Ayahuasca and Drug Interaction: The Good, the Bad, and the Soul

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Disclosure

- Benjamin Malcolm is both an owner and employee of Spirit Pharmacist LLC. He plays an advisor role in exchange for stock in the non-publicly traded company Kaivalya Kollectiv. He functions as a psychopharmacology consultant and has existing financial relationships with several retreat center organizations. He does not own any stock or company that aims to develop pharmaceutical or supplement products.

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Ayahuasca & MAOIs - Learning Objectives

- Describe pharmacological properties of harmala alkaloids in ayahuasca
- Define adverse reactions associated with food and dietary interactions with ayahuasca such as hypertensive crisis and serotonin toxicity
- Construct management strategies to avoid adverse reactions from interacting foods and drugs
- Discuss observational, clinical, and toxicologic studies relating to ayahuasca use

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Introduction to Monoamine Oxidase Inhibitors (MAOIs)

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What's in Ayahuasca?

Plant	Main Compounds	Properties
Banisteriopsis Caapi (Ayahuasca)	β-carbolenes or harmala alkaloids • Harmine • Harmaline • Tethrahydroharmine (THH)	Inhibits Monoamine Oxidase (MAOI)*
Psychotria viridis (Chacruna) or *Diploterys cabrerana (Chaliponga)*	N-N-dimethyltryptamine (DMT)	Psychedelic

*In traditional cultures, the ayahuasca vine is thought to mediate healing effects. Harmala alkaloids have also demonstrated potential therapeutic properties for a number of psychiatric or neurologic illnesses

Callaway JC, Raymon LP, Hearn WL, et al. Journal of analytical toxicology 1996;20:492-7.

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What's in Ayahuasca?

- **Harmala alkaloids or β-carbolenes (MAOIs)**

- **Psychedelic (DMT)**

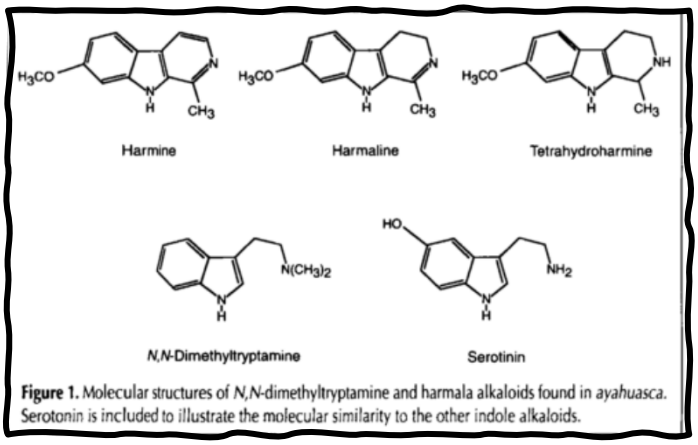

Figure 1. Molecular structures of *N,N*-dimethyltryptamine and harmala alkaloids found in *ayahuasca*. Serotonin is included to illustrate the molecular similarity to the other indole alkaloids.

Callaway JC, Raymon LP, Hearn WL, et al. Journal of analytical toxicology 1996;20:492-7.

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What is Pharmahuasca?

- Non-traditional combinations of MAOIs and psychedelic tryptamines collectively termed 'pharmahuasca'
- Psilocybin + MAOIs has not been reported to cause toxicity, although considerably intensifies effects
- MAO inhibition from ayahuasca, Syrian rue (*peganum harmala*), or pharmaceuticals (moclobemide)
- Can be used orally like ayahuasca or is sometimes combined on dried herbs and smoked (Changa)

Ott J. Journal of psychoactive drugs 1999;31:171-7. Ott J. Journal of psychoactive drugs 2001;33:273-81.

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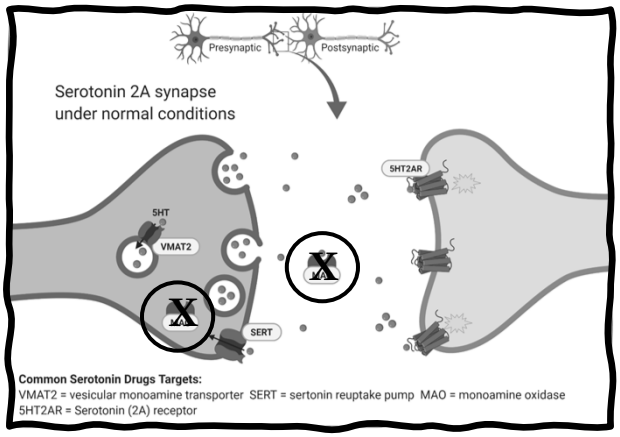
What is MAO & MAOIs?

- MAO is an enzyme responsible for degrading substances with an 'amine' group
  - Monoamine neurotransmitters
  - Dietary amines
- Drugs that inhibit MAO are termed monoamine oxidase inhibitors (MAOIs)
- Drug - drug or dietary -dietary interactions may lead to Serotonin Syndrome (SS) or Hypertensive Crisis (HC) with MAOIs, respectively



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The Role of Monoamine Oxidase (MAO)

- MAO protects the body by metabolizing dietary monoamines as well as monoamines used as neurotransmitters

Role	Metabolic Function	Location in Body
Natural defense	degrading biogenic amino acids or drugs from diet: tyramine, DMT	Small intestine, liver
Regulation of neurotransmission	degrading monoamine neurotransmitters: serotonin, norepinephrine, and dopamine	Peripheral: Blood vessel lining
		Central: Brain neurons

Riba J, et al. Drug testing and analysis 2012;4:610-6 Kalgutkar AS et al Chem Res Toxicol. 2001 Sep;14(9):1139-62.

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N-N-Dimethyltryptamine (DMT)

- Potent entheogen
  - Structurally related to serotonin
  - Commonly occurs in natural world
  - Endogenously produced
- Metabolized by Monoamine Oxidase (MAO)
- Lacks oral bioavailability when taken alone

Parameter	Smoked or Injected	Oral (Ayahuasca)
Onset	< 10 seconds	20-60 min
Peak	2-5 min	60-120 min
Duration	10-30 min	4-6 hrs
T ½	~3 min	1 hour

Comparative pharmacokinetics of DMT by ROA

Callaway JC, McKenna DJ, Grob CS, et al. Journal of ethnopharmacology 1999;65:243-56. Callaway JC, Raymon LP, Hearn WL, et al. Journal of analytical toxicology 1996;20:492-7. Strassman RJ, Qualls CR. Archives of general psychiatry 1994;51:85-97.

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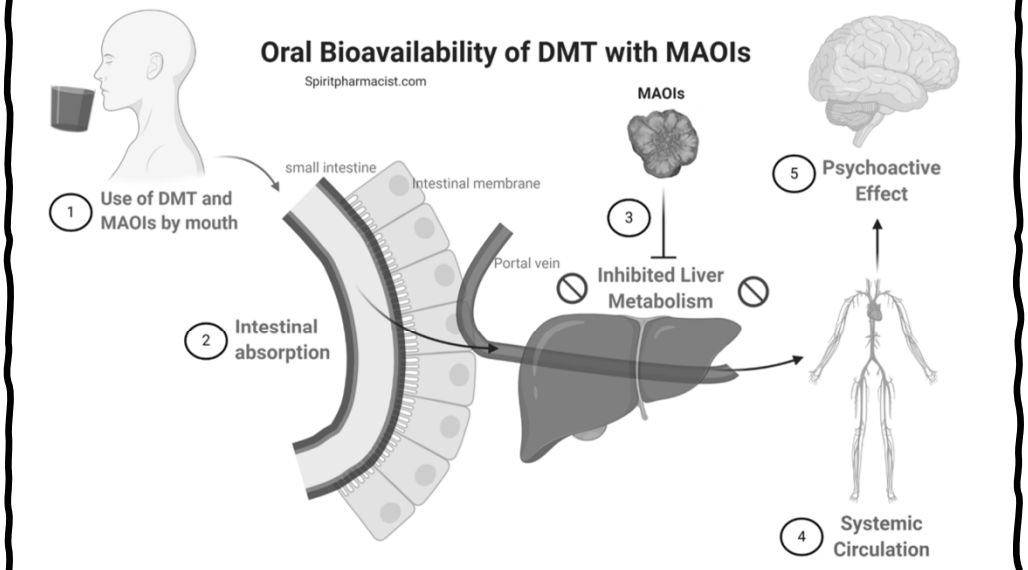

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Two Varieties of MAO: Isoenzymes A & B

MAO-A

Metabolizes: **Norepinephrine, Serotonin, Dopamine, Tyramine**

Peripheral: Liver, GI, Lungs, Vascular Endothelium

Central: Found in nerve terminals of neurons and glial cells

MAO-B

Metabolizes: Phenethylamine, **Dopamine, Tyramine**

Peripheral: Platelets, Liver

Central: Found in synapses between neurons and glial cells

Kalgutkar AS et al Chem Res Toxicol. 2001 Sep;14(9):1139-62.

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MAO Inhibition: *Ayahuasca* vs. Pharms

Reversible - Ayahuasca

- Harmala alkaloids or β-carbolines
  - Harmine, harmaline, tetrahydroharmine
- T ½ for harmala alkaloids range from 2 hours (harmine) to 11 hours (tetrahydroharmine)
- **Little effect predicted 48-72 hours after ingestion and metabolic capacity recovered**

Irreversible - Pharms

- Pharmaceutical MAO inhibitors
- Antidepressants invented in 1950's
  - Rarely used today: tranylcypromine, phenelzine, isocarboxazid
- **Requires 2 weeks for body to make new MAO and restore metabolic capacity of body**

Callaway JC, McKenna DJ, Grob CS, et al. Journal of ethnopharmacology 1999;65:243-56.

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Pharmaceutical MAOIs

Monoamine Oxidase Inhibitor	MAO-A	MAO-B	Reversible?	Notes
Phenelzine (Nardil) **Tranylcypromine (Parnate)** **Isocarboxazid (Marplan)**	X	X	No	• Non-selective & irreversible MAOIs • Highest risk of SS or HC • Must avoid 5HT drugs ≥5 half-lives prior • Must avoid 5HT drugs 2 weeks after
Selegiline (Emsam) **Rasagaline (Azilect)**	--	X	No	• Low risk of SS or HC • Selegeline inhibits MAO-A when dose is high (≥9mg/day)
Moclobemide (Amira, Aurorix, Clobemix , Depnil, Manerix)	X	--	Yes	• Reversible Inhibitor of MAO-A (RIMA) • Lower potential for SS or HC • Must avoid 5HT drugs ≥5 half-lives prior • Can restart 5HT drugs 24 hours after

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β-carboline (harmala alkaloid) MAOIs in *Banisteriopsis Caapi*

MAOI	MAO-A	MAO-B	Reversible?	Half-life (min)	Eliminated (hours)
Harmaline	X	±	Yes	--	Likely 24-72 hours
Harmine	X	±		115 ± 60	15 hours
Tetrahydroharmine (THH)	X			532 ± 291	68 hours
Harmol	X			--	--
Banistenoside A	X			--	--
Banistenoside B	X			--	--

Boxes with -- denote a lack of testing in human subjects or inability to find information
Boxes with ± denote a mild effect or effect that is questionably relevant clinically
Boxes that are blank denote lack of effect

Pathak, A., et al. Cent Nerv Syst Agents Med Chem, 2016. 16(2): p. 81-97. Samoylenko, V., et al. J Ethnopharmacol, 2010. 127(2): p. 357-67. Callaway, J.C., et al. J Ethnopharmacol, 1999. 65(3): p. 243-56.

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Which of the following is true about harmala alkaloid inhibition of MAO?

A) Harmalas strongly inhibit both MAO-A and MAO-B
B) Harmalas are irreversible inhibitors of MAO-A
C) Harmalas are reversible inhibitors of MAO-A
D) Harmalas do not affect liver enzymes CYP2D6 or CYP3A4

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Serotonin Syndrome & Hypertensive Crisis

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Toxicity with MAO-A inhibitor interactions: SS & HC

Serotonin Syndrome (SS)	**Hypertensive Crisis (HC)**
• Results from excessive serotonin signaling in synapse • Classically caused by combining MAO-A inhibitors with drugs that block 5HT reuptake (SSRIs + others) or drugs that release 5HT (MDMA + others)	• Results from inability to degrade tyramine or excessive NE & DA signaling • Caused by combining MAO-A inhibitors with dietary tyramine or drugs that release NE or DA (methamphetamine, *d*-amphetamine)

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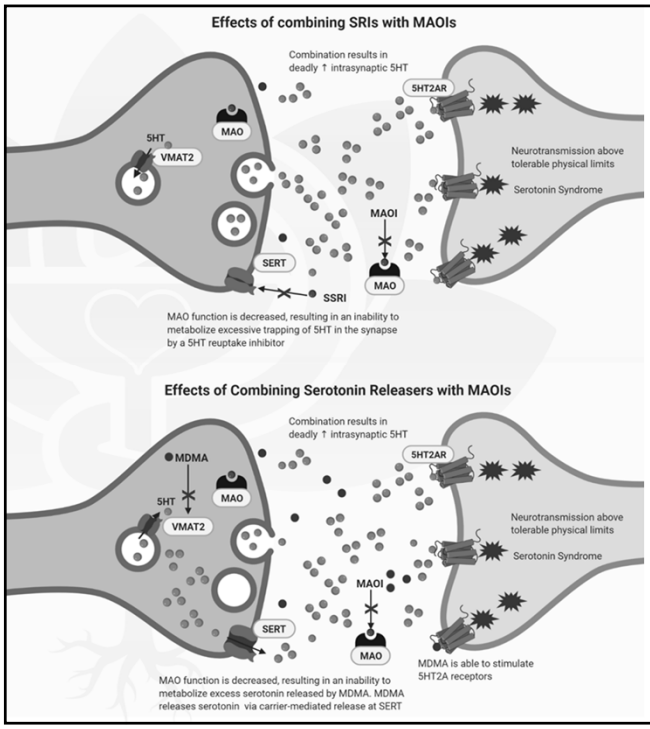

Classic Mechanisms of Serotonin Syndrome with MAOIs

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Serotonin Syndrome (SS)

- Signs & Symptoms (at least 3)
  - Agitation
  - Diaphoresis (sweating)
  - Tremor
  - Diarrhea
  - Hyperreflexia
  - Autonomic instability
  - Rigidity
  - Myoclonus
  - Hyperthermia

Red denotes 'hallmark' signs of SS

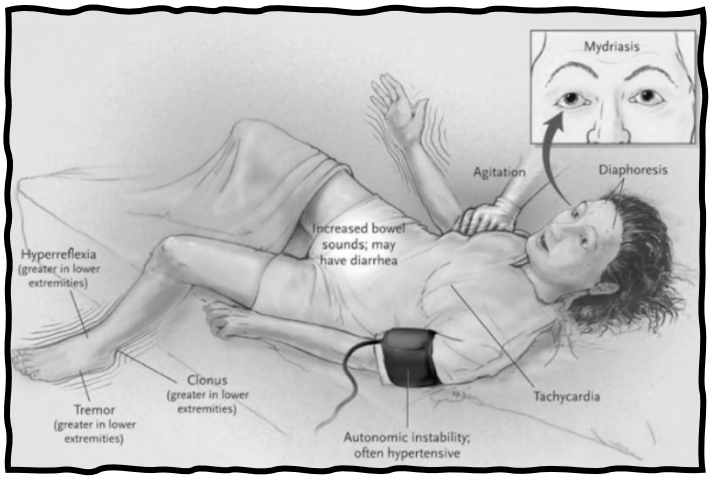

Figure from Boyer, E. W. and M. Shannon (2005). 352(11): 1112-1120.

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Spectrum of Serotonin Toxicity

Severity*	Mild	Moderate	Severe (Serotonin Syndrome)
Signs & Symptoms	↑ blood pressure (Hypertension) ↑ Heart rate (Tachycardia) Pupil dilation (Mydriasis) Twitchy nerves, shaky (Hyperreflexia) Afebrile or low fever (<38.5C or 101.3F) Anxiety & restlessness	**Seizure-like activity (Myoclonus)** **Fever (38.5-40C or 101.3-104F)** Hyperactive bowels Agitation	**Fluctuating or unstable blood pressure and heart rate** **Fever (>40C or 104F)** **Delirium or coma** **Muscle rigidity**
Management	Watchful waiting and supportive measures	**Activate emergency response system (911) and/or report to hospital for any bolded symptom**	
	Consider cooling if any fever	Cooling (colder environment, ice packs) Benzodiazepines (IM preferable) Hospital treatments (mechanical ventilation, advanced support, dantrolene)	
Likely causes	Psychedelics at moderate or high doses Combinations of serotonergic medications that are not MAOIs	Psychedelic or antidepressant overdose Combination of psychedelics or serotonergic medication that contain MAOIs	

*Categories of serotonin toxicity represented in this chart are not medically recognized diagnostic categories.

Sternbach, H. (1991). Am J Psychiatry, 1991. 148(6): p. 705-13.
Gillman, P. K. (2005). Br J Anaesth 95(4): 434-441.
Dunkley, E.J.C., et al (2003). QJM: An International Journal of Medicine. 96(9): p. 635-642.
Uddin, M.F., et al., (2017) J Clin Diagn Res, 2017. 11(9): p. Oe05-oe07
Wang, R. Z., et al. (2016). Cleve Clin J Med 83(11): 810-817.

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Which of the following is/are red flags for serotonin toxicity when using psychedelics? (select all that apply)

A) Fever > 101F
B) Spontaneous myoclonus
C) Physical effects that outlast expected psychological effects
D) Dilated pupils
E) Hallucination

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Toxicity or Healing?

Serotonin Toxicity	Psychedelic Somatic Response
• Spontaneous clonus -cannot stop • Fever >101F • Muscle rigidity • Unstable blood pressure and heart rates • Agitation • Serotonin effects that are prolonged compared to duration of psychedelic experience	• Mild hyperreflexia - controllable shaking • Transient somatic sensations or purging: nausea, diarrhea, vomiting, sweating • Serotonin effects peak with experience and decrease as experience ends

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Tyramine-mediated Hypertensive Crisis (HC)

- HC aka 'Cheese Reaction' caused by inability to breakdown tyramine
  - Tyramine found in fermented foods
  - Low tyramine diet required when using pharmaceutical MAO-A inhibitors (MAOIs)
- Risk of reaction is proportional to amounts of tyramine ingested
- Symptoms of reaction
  - Thumping and forceful heartbeat, slowed heart rate, pale complexion (pallor), rapid onset severe headache, chest tightness

Cooper AJ. Br J Psychiatry Suppl. 1989 Oct;(6):38-45.

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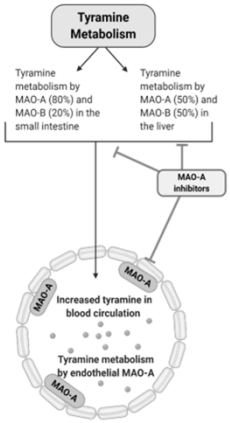
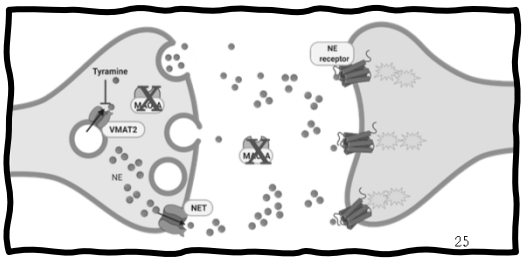
MAOIs & HC: Cheese Reaction

- Tyramine ingestion when MAO-A is inhibited causes NE to leak in blood vessel linings resulting in vasoconstriction, very high blood pressures, and risk of stroke or brain hemorrhage





Moussa B et al. Nature Reviews Neuroscience 7, 295-309 (April 2006). Fig 5

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Food Interactions

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How Do You Avoid Ayahuasca Associated Toxicity with Food or Drugs?

Dieta!

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Dieta In The Context Of This Talk

- Limited to aspects that present risk for adverse physiologic outcomes
- Recommended dietas may be longer and contain additional restrictions besides what is discussed
- There are many reasons/benefits for doing a dieta in preparation for ayahuasca that have nothing to do with avoiding adverse physiological reactions
  - Spiritual preparation and focus
  - Re-sensitization
  - Habit disruption
  - Tradition

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Food & Drink To Avoid with Ayahuasca

Foods*	Beverages*
Aged cheeses Air-dried, aged, or fermented meats, sausages or salami Pickled herring Soy sauce Sauerkraut Fava beans and other broad bean pods Tofu Concentrated yeast extract Food that is spoiled Overripe fruits Miso soup Chocolate	Tap beers Non-pasteurized beer Chianti Vermouth Kombucha Acidophilus milk Caffeinated beverages

*list may not be all inclusive; most foods can be consumed in moderation and risk of reactions are proportional to amounts of tyramine ingested. See https://psychotropical.info/wp-content/uploads/2017/11/MAOI_diet_drug_interactions_2016.pdf for detailed information on different foods in combination with MAOIs

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How Long Do I Have to Wait? Food

- Before ayahuasca
  - Tyramine has a T ½ of approximately 30 minutes
  - Should be eliminated completely after ~3hrs
- After ayahuasca
  - Harmala alkaloids have a T ½ of approximately 2-11 hours
  - Should be eliminated completely by 48-72 hours
  - Metabolism is variable and may take longer in some individuals

Callaway JC, McKenna DJ, Grob CS, et al. Journal of ethnopharmacology 1999;65:243-56.
VanDenBerg CM, et al. Journal of clinical pharmacology 2003;43:604-9.
Callaway JC. Journal of psychoactive drugs 2005;37:157-61.

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Drug Interactions

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The Good: Drugs That Can be Combined with Ayahuasca?*

- Drugs that do not bind monoamine (5HT, NE, DA) reuptake pumps or release monoamines (5HT, NE, DA) are generally low risk

Emergency

- Benzodiazepines (e.g. lorazepam (Ativan), alprazolam (Xanax), clonazepam (Klonopin))
- Albuterol/Salmeterol (ProAir, Ventolin)
- Epinephrine (Epi-pen)
- Antipsychotics (except ziprasidone)
- Naloxone (Narcan)
- Antihypertensives

Pain Medications

- NSAIDs (ibuprofen, naproxen)
- Acetaminophen/paracetamol
- Hydrodocone, oxycodone, morphine, buprenorphine
- Gabapentin, pregabalin

Herbs

- Guayusa
- Cannabis

Ceremonial/Recreational

- Phenethylamines
  - Mescaline ≥24 hours later
- Tryptamines
  - DMT, psilocybin, LSD

Sacraments

- Smoked tobacco & rapé snuffs generally ok: caution with blends containing coca leaf (cocaine), yopo (5-MeO-DMT & bufotenine)

*List is not all inclusive; ability to combine drugs without a life-threatening reaction does not mean that combining drugs has no effect or is optimal for healing

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The Bad: Drug Contraindications with Ayahuasca*

- **Antidepressants**
  - Antidepressants (SSRI, SNRI, clomipramine, imipramine)
  - Lithium
- **Antipsychotics**
  - Ziprasidone
- **Stimulants**
  - Amphetamine, methamphetamine
  - Methylphenidate
  - Cocaine
- **Herbs**
  - St John's Wort

Cough & Cold
- Dextromethorphan (Robitussin)
- Pseudoephedrine (Sudafed)
- Chlorpheniramine

Weight loss drugs/supplements
- Phentermine (Adipex)
- Ephedra (Ma Huang)

Pain Medications
- Methadone
- Tramadol
- Meperidine
- Tapentadol

Migraine medications
- Ergotamine

Parkinson's
- Levodopa/carbidopa

Ceremonial/Recreational
- Phenethylamines
  - MDMA, 2Cx, DOx , NBOMe
- Tryptamines
  - 5-MeO-DMT
- Cathinones
  - Mephedrone, methylone, MPDV

Purgative Sacraments
- Kambo
- Tobacco cleanses

Malcolm BJ, Lee KC. Mental Health Clinician 2017;7:39-45 Gilman K. PsychoTropical Commentaries 2017;1:105.

*List may not be all inclusive

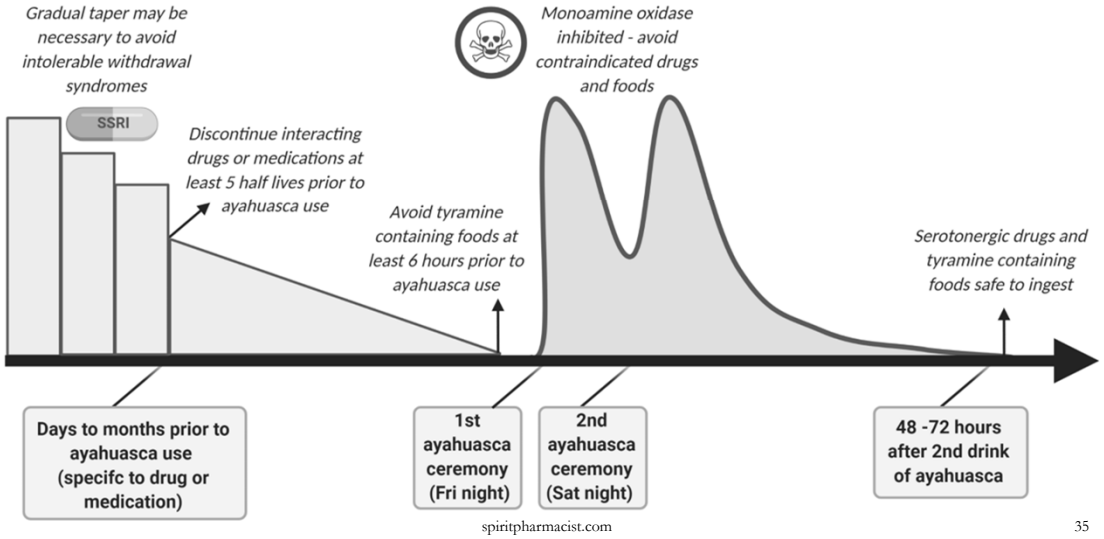
How Long To Avoid? Drugs

- **Length of drug avoidance necessary depends on half-life of drug in question**
  - A drug may have active metabolites that also present risk
  - Some drugs may need to tapered to safely discontinue

Rule of Thumb: wait ***at least*** 5 half-lives of the drug after discontinuing prior to ingesting ayahuasca
- If a drug has a half-life of 24 hours then avoid for at least 5 days before ingesting ayahuasca
- Longer times should be considered due to variations in individual metabolism

- Drug half-lives can vary drastically
  - Fluoxetine (Prozac) has a half-life of 4-6 days and has an active metabolite (norfluoxetine) that has a half-life of 16 days → needs to be stopped ≥6 weeks before ayahuasca

Planning a Weekend Ayahuasca Retreat



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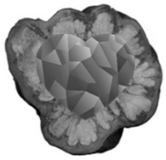
The Soul: Personal Interactions



- Every person is in a relationship with all things they ingest or consume
  - Relationships may be healthy or not
- Lack of risk for severe adverse reactions may not preclude lack of 'psychological interaction'
- One must evaluate the relationships they have and decide for themselves if there is an 'interaction' for them

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Which of the following drugs do you predict to be dangerous with MAOIs?

A) A drug that releases serotonin
B) A drug that increases GABA neurotransmission
C) A drug that binds to opioid receptors
D) All of the above

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Toxicity and Adverse Reactions

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Cardiovascular Effects of Ayahuasca vs. IV N,N-DMT

Route of DMT	Dose (mg/kg)	Peak effect in minutes	Heart Rate ↑ BPM	Systolic BP ↑ mmHg	Diastolic BP ↑ mmHg
Intravenous	0.4	2	26	35	30
Oral	0.5	45	6.4	8.8	10.4
Oral	0.75	45	8	13.4	9.8
Oral	1	45	9.2	13.8	8.6

- Use of Ayahuasca by oral route associated with lower cardiovascular stress than IV DMT
- Cardiovascular increases observed lower than MDMA or psilocybin
- Cardiovascular risk appears low, although could be highly variable (e.g panic reactions)

Table adapted from Gable RS. Addiction (Abingdon, England) 2007;102:24-34. Riba J, Rodriguez-Fornells A, Urbano G, et al. Psychopharmacology 2001;154:85-95. Strassman RJ, Qualls CR. Archives of general psychiatry 1994;51:85-97.

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What is a Lethal Dose of Ayahuasca?

- Estimated to be 20x typical ceremonial dose
- Typical dose (75kg or 165lb adult):
  - 0.5-1mg/kg DMT = 37.5-75mg DMT
  - 60-125mg harmine
  - 4-9 mg harmaline
  - 50-100mg tetrahydroharmine (THH)
- Propensity to produce vomiting likely limits feasibility of consuming (and absorbing) 20 doses of ayahuasca at once
- Considerable variability has been found in contents of DMT and harmala alkaloids in different ayahuasca brews

Riba J, Rodriguez-Fornells A, Urbano G, et al. Psychopharmacology 2001;154:85-95. Gable RS. Addiction (Abingdon, England) 2007;102:24-34.

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Ayahuasca & Poison Control Calls

- Descriptive analysis of calls to US Poison Control Centers 2005-2015 (n=538)
  - Increasing over time period studied
- Demographics of affected individuals
  - 81% male; median age 21
- Unable to verify contents of ayahuasca or other concurrent drugs users were taking
  - Suspicion for 'pharmauasca' or ayahuasca + other drugs in experimental use settings

Serious Adverse Effects

92 admissions to critical care units
58 admissions to non-critical care units
28 cases of breathing tube placement
12 cases of seizures
7 cases of respiratory arrest
4 cases of cardiac arrest
3 fatalities

Heise CW, Brooks DE. Journal of medical toxicology : official journal of the American College of Medical Toxicology 2016.

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Adverse Psychological Reactions

- 33 (6%) of US poison control calls admitted to psychiatric ward
  - Case reports of persistent & psychotic or manic reactions after ayahuasca
  - Traumatization possible with difficult or traumatic experiences
- Does ayahuasca cause psychosis?
  - No differences in rates of psychotic disorders among youth members of the UDV compared to that of the general population
  - Overlap between sensorimotor gating deficits seen in schizophrenia and elicited by DMT
  - Avoid in persons with a history of psychosis (schizophrenia) or mania (bipolar disorder)

dos Santos RG. Journal of psychoactive drugs 2013;45:179-88. dos Santos RG. Journal of psychoactive drugs 2013;45:68-78. Gable RS. Addiction (Abingdon, England) 2007;102:24-34. Szmulewicz AG, et al. International journal of bipolar disorders 2015;3:4. Heise CW, Brooks DE. Journal of medical toxicology : official journal of the American College of Medical Toxicology 2016.

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A new drug named Seratanin has come to market. You research this compound and find that it works by blocking serotonin reuptake, lacks active metabolites, and has an elimination half life of ~48 hours. Which of the following do you predict?

A) It could be dangerous with ayahuasca if not avoided for at least 10 days prior
B) It could be dangerous with ayahuasca if not avoided at least 48 hours prior
C) It could be dangerous with ayahuasca if not avoided at least 6 days prior
D) It is unlikely to be dangerous with ayahuasca

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Clinical & Observational Research

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Recent Research in Ayahuasca

- Acute decrease in default mode network (DMN) activity
- Small clinical studies positive for
  - Depression
  - Substance Use Disorders
- Anecdotal reports for positive effects in variety of medical and psychiatric health conditions

McKenna D, Riba J. Current topics in behavioral neurosciences 2015. Osorio Fde L et al. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999) 2015;37:13-20.
Sanches et al. Journal of clinical psychopharmacology 2016;36:77-81. Thomas G, et al. Current drug abuse reviews 2013;6:30-42.

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Observational Research

- No increase in psychiatric symptoms amongst healthy ayahuasca drinkers
  - Adoption of preventative health behaviors common
- Increases in openness related personality traits with long term & frequent use

Bouso JC, et al. PLoS One 2012;7:e42421.
Barbosa PC, et al. Journal of psychoactive drugs 2009;41:205-12.

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Summary & Conclusions

MAOIs in *Ayahuasca* are safe when participants are screened appropriately; interacting food & drugs are avoided; the participant prepares adequately, enters a ceremonial container that is trusted & secure, and integrates their experience

Food & drug interactions can be complex, although dangerous interactions are reasonably well documented and not difficult to avoid for most foods & drugs

Despite many similarities in structure and mechanism of action, it seems apparent that some tryptamines may be dangerous with MAOIs such as 5-MeO-DMT while others are not reported to be toxic such as N,N-DMT or psilocybin

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