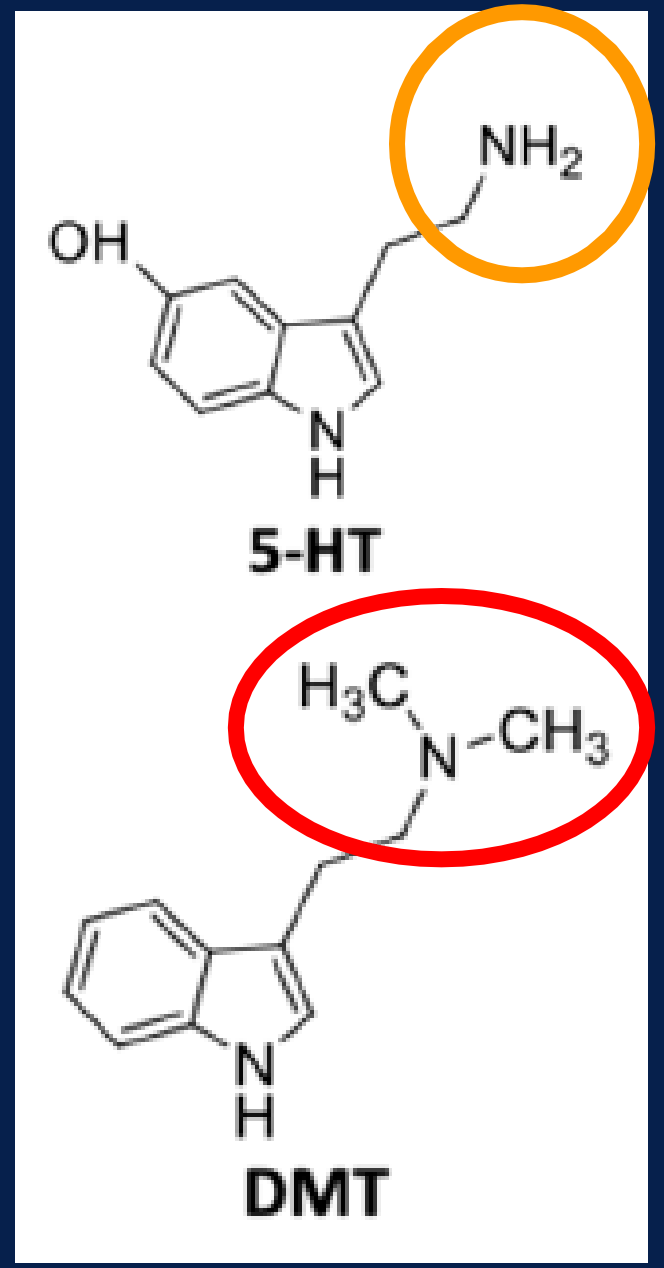
Ayahuasca: prepared from *B. caapi* + *P. viridis*



Rodriguez, et al. 2022

N,N dimethyltryptamine (DMT)

- Potent, short-acting tryptamine/hallucinogen
  - Agonist
    - 5-HT2A, 5HT2C, 5HT1A
    - σ-1
    - TAAR1
- Rapid/overwhelming action, regardless of route
  - Onset: 15 sec
  - Peak: 5 min
  - Duration: <1 hour



Brito-da-Costa, et al. 2020

N,N dimethyltryptamine (DMT)

- Metabolism:
  - Primarily via MAO-A
    - Oral administration
      - → rapid metabolism by intestinal MAO-A enzymes
- Major urinary metabolites
  - 3-IAA and 3 indole-aceturic acid
    - DMT-NO and NMT predominate when given with MAOI

Brito-da-Costa, et al. 2020

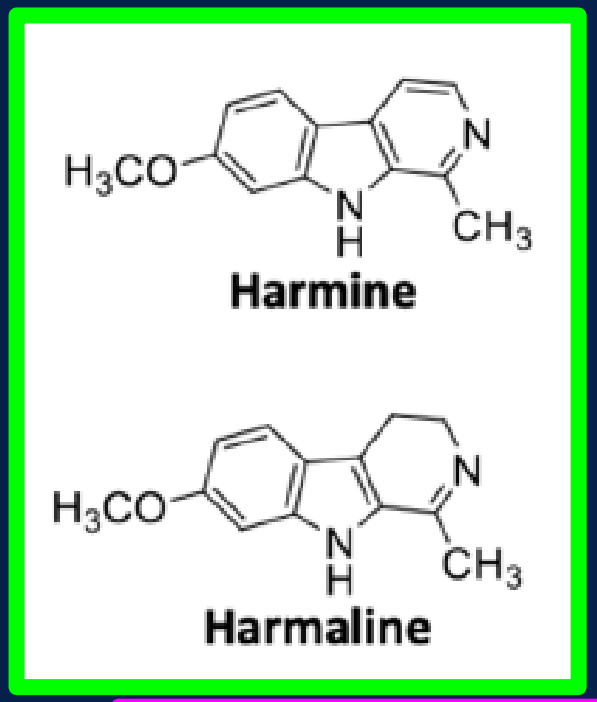
DMT metabolism

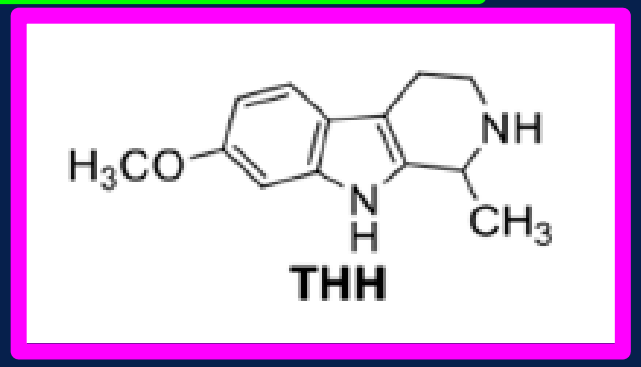
- DMT alone
  - Half-life: 5-17 min
    - Oral:
      - 3-IAA (97%)
      - DMT-NO (3%)
    - Smoked:
      - 3-IAA (63%)
      - DMT-NO (28%)
      - DMT (10%)

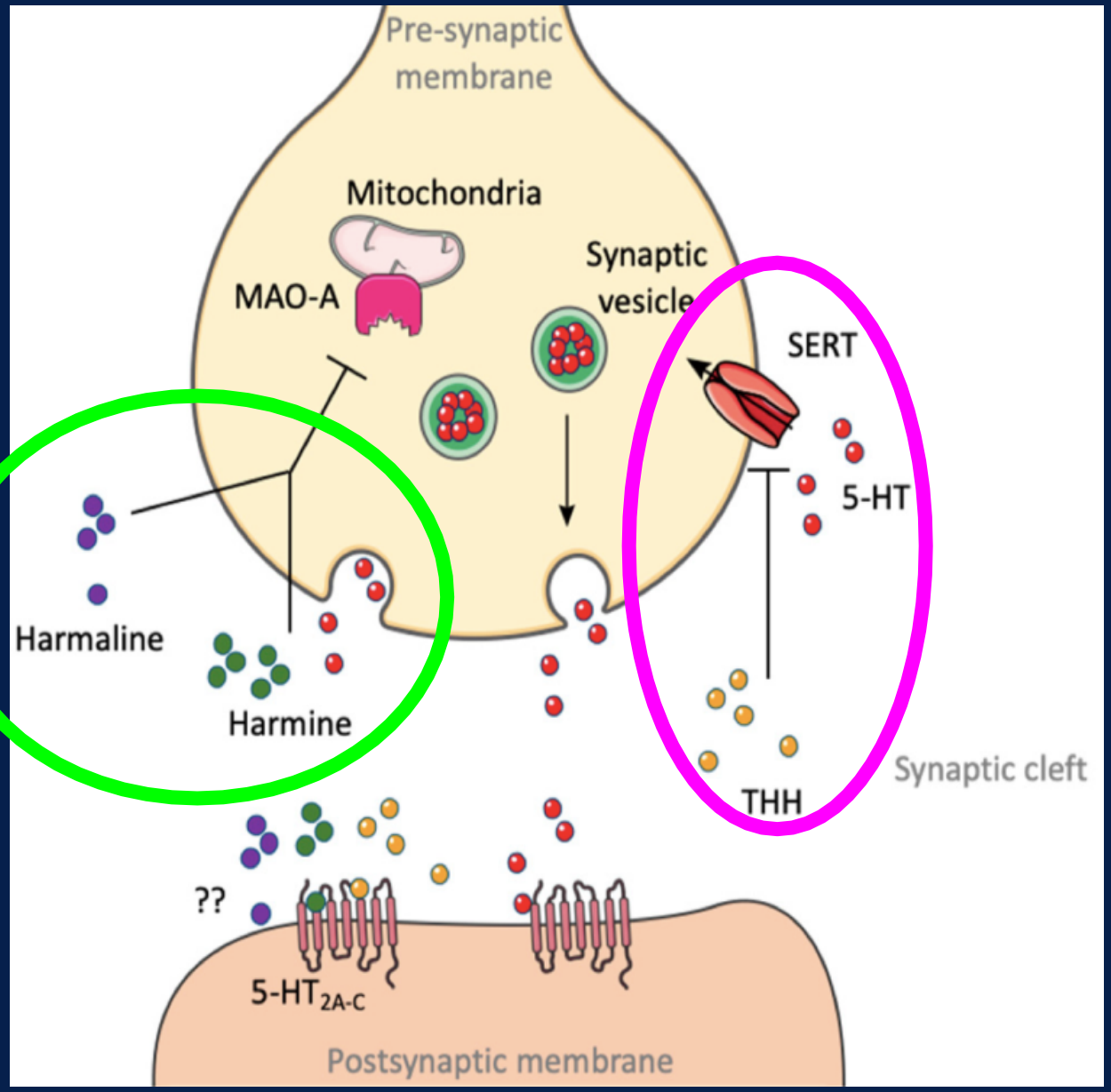
- Ayahuasca
  - Half-life: 1-4 hours
  - Recovery in urine:
    - 3-IAA (50%)
    - DMT-NO (10%)
    - DMT (1%)
    - 2-MTHBC + NMT (0.2%)

Brito-da-Costa, et al. 2020

β-carboline alkaloids







Brito-da-Costa, et al. 2020

Toxicity

- DMT → serotonergic toxicity (systemic neuroexcitation)
  - Psychosis
    - Higher doses → hallucinations more predominant

- Harmaline alkaloids
  - Weak serotonergic effects
  - Potentiate/prolong DMT effects, particularly when taken orally
  - Amplify and prolong effects of other serotonergic xenobiotics

Hamil, et al. 2019; Brito-da-Costa, et al. 2020;
Barbaric, et al. 2020

Testing

- How to confirm ayahuasca exposure?
  - DMT
    - Short half-life
    - Cross reacts with amphetamine urine immunoassay
    - LC/MS/MS or GC/MS necessary for detection
  - Harmala alkaloids
    - More sensitive and specific, generally better approach
    - Harmine, harmaline, and THH
    - LC/MS/MS or GC/MS necessary for detection

Brito-da-Costa, et al. 2020

Ayahuasca

- **Present day use**
  - Ayahuasca tourism
    - → Foreign travel to participate in indigenous ceremonial rituals
  - Headshops
  - Illegal in US, Canada, Netherlands, and France

- **Clinical effects**
  - DMT
    - Absence of hallucinogen cross tolerance, unique to DMT
    - Sigma-1 agonist → antidepressant effects
  - Harmine: antidepressant effects via MAOI

Hamil, et al. 2019; Brito-da-Costa, et al. 2020

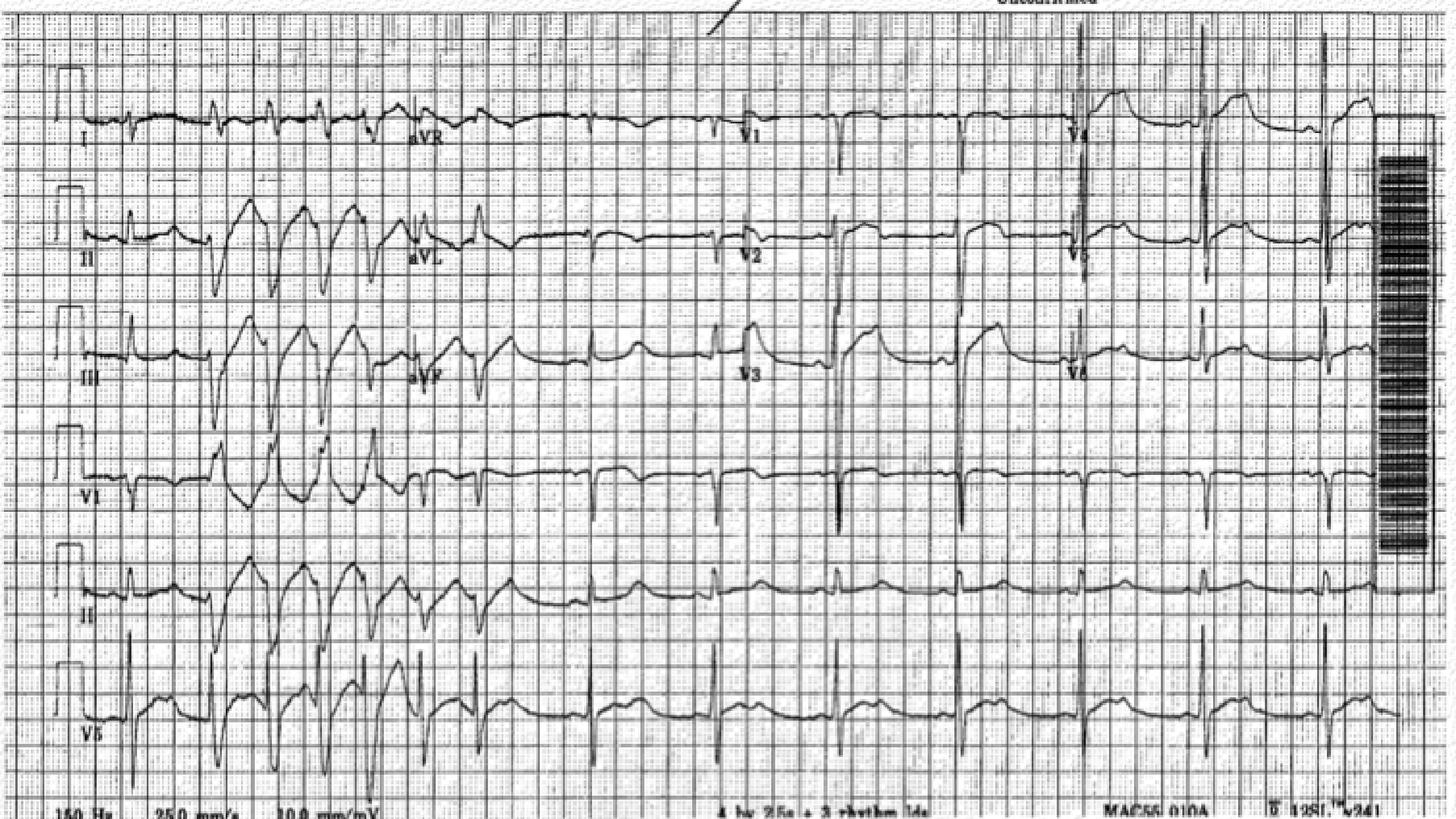
N,N dimethyltryptamine (DMT)

- Metabolism:
  - Primarily via MAO-A
    - Oral administration
      - → rapid metabolism by intestinal MAO-A enzymes

- Major urinary metabolites
  - 3-IAA and 3 indole-aceturic acid
    - DMT-NO and NMT predominate when given with MAOI

21 year with Marfan Syndrome Presents to the Emergency Department

- Ingests an herbal substance 1 hour prior to arrival
- Ingests more in the emergency department
- Ingests to treat his psychiatric issues
- Wanted to be monitored


I
II
III
V1
V5
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aVL
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V2
V3
V4
V6
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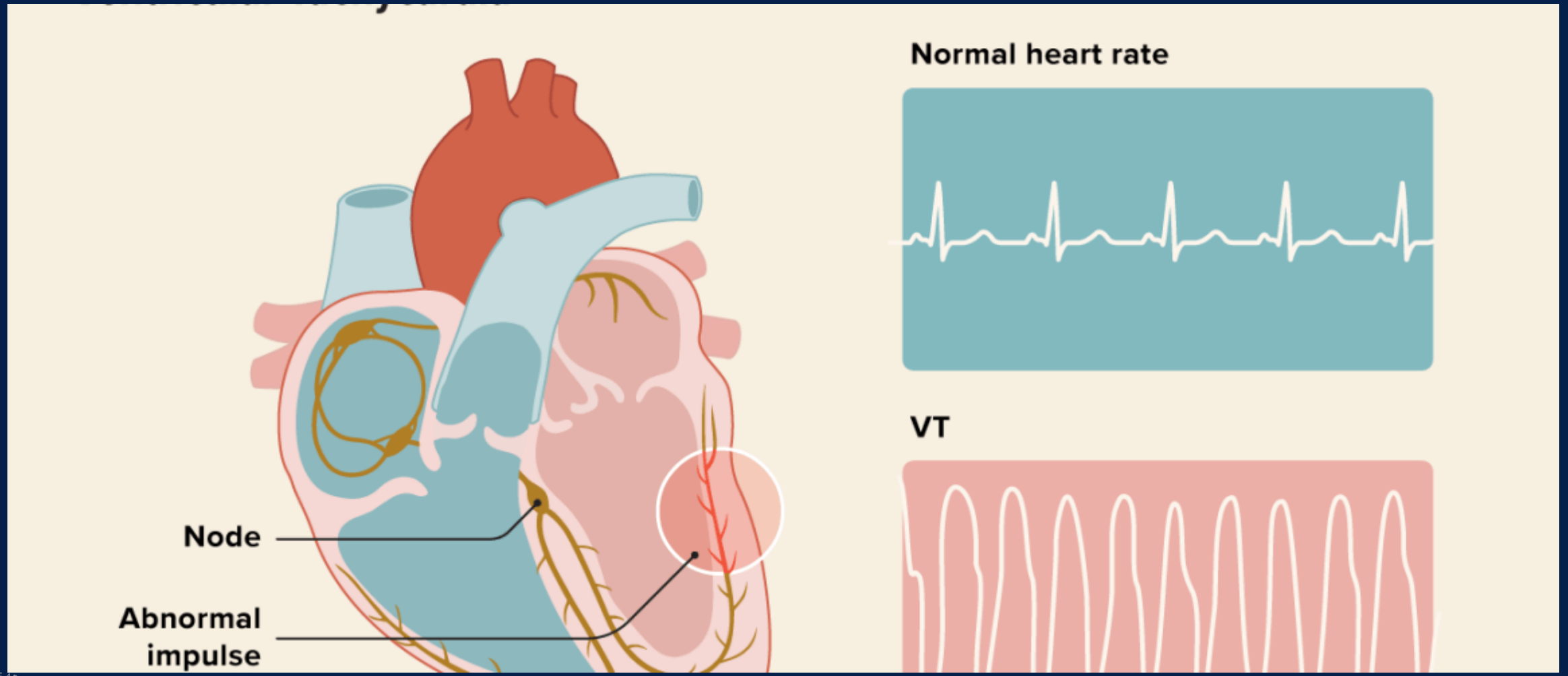
10.0 mm/mV
4 hr 25s + 3 rhythm 1ds
MAC55 0104
S 1251 V241

Case Conclusion



He keeps going in and out of v-tach

ADDICTION & RECOVERY

WHAT IS IBOGAINE?

nature medicine

Article

https://doi.org/10.1038/s41591-023-02705-w

Magnesium–ibogaine therapy in veterans with traumatic brain injuries

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Published online: 05 January 2024

Check for updates

Kirsten N. Cherian[1,8], Jackob N. Keynan[1,8], Lauren Anker[1], Afik Faerman[1], Randi E. Brown[2], Ahmed Shamma[1], Or Keynan[1], John P. Coetzee[1,3], Jean-Marie Batail[1], Angela Phillips[1], Nicholas J. Bassano[1], Gregory L. Sahlem[1], Jose Inzunza[4], Trevor Millar[4], Jonathan Dickinson[4], C. E. Rolle[1], Jennifer Keller[1], Maheen Adamson[5,6], Ian H. Kratter[1,9] & Nolan R. Williams[1,7,9]

Traumatic brain injury (TBI) is a leading cause of disability. Sequelae can include functional impairments and psychiatric syndromes such as post-traumatic stress disorder (PTSD), depression and anxiety. Special Operations Forces (SOF) veterans (SOVs) may be at an elevated risk for these complications, leading some to seek underexplored treatment alternatives such as the oneirogen ibogaine, a plant-derived compound known to interact with multiple neurotransmitter systems that has been studied primarily as a treatment for substance use disorders. Ibogaine has been associated with instances of fatal cardiac arrhythmia, but coadministration of magnesium may mitigate this concern. In the present study, we report a prospective observational study of the Magnesium–Ibogaine: the Stanford Traumatic Injury to the CNS protocol (MISTIC), provided together with

- Cherian et al. Nat Med 2004. https://doi.org/10.1038/s41591-023-02705-w
- https://med.stanford.edu/news/all-news/2024/01/ibogaine-ptsd.html#:~:text=and%20depression%20Story-,Psychoactive%20drug%20ibogaine%20effectively%20treats%20traumatic%20brain%20injury%20in%20special,veterans%20with%20traumatic%20brain%20injuries.

I Tried Ibogaine, the Psychedelic Anti-Addiction Drug

Supporters claim the powerfully hallucinogenic tree-bark derivative can break the cycle of addiction and eliminate withdrawal.

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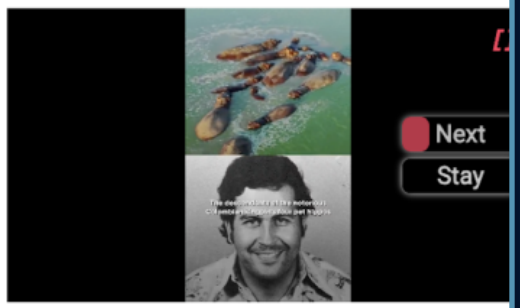
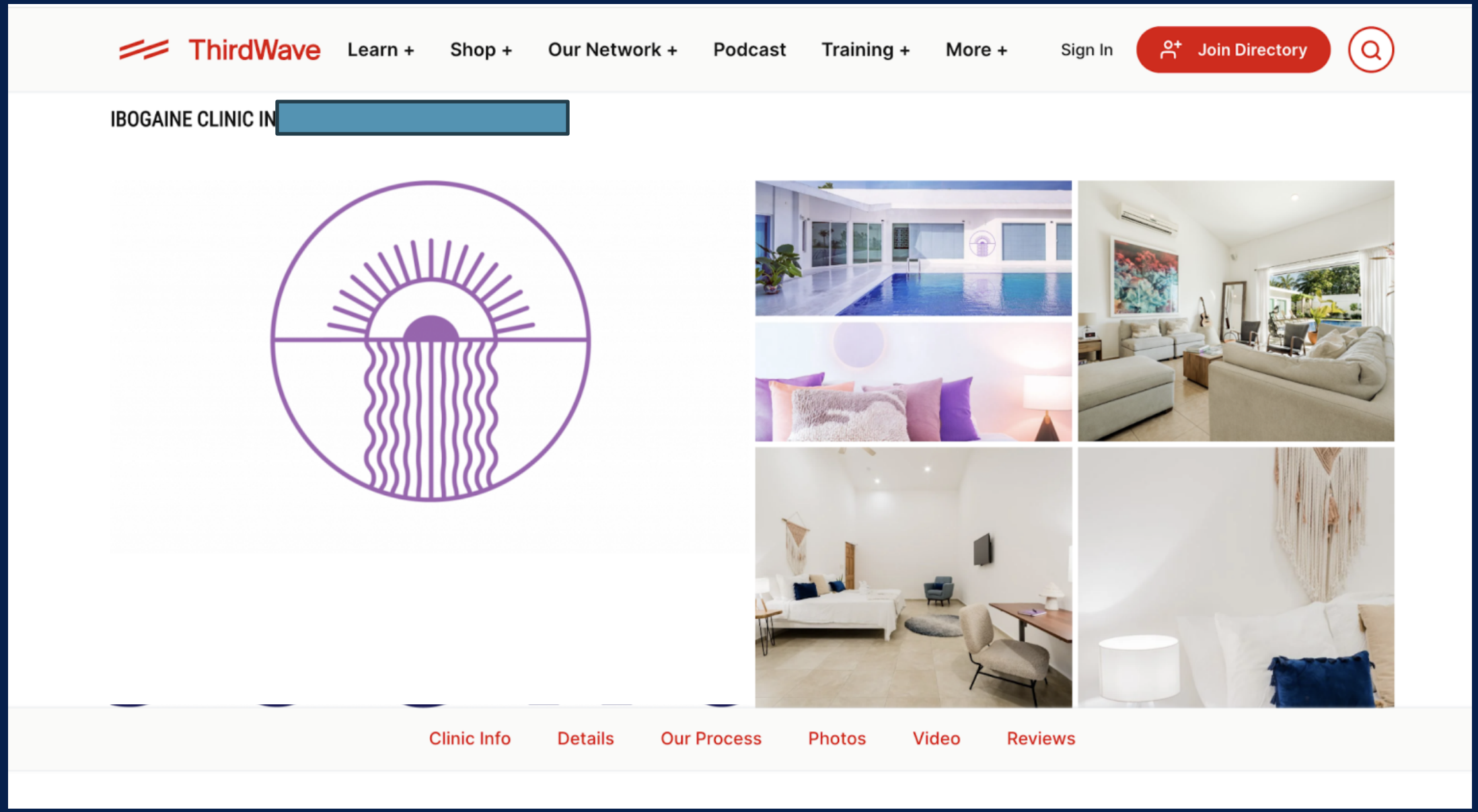
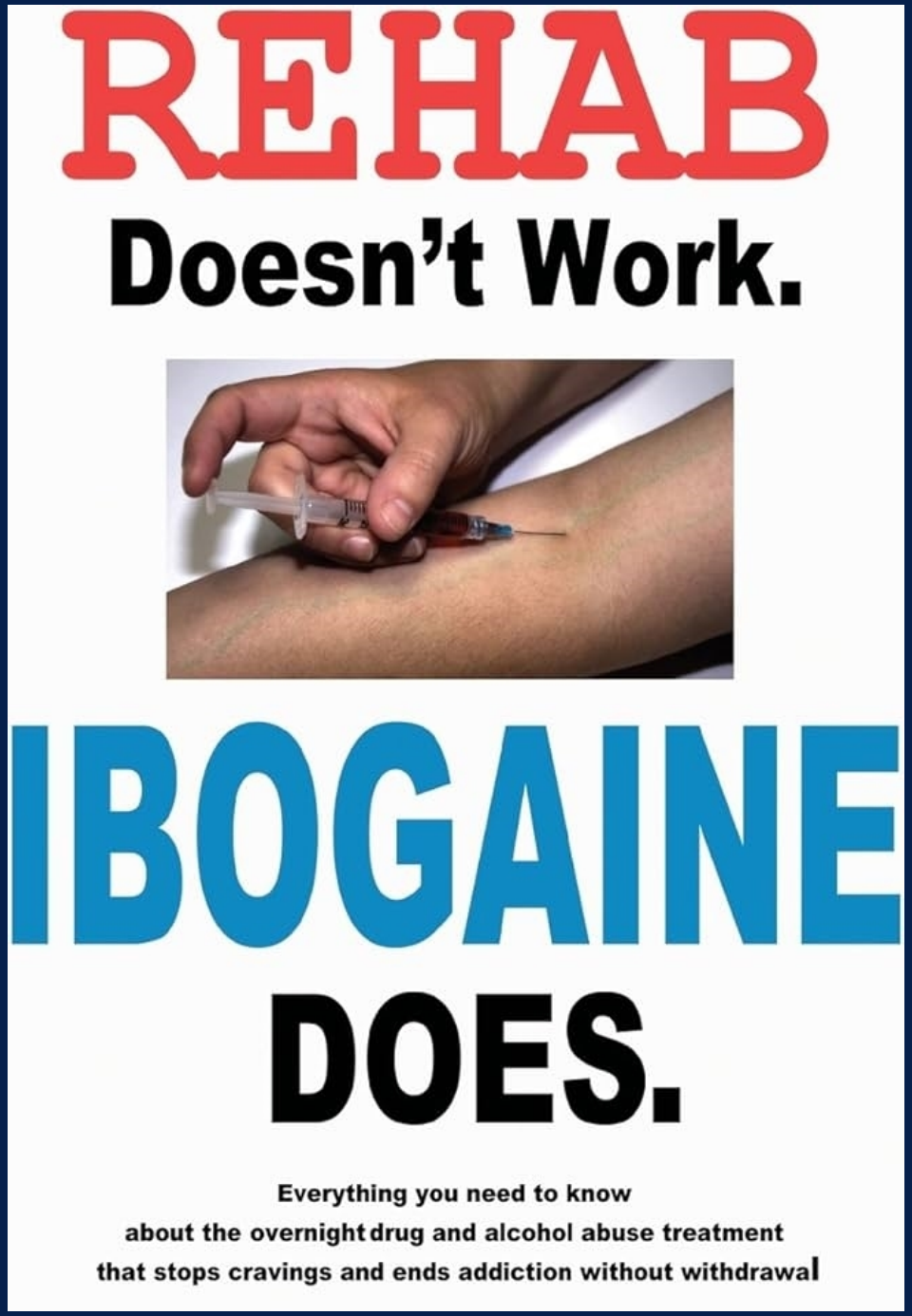


https://www.vice.com/en/article/3addj9/i-tried-ibogaine-drug-addiction-treatment



https://thethirdwave.co/directory/clinics/ibogaine/quintana-roo/beond/

Rehab doesn't work. Ibogaine does. The broken promise of traditional rehab fails millions of alcoholics and addicts every year. Sadly, most of them don't even know that there is a natural medicine called ibogaine that ends addiction - without withdrawal - and then eliminates the cravings for drink or drugs that guarantee relapse. One ibogaine treatment accomplishes overnight what no rehab has ever been able to do. It's not easy, however.
In America, the land of The War on Drugs, ibogaine is illegal.

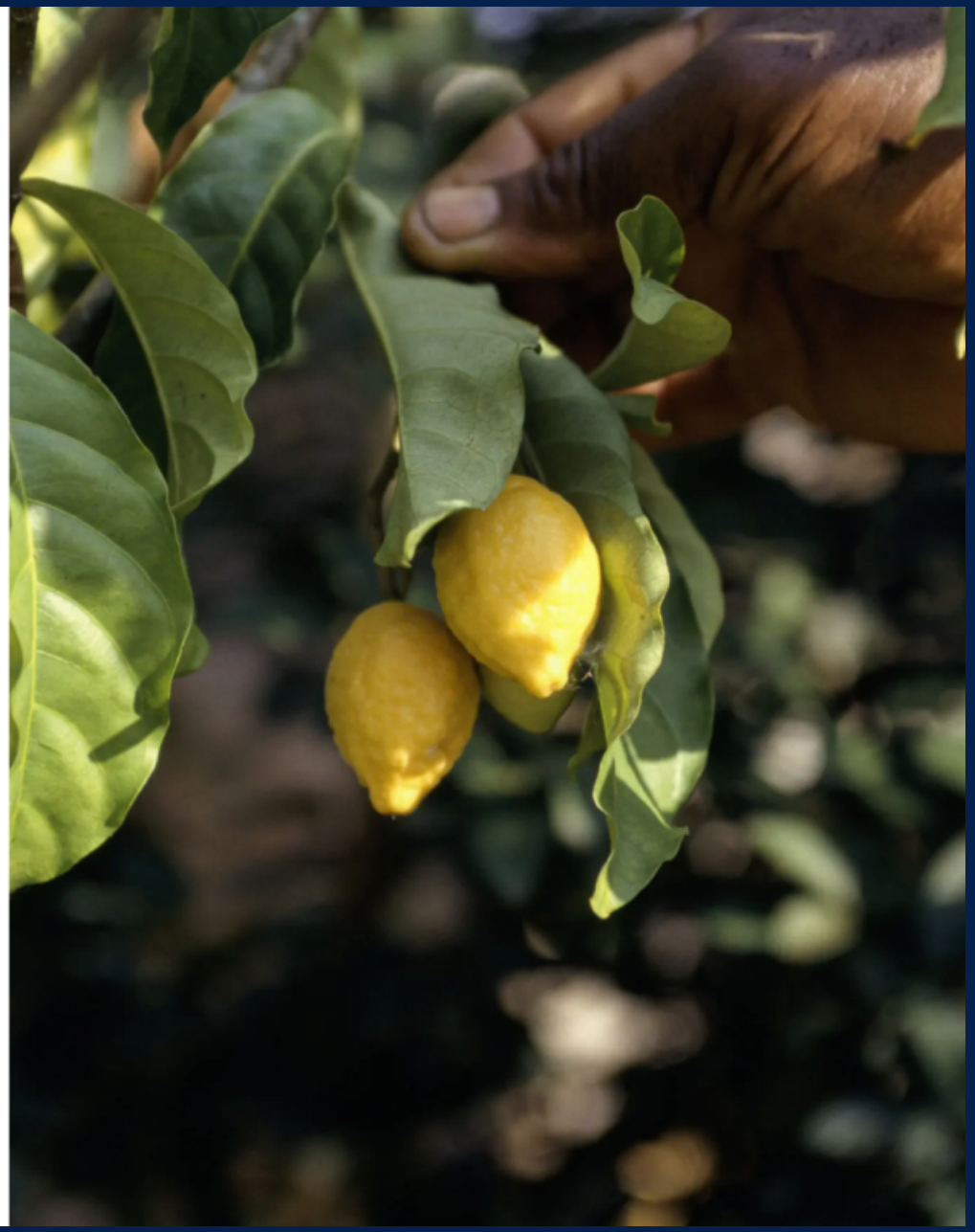


The New York Times

Account

Powerful Psychedelic Gains Renewed Attention as a Treatment for Opioid Addiction

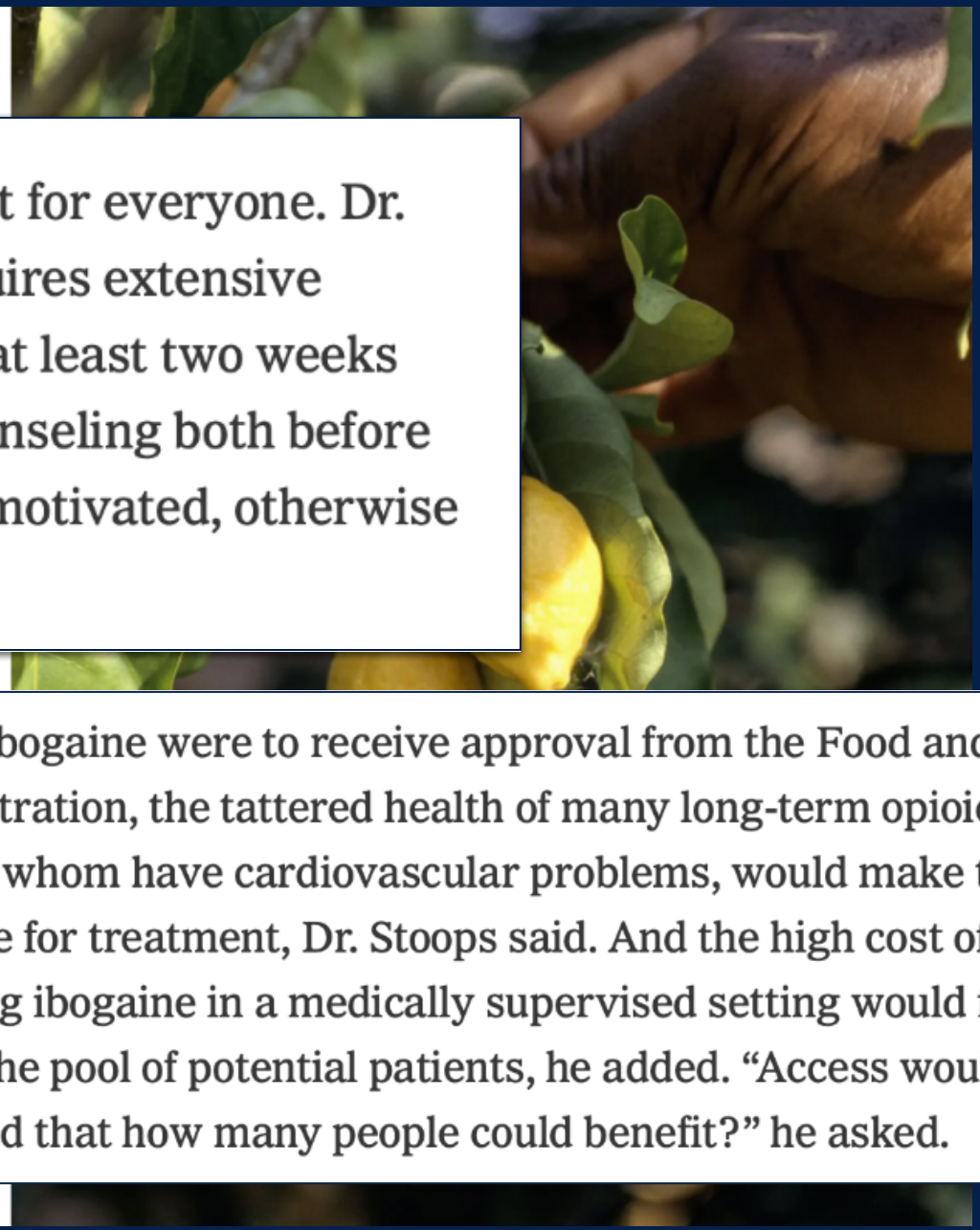
New research is stirring interest in ibogaine, which appears to help ease the agony of detox and prevent relapse. Used in other countries, it remains illegal in the U.S.



https://www.nytimes.com/2024/03/05/health/ibogaine-psychedelic-opioid-addiction.html

The New York Times

Account



Practitioners warn that ibogaine therapy is not for everyone. Dr. Rasmussen's clinic in Brazil, for example, requires extensive preparation, including abstaining from drugs at least two weeks before the treatment and several weeks of counseling both before and after. "It's hard work, and you have to be motivated, otherwise you won't experience the benefits," he said.

Addiction

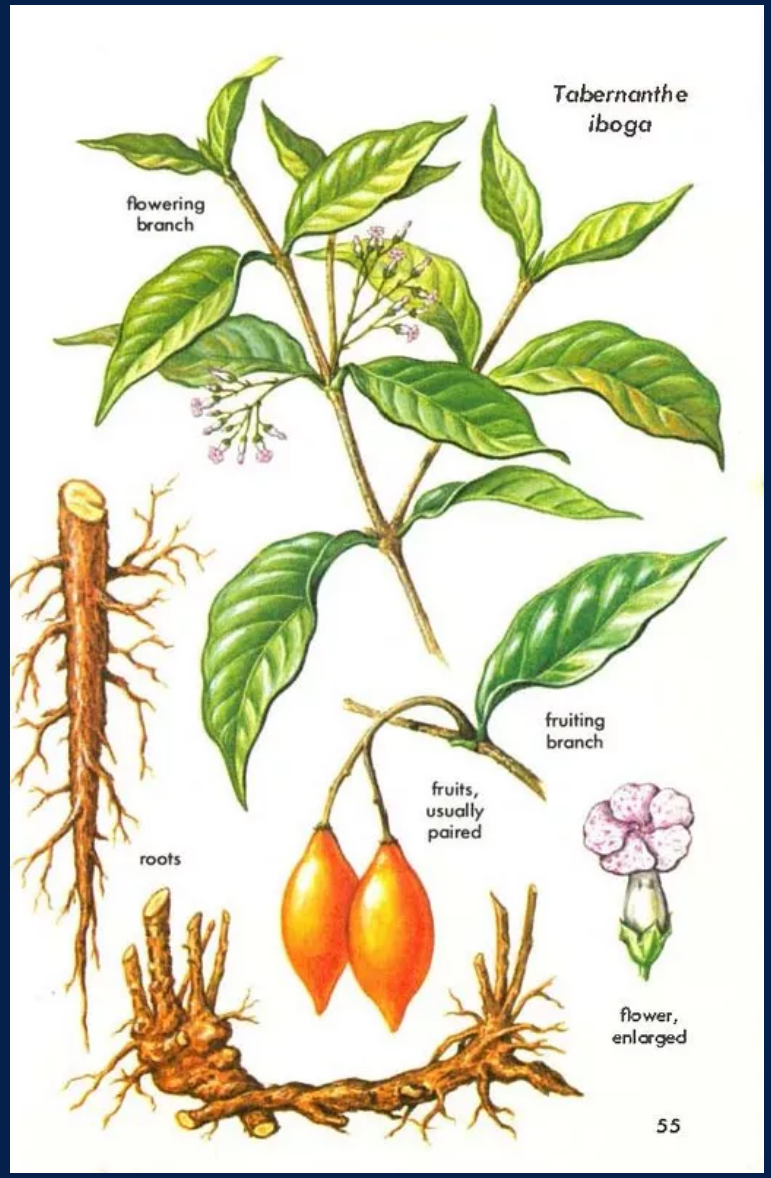
New research is stirring interest in ibogaine, v
to help ease the agony of detox and prevent re
other countries, it remains illegal in th

Even if ibogaine were to receive approval from the Food and Drug Administration, the tattered health of many long-term opioid users, many of whom have cardiovascular problems, would make them ineligible for treatment, Dr. Stoops said. And the high cost of providing ibogaine in a medically supervised setting would further reduce the pool of potential patients, he added. "Access would be so restricted that how many people could benefit?" he asked.

https://www.nytimes.com/2024/03/05/health/ibogaine-psychedelic-opioid-addiction.html

- Plant native to central Africa
- Serotonin receptor inhibition
- Blocks the hERG receptor
- Is part of religious use in Zaire

- First marketed as a pharmaceutical in France
- In the 1960s people with OUD identified it as a treatment for withdrawal



https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2018.00529/full

Pathophysiology

100 Years of Ibogaine: Neurochemical and Pharmacological Actions of a Putative Anti-addictive Drug

PIOTR POPIK*, RICHARD T. LAYER, AND PHIL SKOLNICK

Popik P, et al. 1995

Available online at www.sciencedirect.com

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Journal of ETHNO-PHARMACOLOGY

www.elsevier.com/locate/jethpharm

The ibogaine medical subculture

Kenneth R. Alper[a,b,*], Howard S. Lotsof[c], Charles D. Kaplan[d]

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Treatment of Acute Opioid Withdrawal with Ibogaine

Kenneth R. Alper, M.D., Howard S. Lotsof,
Geerte M. N. Frenken, M.F.A., Daniel J. Luciano, M.D.,
Jan Bastiaans, M.D.†

TABLE 1. **Demographic and drug use characteristics of study sample**

Gender	22 (67%) male, 11 (33%) female
Mean Age	27.3 ± 4.7 years
Ethnicity	32 Caucasian, 1 Surinamese
Mean daily heroin use	.64 ± .50 grams/day
Predominant route of heroin self administration	26 intravenous, 4 intranasal, 3 smoking
Mean duration of heroin use	6.2 ± 5.8 years
Number of subjects with concurrent methadone maintenance	8 (24%)
Mean methadone dose (N = 8)	48 ± 30 milligrams
Number of subjects additional seeking treatment for concurrent cocaine use	8 (24%)
Mean daily cocaine use (N = 8)	1.4 ± 2.3 grams

TABLE 2. **Opioid detoxification with ibogaine: outcomes (N = 33)**

N	Signs of Opioid Withdrawal Post-Treatment	Drug Seeking During the 72 Hour Post-Treatment Interval
25	Fully resolved at 24 hours	−
4	Fully resolved at 24 hours	+
1	Partial resolution at 24 hours (sweating) fully resolved at 48 hours	−
1	Partial resolution at 24 and 48 hours (chills)	−
1	Multiple opioid abstinence signs	+
1	Fatality at 19 hours	?

Medical Complications

JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, March 2012, Vol. 57, No. 2
doi: 10.1111/j.1556-4029.2011.02008.x
Available online at: onlinelibrary.wiley.com

PAPER

TOXICOLOGY

Kenneth R. Alper,[1] *M.D.; Marina Stajić,*[2] *Ph.D.; and James R. Gill,*[3] *M.D.*

Fatalities Temporally Associated with the Ingestion of Ibogaine

More than

$700 million

The total amount of funding that federal agencies allocated to projects involving ibogaine or its derivative, MC-18, between 2008 and 2018.

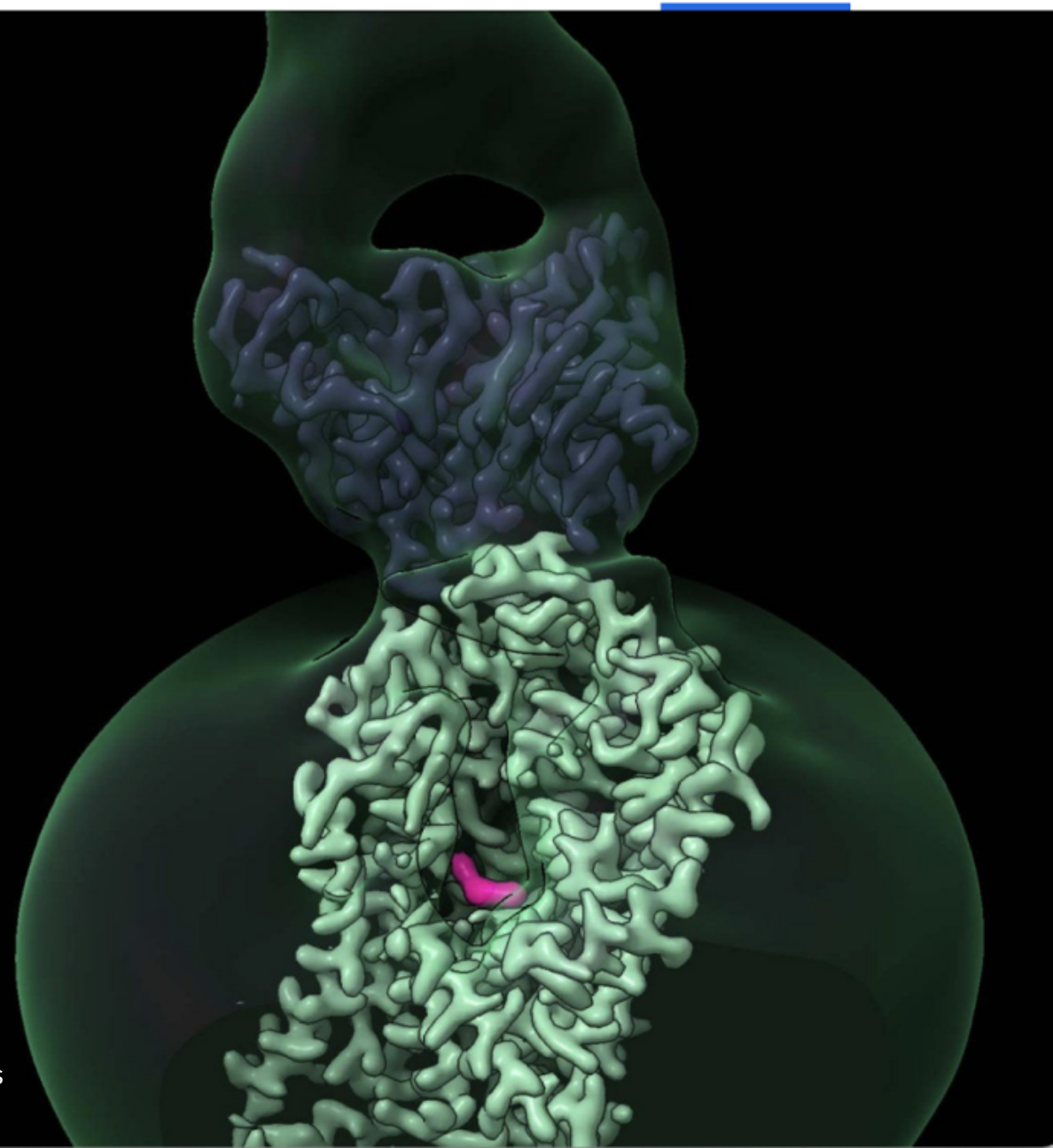
Healio

Research • May 2, 2023

Psychedelic Inspires New Treatments for Addiction and Depression

Targeted Molecules Are More Powerful Than SSRI Antidepressants and Avoid Ibogaine's Dangerous Side Effects

By Levi Gadye



https://www.ucsf.edu/news/2023/05/425246/psychedelic-inspires-new-treatments-addiction-and-depression

Final Takeaways/Summary

- Ketamine, Psilocybin, MDMA, Ibogaine, DMT are all being evaluated for potential therapeutic uses and their pharmacology and toxicities differ between the drugs
- There has been some evidence that in lower doses, side effects seem lower in ketamine, psilocybin, and MDMA
- These substances have been around for many years and current renewed interest indicates further research necessary

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