Ayahuasca: Spiritual Pharmacology & Drug Interactions

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AWARE PROJECT

Can Science be Spiritual?

"Science is not only compatible with spirituality; it is a profound source of spirituality. When we recognize our place in an immensity of light years and in the passage of ages, when we grasp the intricacy, beauty and subtlety of life, then that soaring feeling, that sense of elation and humility combined, is surely spiritual. The notion that science and spirituality are somehow mutually exclusive does a disservice to both." – *Carl Sagan*

Disclosures & Disclaimers

- No conflicts of interest to disclose – I don't get paid by pharma and have no potential to profit directly from ayahuasca
- This presentation is for information purposes only, none of the information presented should be used in replacement of medical advice or be considered medical advice
- This presentation is not an endorsement of illicit activity

Presentation Outline & Objectives

Describe what is known regarding *ayahuasca's* pharmacology

Outline adverse food and drug combinations with *ayahuasca* as well as strategies for risk management

Provide an overview of spiritual pharmacology and current clinical data supporting potential of *ayahuasca* for treatment of mental illness

Pharmacology Terms

Drug

- Term used synonymously with substance or medicine in this presentation and in pharmacology
- **No offense intended if I call your medicine or madre a drug!** ☺

Bioavailability

- **The amount of a drug that enters the body and is able to have an active effect**
- Route specific: bioavailability is different between oral, intranasal, inhalation (smoked), and injected routes of administration (IV, IM, SC)

Half-life (T ½)

- **The amount of time it takes the body to metabolize/eliminate 50% of a drug**
  - E.g. If a drug has a T ½ of 2 hours; then 50% will remain after 2 hours, 25% after 4 hours, 12.5% after 6 hours, 6.25% after 8 hours etc.

- **Rule of Thumb: Drug is considered "gone from system" at around 4-5x half-life**
  - Exceptions:
    - Some drugs may have metabolites that have activity of their own
    - Average population estimates of metabolism may not represent an individual's metabolism

Ayahuasca – Metabolism & Interaction Potential

What's In Ayahuasca?

- Combination of (at least) two plants
  - *Banisteriopsis caapi* provides harmala alkaloids (aka β-carbolines)
  - *Psychotria viridis* or *Diploterys cabrerana* provides N-N-dimethyltrypramine (DMT)
- Plants brewed together into a concentrated decoction
  - The beverage that's consumed
- Shamans may add other plants (e.g. toé)
  - Increased potency?
  - Increased risk?
  - Increased healing potential?

What's in Ayahuasca?

Harmala alkaloids or β-carbolenes

N-N-Dimethyltryptamine (DMT)

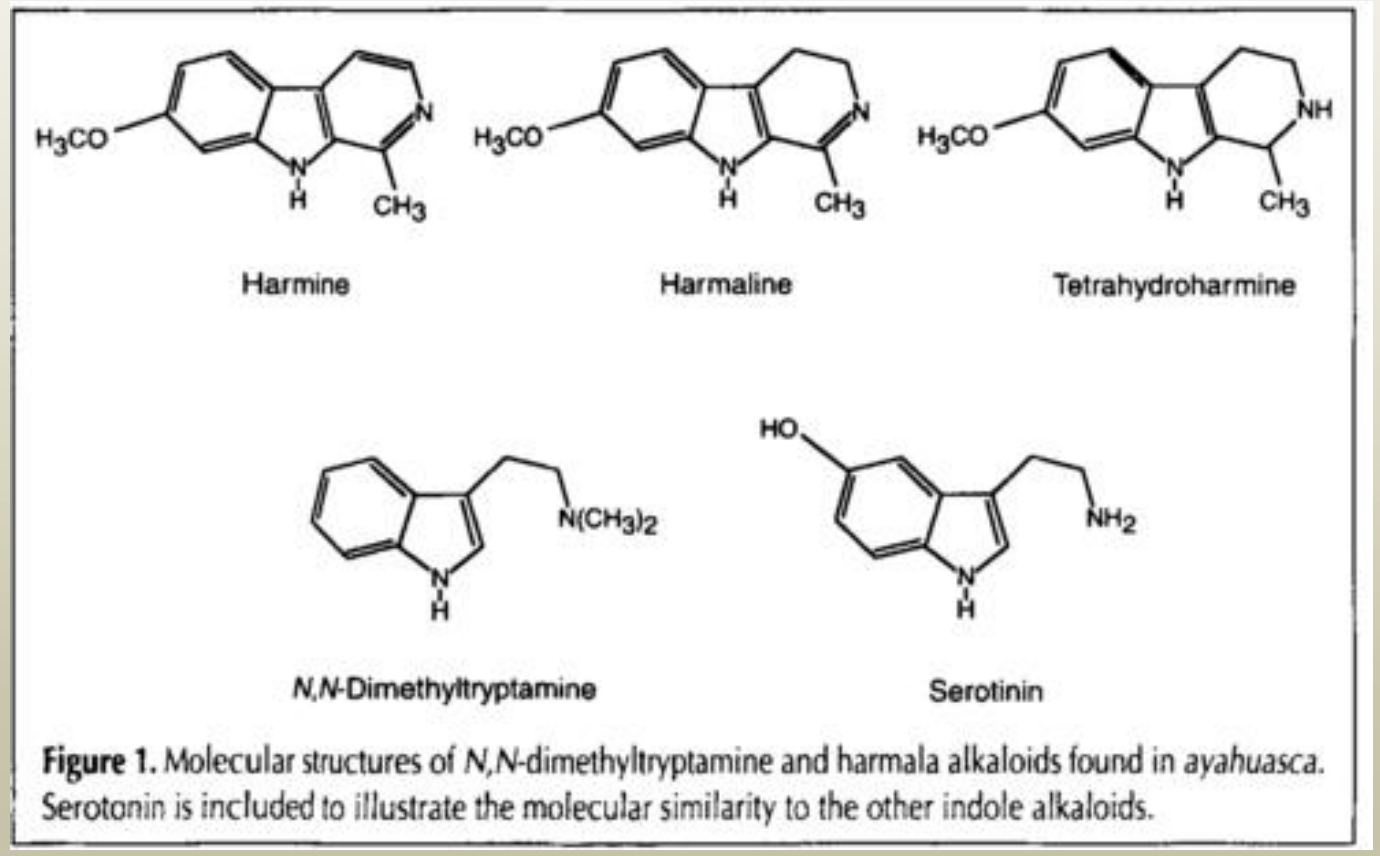


Figure 1. Molecular structures of *N,N*-dimethyltryptamine and harmala alkaloids found in *ayahuasca*. Serotonin is included to illustrate the molecular similarity to the other indole alkaloids.

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

N-N-Dimethyltryptamine (DMT)

- **Potent entheogen**
  - Structurally related to serotonin
  - Commonly occurs in natural world
- 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 route of administration

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.

The Role of Monoamine Oxidase (MAO)

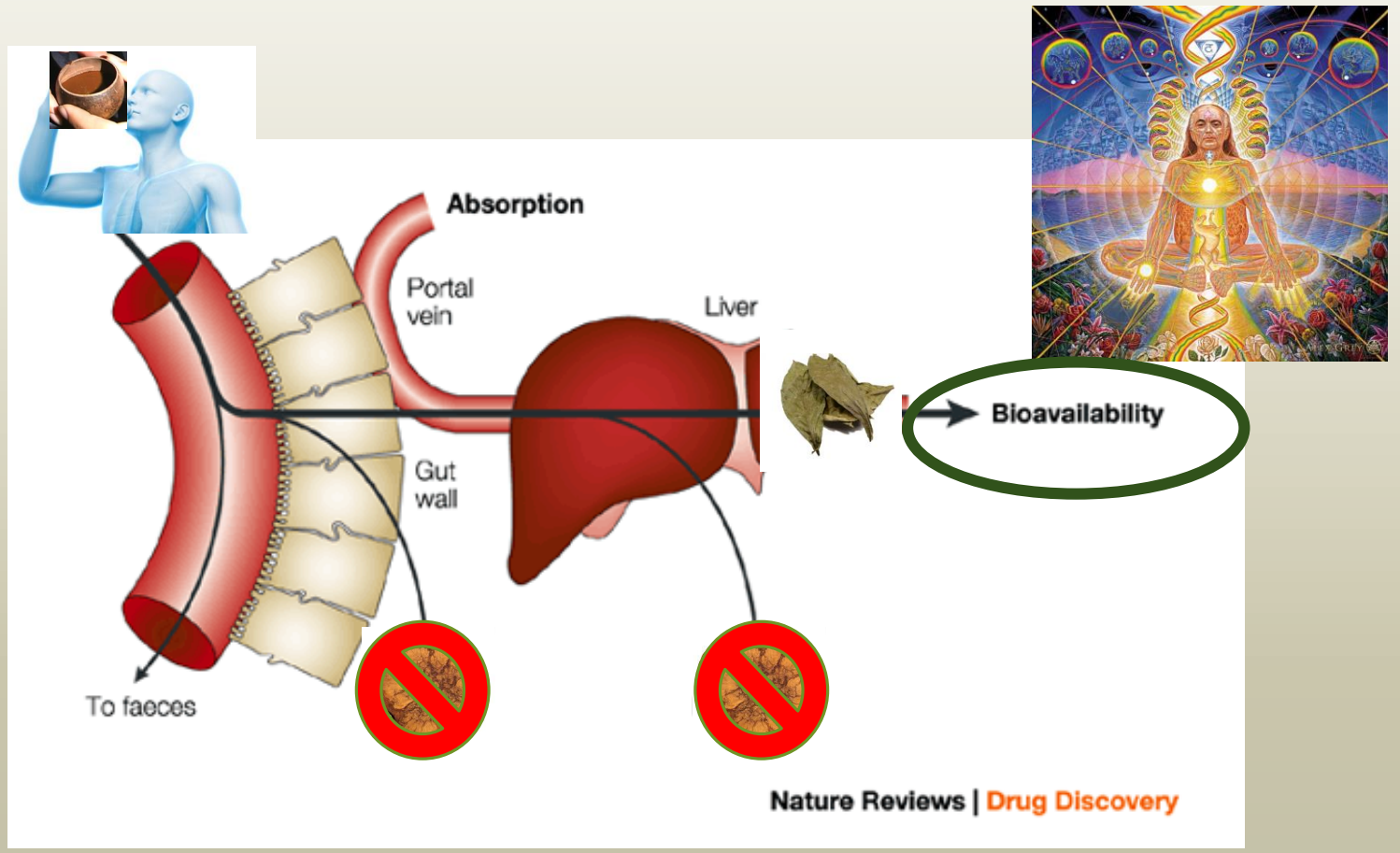
Role	Metabolic Function	Location in Body
Natural defense	degrading biogenic amino acids or drugs from diet: **tyramine, DMT**	Small intestine, liver
Regulation of neurotransmission	degrading monoamine neurotransmitters: **serotonin, norepinephrine, and dopamine**	Peripheral: Blood vessel lining
		Central: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

Why is the *Caapi* Vine Necessary?

- Provides harmala alkaloids
  - Temporary inhibition of MAO
  - **Makes DMT bioavailable by mouth**
  - **Also psychoactive**

- Liver is positioned as natural defense mechanism
  - “first pass effect”



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 8 hours (tetrahydroharmine)
- **Little effect predicted 24-48 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.

MAO Inhibition & Toxicity: **Food**

Risk of severe adverse reaction if tyramine ingested

Tyramine found in fermented or aged foods

- Smelly cheese → “cheese reaction”

“Cheese reaction” → Very high blood pressures (↑ risk of stroke etc.)

MAO Inhibition & Toxicity: **Drugs**

Serotonin Syndrome

- Inability to degrade serotonin, norepinephrine, or dopamine leads to excessive neurotransmitter signaling and related toxicity

Signs & Symptoms:

- Unstable vital signs
- Muscle rigidity
- Convulsions
- Fevers
- Hyper-responsive reflexes

Ayahuasca – Management of Interaction Potential

How Do You Avoid Ayahuasca Associated Toxicity?

Dieta!

Dieta In The Context Of This Talk

- Limited to aspects that present risk for adverse physiologic outcomes if violated
- Recommended dietas may be longer and contain additional restrictions besides what is discussed today
- 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

Food & Drink To Avoid with MAO Inhibition (Ayahuasca)

Foods to avoid with MAOI*	Beverages to avoid with MAOI*
• 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 (ok in moderation)	• Tap beers • Non-pasteurized beer • Chianti • Vermouth • Kombucha • Acidophilus milk • Caffeinated beverages (coffee) *list is not all inclusive

How Long Do I Have to Wait? **Food**

Tyramine has a T ½ of approximately 30 minutes
- Should be eliminated completely by 6 hours

Harmala alkaloids have a T ½ of approximately 2-8 hours
- Should be eliminated completely by 48 hours
- Metabolism is variable and may take longer in some individuals

Before ayahuasca
- Tyramine containing foods should be avoided for at least 24 hours

After ayahuasca
- Tyramine containing foods should be avoided for at least 72 hours

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.

Drug Interactions

- Complex and poorly understood with *ayahuasca*
  - Interaction potential mostly theoretical and extrapolated from risks with pharmaceutical MAOIs
  - Case reports confirm potential for harm
- Drugs that act to potentiate serotonin, norepinephrine, and dopamine likely present highest risks
  - Many! When in doubt avoid and ask!!
- Non-neurotransmitter based interactions
  - Additive effects > increased dizziness?

Callaway JC, et al. Journal of analytical toxicology 2006;30:406-7; author reply 7. Sklerov J et al. Journal of analytical toxicology 2005;29:838-41. dos Santos RG. Journal of psychoactive drugs 2013;45:179-88. Callaway JC, Grob CS. Journal of psychoactive drugs 1998;30:367-9. Shen HW, et al. Current drug metabolism 2010;11:659-66.

Potential Drug Interactions – Some Examples*

Psychotropics
- Antidepressants (Prozac, Venlafaxine)
- Antipsychotics (Olanzapine)
- Lithium, mood stabilzers
- Antiepileptics

Herbs
- St John's Wort

Migraine medications
- Ergotamine
- Triptans (e.g. sumatriptan or Imitrex)

Antiemetics
- Metoclopramide

Cough & Cold
- Dexteromethorphan (Robitussin)
- Pseudoephedrine (Sudafed)

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

Pain Medications
- Methadone
- Tramadol

Stimulants
- Amphetamines (Adderall, meth)
- Cocaine
- Caffeine

Parkinson's
- Levodopa/carbidopa
- Pramipexole

Ceremonial/Recreational
- Phenylethylamines
  - MDMA, 2C compounds, mescaline, NBOMe
- Tryptamines
  - 5-MeO-DMT, LSD
- Cathinones
  - Mephedrone, methylone, MPDV

*List is not all inclusive

Malcolm BJ, Lee KC. Mental Health Clinician 2017;7:39-45.

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

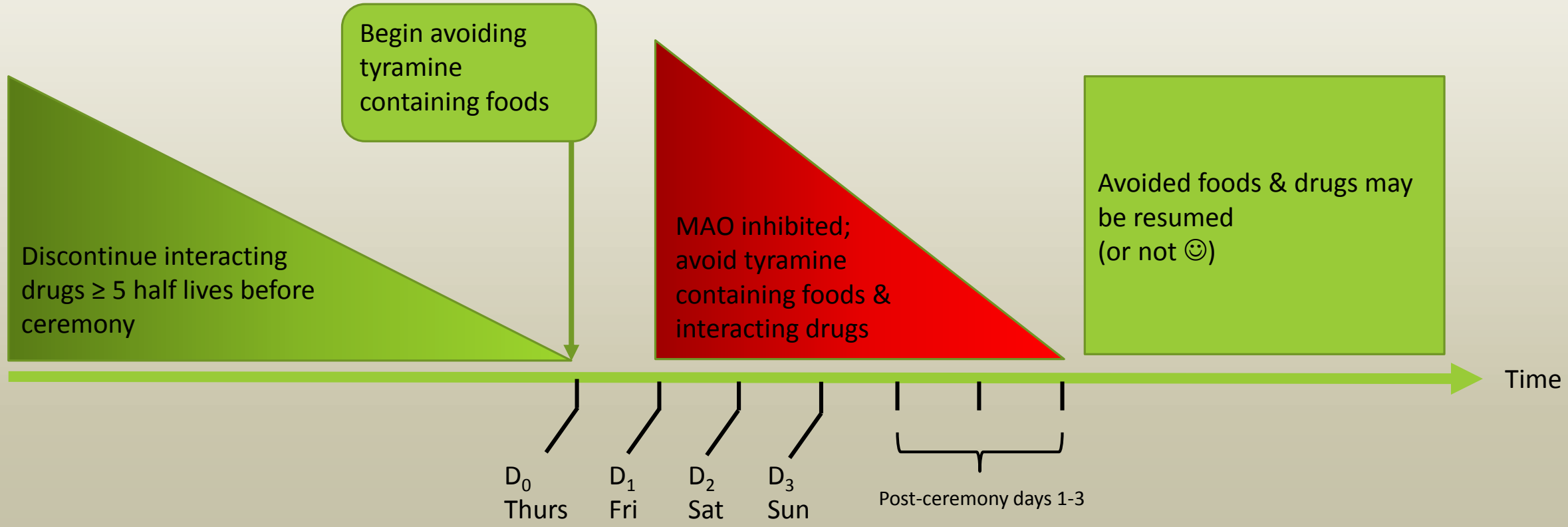
Rule of Thumb: wait ***at least*** 5 half-lives of the drug after discontinuing prior to ingesting ayahuasca

- 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 → may need to be stopped ≥6 weeks before ayahuasca

Planning a Weekend *Ayahuasca* Ceremony



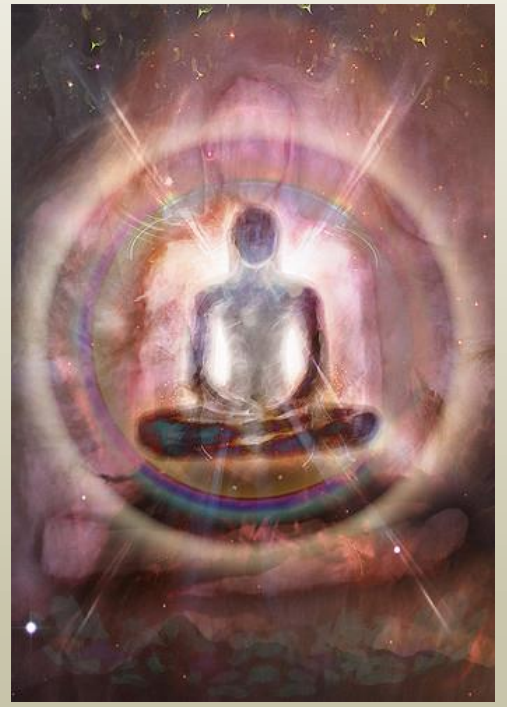
Ayahuasca – Spiritual Pharmacology

Spirituality & Mental Health

- Spirituality may be defined as a sense of interconnection with others and environment
  - High levels of spirituality appears to be protective against many mental health conditions
  - Lack of spirituality increasingly recognized as factor in development of poor mental health

Psychedelics & Spirituality

- Psychedelics are able to (fairly) reliably induce mystical experiences
- Mystical experience characterized by:
  - Sacredness and positive mood
  - Unity of all things; oneness
  - Ineffability
  - Transcendence of time and space
- Mystical experiences may increase spirituality in both short & long term
- Other possible beneficial effects of psychedelics
  - Increased empathy & insight
  - Facilitation of trauma processing
  - Immunomodulation
  - Physical healing



Griffiths RR, et al. Psychopharmacology (Berl). 2011 Dec;218(4):649-65

Spiritual Pharmacology - DMT

Psychedelics, including DMT, have complicated mechanisms of action

- Induction of a neuronal state of high plasticity (potential for change)

Serotonin 2A (5HT2A) receptor stimulation commonly produces psychedelic effects

- Similar in psilocin (4-phosphoryloxy-DMT), LSD, DOM, MDMA, mescaline
- No psychedelic effect observed when 5HT2A blocking drugs given prior to psychedelic

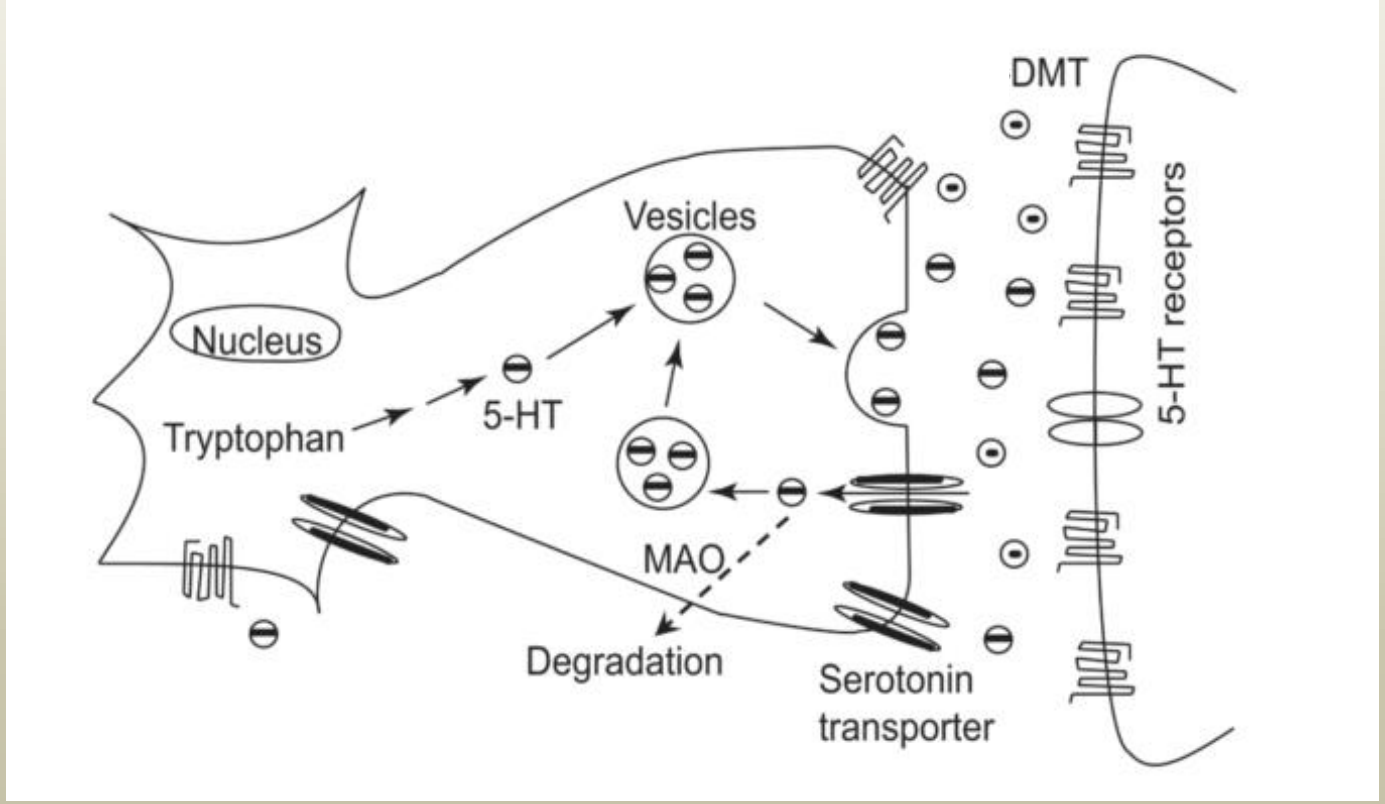
Recent interest in modulatory effects on immune and endocrine systems

DMT binds to:

- Serotonin Receptors: 5-HT1A, 5-HT1B, 5-HT1D, **5-HT2A**, 5- HT2B, 5-HT2C, 5-HT5A, 5-HT6 and 5-HT7
- Glutamate receptors
- TAAR & σ-1 receptors
- Gene transcription factors

Carbonaro TM, Brain research bulletin 2016;126:74-88. dos Santos RG.. Journal of psychoactive drugs 2014;46:383-8.

DMT in the Neuronal Synapse



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Spirituality & Mental Health

- Many spiritual interventions tend to increase mental health
  - Mindfulness & meditation, gratitude & prayer, psychedelic-assisted psychotherapy, ceremonial psychedelic use
- Some spiritual beliefs can be negative to mental health
  - Provider misunderstanding, punitive images of spirit, visions turned delusions
- Care & expertise required to guide participants appropriately!
  - Preparation, experiential support, integration

Weber SR, Pargament KI. Current opinion in psychiatry 2014;27:358-63. Goncalves JP, et al. Psychological medicine 2015;45:2937-49.

Adverse Psychological Reactions

Generally ayahuasca produces beneficial psychological reactions although not always

- Case reports of persistent & psychotic reactions after ayahuasca
- Case report of switch to mania after taking ayahuasca for depression
- Traumatization possible with difficult 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

May be best to avoid in people 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.

Recent Research in Ayahuasca

Decreased self-referential thinking associated with default mode network (DMN) activity

Small clinical studies positive for

- Depression
- Substance Use Disorders

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. 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.

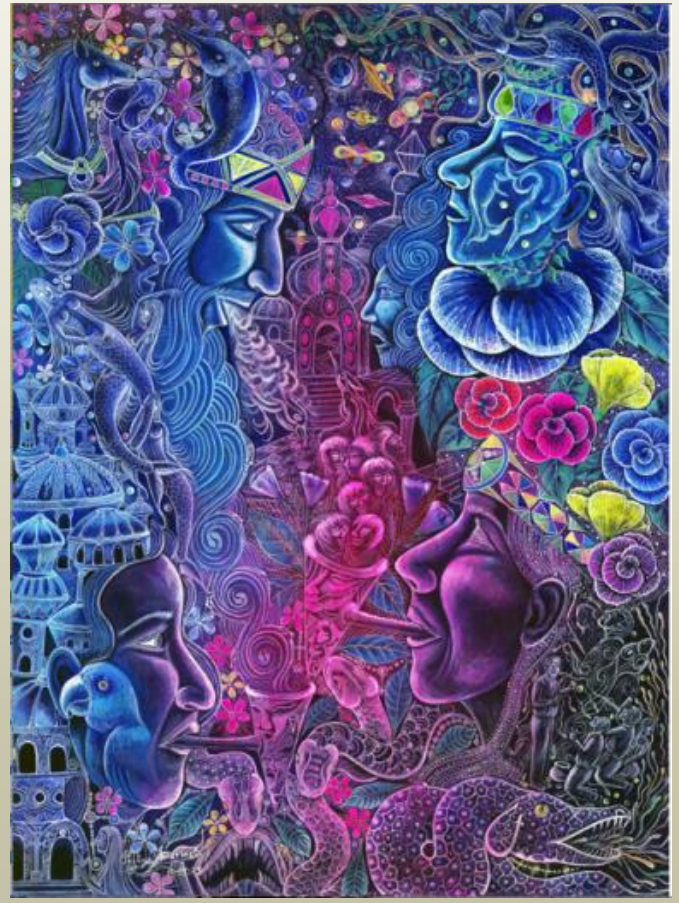
Summary & Conclusions

Ayahuasca is 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 are poorly understood, although utilizing drug pharmacology and extrapolating risks from pharmaceutical MAOIs is a reasonable approach

The science of spirituality and drug-induced mystical experiences is growing rapidly, collapsing long-standing dualistic tensions between disciplines, and many people suffering psychologically may be able to benefit from a drug-induced mystical experience

Questions?



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