

## Ayahuasca: An ancient sacrament for treatment of contemporary psychiatric illness?

Benjamin J. Malcolm, PharmD, MPH<sup>1</sup>

Kelly C. Lee, PharmD, MAS, BCPP, FCPP<sup>2</sup>

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### Abstract

*Ayahuasca* is a traditional psychoactive sacrament that's been used in Amazonian shamanic rituals for hundreds of years. *Ayahuasca* is notorious for its psychedelic properties produced from the combination of monoamine oxidase inhibitors (MAOIs) found in the *Banisteriopsis caapi* vine and N-N-dimethyltryptamine from *Psychotria viridis* or *Diplopterys cabrerana*. Recently, ritual use of *ayahuasca* has increased and garnered attention for its potential in treating mental illnesses, such as substance use and depressive disorders. Due to its MAOI properties, there are serious drug interactions that may be of concern among patients who participate in *ayahuasca* use. The objectives of this paper are to describe *ayahuasca*'s pharmacology, potential drug interactions, and clinical data for its treatment potential in psychiatric illness.

**Keywords:** *ayahuasca*, monoamine oxidase, dimethyltryptamine, sacrament, harmine

<sup>1</sup> (Corresponding author) Assistant Professor of Pharmacy Practice, Western University of Health Sciences College of Pharmacy, Pomona, California, [bmalmcol@westernu.edu](mailto:bmalmcol@westernu.edu), ORCID: <http://orcid.org/0000-0002-9293-9036>; <sup>2</sup> Associate Professor of Clinical Pharmacy and Associate Dean for Assessment and Accreditation, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California at San Diego, San Diego, California; Residency Program Director, PGY2 Psychiatric Pharmacy Residency, University of California at San Diego Health, San Diego, California, ORCID: <http://orcid.org/0000-0002-1674-4210>

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psychiatric illnesses, including depression and substance use disorders.<sup>1</sup>

*Ayahuasca* is used in shamanic ceremonies by indigenous peoples of the Amazon.<sup>2</sup> Ceremonies are conducted at night and outlast the psychedelic effects of *ayahuasca* by a few hours. They are led by a shaman who provides the brew for each participant to drink and spiritual support. One to 2 drinks are typically offered per evening, and rituals may be conducted a few evenings in a row. A person's baseline mindset a priori to drug ingestion as well as the physical surroundings to the drug experience are thought to be crucial to minimizing harm and maximizing potential for benefit. These parameters are described in psychedelic literature as "set and setting."<sup>3</sup> In ritual context, the user prepares and approaches the experience with intention along with ingesting in a supportive, supervised, and spiritual setting, which is hypothesized to augment any potential benefits. *Ayahuasca* drinkers are primarily seeking a vehicle of self-development or healing, including treatment of psychiatric illness.<sup>4,5</sup> Although the psychedelic effects of the *ayahuasca* attract the most attention in the literature and media, both preparation

### Background

Psychedelic plant medicines, such as psilocybin-containing mushrooms, mescaline-containing San Pedro and Peyote cacti, and N-N-dimethyltryptamine (DMT) decoctions collectively termed *ayahuasca*, have been used for thousands of years as ritual sacraments. Recently, there's been renewed interest in psychedelics as a treatment for

and integration phases pre- and postceremony are integral components to ritual *ayahuasca* use.

The Santo Daime and União do Vegetal (UDV) are two of the largest modern-day *ayahuasca* churches. Church membership has expanded to every inhabited continent.<sup>2,6</sup> N-N-dimethyltryptamine is currently a schedule I controlled substance in the United States although the right to ritual drinking of *ayahuasca* for members of the UDV has been upheld by the Supreme Court under the Religious Freedom Restoration Act. Consumption in native areas of the Amazon as well as nonsanctioned ritual use in the West is also growing.<sup>7</sup> The legal status of DMT poses a considerable barrier to adequate research of *ayahuasca* in the treatment of psychiatric illness.<sup>8</sup>

## Pharmacology of Ayahuasca

*Ayahuasca*'s psychedelic activity is attributed to DMT-containing plants *Psychotria viridis* or *Diplopterys cabrerana*. N-N-dimethyltryptamine, a tryptamine psychedelic, is a nonselective serotonin agonist although psychedelic effects have been primarily attributed to 5-hydroxytryptamine (5-HT)<sub>2A</sub> receptors.<sup>9</sup> N-N-dimethyltryptamine is endogenously produced, structurally similar to serotonin, and is also a ligand for trace amine associated receptor and  $\sigma$ -1 receptors.<sup>10-12</sup> Subjective effects of *ayahuasca* correlate closely with DMT blood concentrations; onset occurs around 20 minutes, peaks between 60 and 120 minutes, and resolution around 240 to 300 minutes. The half-life is approximately 1 hour.<sup>13,14</sup>

N-N-dimethyltryptamine lacks oral bioavailability under normal circumstances due to degradation by gastrointestinal and hepatic monoamine oxidase (MAO).<sup>15</sup> *Banisteriopsis caapi* is a vine that contains a group of harmala alkaloids (also known as  $\beta$ -carbolines) that inhibit MAO-A and promotes oral bioavailability of DMT, eliciting a 4- to 6-hour psychedelic experience when brewed together with the aforementioned plants.<sup>16</sup> Harmaline, harmine, and tetrahydroharmine are the primary harmala alkaloids responsible for bioactivation of DMT.<sup>17</sup> Harmala alkaloids have psychoactive properties of their own and bind at dual specificity tyrosine phosphorylated and regulated kinase 1A, 5HT<sub>2A/C</sub>, dopamine transporters, and imidazoline I<sub>2</sub> receptors.<sup>11</sup> Harmala alkaloids exhibit reversible and selective inhibition of MAO-A, which differentiates them from irreversible pharmaceutical MAOIs.<sup>18-20</sup> Reversible MAOIs, such as moclobemide, have a reduced propensity to lead to serotonin syndrome and hypertensive crises.<sup>21-23</sup> Harmine has been shown to produce serotonin syndrome and myoclonic syndrome in rodents injected with tryptophan.<sup>24</sup> Oral doses associated with ritual consumption in humans are at least an order of magnitude lower.<sup>11,25</sup>

Randomized, placebo-controlled trials of acute administration of *ayahuasca* in humans have demonstrated an acceptable safety profile using freeze-dried *ayahuasca* extracts.<sup>25-34</sup> Doses of DMT administered ranged from 0.5 to 1 mg/kg.<sup>26</sup> Concentrations of harmala alkaloids may display more variability than concentrations of DMT although they were reported as 1.4 mg/kg harmine, 1.15 mg/kg tetrahydroharmine, and 0.9 mg/kg harmaline in 1 study.<sup>27,30</sup> Doses of up to 3.4 mg/kg harmine have been tolerated.<sup>11,25</sup> The estimated lethal dose of *ayahuasca* determined in a pharmacologic safety review article<sup>27</sup> was about 20 times the average amount consumed in ritual contexts. This may suggest a low therapeutic index with concentrated brews or repeat dosing of *ayahuasca* although propensity to induce vomiting may limit consumption.

## Drug and Dietary Interactions

Due to MAO inhibition by harmala alkaloids, *ayahuasca* carries a higher risk of drug interactions than other psychedelics. *Ayahuasca* has previously been recognized to have interaction potential with selective serotonin reuptake inhibitors.<sup>35</sup> *Ayahuasca* should also be avoided with other serotonergic agents, including tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, trazodone, and St John's wort. Non-antidepressants, such as lithium, triptans, metoclopramide, levodopa, phentermine, pseudoephedrine, linezolid, methadone, and dextromethorphan, may also have serotonergic effects.<sup>36</sup> Psychoactive drugs, such as phenylethylamines (MDMA, mescaline, 2C compounds), methcathinones or "bath salts" (mephedrone, methylone), and tryptamines (LSD, 5-MeO-DMT, psilocybin) are high-risk combinations as fatalities have been reported when combined with harmala alkaloids in a recreational setting.<sup>37-40</sup> Alternative combinations of extracted harmala alkaloids with DMT as well as other tryptamines was described by Ott as "Pharmausca" and likely pose similar or greater drug-interaction risks than *ayahuasca*.<sup>39</sup> Harmine is also a substrate and inhibitor of CYP2D6.<sup>11,41</sup> Pharmacokinetic data of *ayahuasca* users suggested genetic polymorphisms of CYP2D6 to play a significant role in harmine metabolism. However, similar DMT concentrations remained despite higher concentrations of harmala alkaloids, which indicates alternative metabolic routes for DMT apart from MAO.<sup>41</sup>

Effects of tyramine intake in subjects taking *ayahuasca* have not been described although extrapolation from pharmaceutical MAOIs suggest an increased risk of hypertensive crisis. Although not necessarily designed to minimize tyramine content, Amazonian *dietas* used in preparation of ritual *ayahuasca* involve bland foods that do not involve alcohol, cheese, or other fermented food items.

## Neuroscience

In neuroimaging studies, *ayahuasca* has been found to increase blood flow to frontal cortical structures, including the medial temporal lobe, amygdala, hippocampus, and parahippocampal gyrus, that are involved in regulation of emotion and memory.<sup>30,31</sup> The temporo-parieto-occipital junction is also activated and involved in association of sensory processes, resulting in synesthesia and other psychedelic phenomena.<sup>30,31</sup> Visual effects of *ayahuasca* have been associated with decreased  $\alpha$ -oscillations produced on electroencephalography, which is likely mediated by 5HT<sub>2A</sub> agonism.<sup>42</sup> Long-term cross-sectional imaging studies in subjects that used *ayahuasca* at least 50 times in the past 2 years have shown increased cortical thickness in the anterior cingulate cortex (ACC) and thinning of the posterior cingulate cortex (PCC).<sup>43</sup> Midline cortical structures, including the ACC and PCC, are involved with the default mode network (DMN), which helps to integrate environmental stimuli with cognitive and emotional processes.<sup>44</sup> Default mode network hyperactivity has been suggested to play a role in depression, attention deficit-hyperactivity disorder, schizophrenia, and anxiety.<sup>45-48</sup> Changes in DMN activity are thought to be beneficial in treating psychiatric illnesses and to be part of *ayahuasca*'s mechanism of action.<sup>35</sup> Changes in DMN activity may underlie the benefits of mindfulness, and *ayahuasca* has been demonstrated to increase mindfulness capacities.<sup>49,50</sup>

## Tolerability

*Ayahuasca*, similar to other tryptamine psychedelics, is not considered to be an addictive substance although formal abuse liability studies are lacking.<sup>51</sup> The drug has not been observed to produce withdrawal in studies to date. *Ayahuasca* is not well tolerated physically and frequently results in nausea, vomiting, and diarrhea as well as other somatic disturbances collectively known as purging or *la purga*. From the perspective of indigenous cultures, these adverse effects are considered to be cleansing and normal. Although a specific mechanism has not been established, these effects are consistent with mild serotonin toxicity. The frequency of vomiting reported with *ayahuasca* as well as being in an acutely altered state may increase risk of aspiration events. Mild and transient increases in cardiovascular parameters, such as increases in diastolic blood pressure of approximately 10 mmHg, as well as the somatic disturbances outlined above were common.<sup>25</sup> Neuroendocrine activity, including transient increases in cortisol (12  $\mu$ g/dL) and prolactin (14 ng/mL) that persist for approximately 6 hours with consequent immunomodulatory changes, has been identified and deserves further study.<sup>33</sup> Many studies have been limited to healthy people with *ayahuasca* experience at baseline, which may skew reports on tolerability or

objective or subjective effects. Few studies<sup>52-54</sup> have included *ayahuasca*-naïve patients or patients diagnosed with a psychiatric illness.

There have been several reports of death, including an alleged homicide during an *ayahuasca* ceremony.<sup>40,55</sup> Circumstances around deaths are generally unclear and may be related to shamans adding additional plants with increased toxicity to brews or inappropriately screening patients for drug interactions. There has never been a death observed during a clinical study.<sup>40</sup> There was a single case report<sup>56</sup> of a switch to mania in a patient with bipolar disorder who consumed ritual *ayahuasca* during a depressive episode. *Ayahuasca* does not appear to increase the risk of precipitating psychosis or schizophrenia among young adults with reported rates in the UDV being equal or less than that of the general population.<sup>27</sup> One case report<sup>57</sup> suggested that repeated use of smoked DMT may precipitate psychosis. Other persistent psychotic-like reactions have been described.<sup>40</sup> One study<sup>58</sup> reported reduced P50 sensory gating suppression with *ayahuasca* use and decreased P50 sensory gating is associated with schizophrenia. Given the paucity of data, *ayahuasca* may best be avoided in patients with a history of mania or psychosis.

## Subjective Effects

Psychological effects have been assessed in short- and longer-term studies of psychiatrically stable church members. One study<sup>59</sup> showed a decrease in working memory with acute administration although stimulus-response interference was decreased. Another showed increases in creative divergent thinking, which may be beneficial to mediating therapeutic interventions.<sup>60</sup> Short-term effects were investigated prospectively in *ayahuasca*-naïve participants ( $n = 28$ ) at 1 to 4 days and 7 to 14 days postritual.<sup>61</sup> The Clinical Interview Schedule-Revised Edition, designed for measurement of minor psychiatric symptoms in community members, showed reduction in psychiatric symptoms.<sup>62</sup> Altered states of consciousness most commonly experienced included visual phenomena, peace, numinous feelings, personal insight, and alterations in body image. However, 1 subject had a distressing reaction that resulted in worry and preoccupation persisting beyond the acute effects of *ayahuasca*. Within 7 to 14 days of use, feelings of serenity, assertiveness, joy, and satisfaction were reported. Other acute dysphoric reactions of approximately 20 minutes in duration have been reported.<sup>40</sup> Longitudinal studies<sup>53,63-65</sup> have demonstrated lower psychopathology scores; reduction in psychiatric symptom rating scales; and spiritual experiences leading to reduced alcohol intake, healthier diet, improved mood, and greater self-acceptance, which may be preventative of future morbidity if sustained. Although

**TABLE: Preliminary studies of *ayahuasca* in substance use and depression**

Study	Population	Intervention	Outcomes	Results
<i>Ayahuasca</i> -assisted therapy for addiction: results from a preliminary observational study in Canada <sup>71</sup>	First Nations band subjects with substance use in past 6 mo (n = 12)	Two open-label <i>ayahuasca</i> ceremonies embedded within 4-d group counseling	Substance use (4WSUS); regulation of emotion (DERS); mindfulness (PHLMS); hope (HS); empowerment (ES): Baseline, 2 wk, monthly × 6 mo	Improvement in mindfulness, empowerment, hopefulness, quality of life ( $P < .05$ )  Less problematic cocaine use ( $P < .05$ ), less alcohol and tobacco use
Antidepressant effects of a single dose of <i>ayahuasca</i> in patient with recurrent depression: a preliminary report <sup>52</sup>	Volunteers with recurrent major depressive disorder (n = 6) in Brazil; none had used illicit drugs or <i>ayahuasca</i> previously	Two-wk washout and observation period, single open-label administration; discharge 24 h postuse  <i>Ayahuasca</i> : 1.76 mg/kg DMT, 0.46 mg/kg harmine	HAM-D (baseline $17.56 \pm 7.73$ ; MADRS (baseline $23.5 \pm 11.14$ ): Baseline, 40 min, 80 min, 140 min, 180 min, d 1, d 7, d 14, d 21 postadministration  Safety scales: BPRS, YMRS	Reduction in HAM-D (d 1 62% reduction $P = .01$ ; d 7 72% reduction $P = .01$ ; d 14 45% reduction $P = .11$ ; d 21 further decrease in HAM-D $P = .01$ )  MADRS similar to HAM-D although d 14 showed significant decrease and d 21 showed significant decrease  No signal for mania or psychosis after dissipation of acute effects
Antidepressant effects of a single dose of <i>ayahuasca</i> in patients with recurrent depression: a SPECT study <sup>54</sup>	Volunteers with recurrent major depressive disorder (n = 17) in Brazil; none had used illicit drugs or <i>ayahuasca</i> previously	Two-wk washout period followed by single open-label administration  <i>Ayahuasca</i> : 1.76 mg/kg DMT, 0.46 mg/kg harmine	HAM-D (baseline $19.24 \pm 5.52$ ), MADRS (baseline $25.6 \pm 7.6$ ): Baseline, 40 min, 80 min, 140 min, 180 min, d 1, d 7, d 14, d 21  Safety scales: BPRS, YMRS  SPECT imaging 4 to 6 h after main effects subsided	Significant reduction in HAM-D, MADRS, and anxious-depression BPRS subscale from 80 to 180 min and from d 1 to d 21 ( $P = .000$ ): d 21 HAM-D $7.56 \pm 4.7$  Increased blood flow to left nucleus accumbens, right insula, and left subgenual area  No change in YMRS or activation subscale of BPRS

4WSUS = 4 Week Substance Use Scale; BPRS = Brief Psychiatric Rating Scale; DERS = Difficulty in Emotion Regulation Scale; DMT = N-N-dimethyltryptamine; ES = Empowerment scale; HAM-D = Hamilton Depression Rating scale; HS = Hope scale; MADRS = Montgomery Asberg Depression Rating Scale; PHLMS = Philadelphia Mindfulness Scale; SPECT = single-photon emission computed tomography; YMRS = Young Mania Rating Scale.

these studies do not show that *ayahuasca* is helpful for improving psychiatric illness, as included patients did not carry psychiatric diagnoses, it does suggest that *ayahuasca* does not induce symptoms of psychiatric illness in healthy subjects.

## Clinical Studies of *Ayahuasca*

A PubMed search using the term “*ayahuasca*” from the time of database inception until September 6, 2016, was conducted for studies investigating the use of *ayahuasca*’s

effects for treatment of psychiatric illness. No randomized trials were identified, and studies were mostly retrospective in design or longitudinal cohort studies. A few open-label prospective experimental studies were found and are summarized in the Table.

Anecdotal clinician reports as well as naturalistic studies suggest *ayahuasca* may have positive effects on substance use disorders.<sup>53,63,66-68</sup> Potential mechanisms in substance use disorders include modulation of serotonergic and dopamine neurotransmission that may help limbic processing of prior trauma and facilitate transcendent experiences.<sup>11,66,69,70</sup> A preliminary observational study<sup>71</sup> (n=12) in Canada reported some benefits in reducing stimulant, alcohol, and tobacco use, including statistically significant reductions in cocaine use (Table).

Two open-label studies<sup>52,54</sup> have investigated the antidepressant effects of *ayahuasca* in patients with recurrent moderate major depressive disorder (Table). One study conducted in 6 patients in an inpatient setting showed rapid and sustained reductions in the Hamilton Depression Rating (HAM-D) scale and Montgomery Asberg Depression Rating Scale (MADRS). The second study assessed the impact of *ayahuasca* consumption on depression with concurrent neuroimaging in 17 patients. Rapid and sustained reductions in HAM-D and MADRS scores were replicated with single administrations without problematic increases in mania or psychosis rating scales.<sup>52,54</sup>

## Conclusions

*Ayahuasca* has a complex pharmacologic mechanism that is not yet fully elucidated although it relies on inhibition of MAO by *banisteriopsis caapi* for bioactivation of DMT. Medication interactions are poorly understood, and *ayahuasca* should be avoided with medications possessing serotonergic potential. Current *ayahuasca* literature is limited by small sample sizes and convenience sampling of practicing church members. Control groups, blinding, or randomization are lacking in many circumstances. A publication bias toward favorable results may be present in the current literature. Various *ayahuasca* brews may vary in contents of active ingredients; however, standardization using freeze-dried extracts may create a different experience in the user than drinking the brew. Therapeutic effects observed may in part be attributable to ritual context opposed to purely a drug effect. Research with *ayahuasca* is difficult to conduct due to legality issues. Ritual use of *ayahuasca* has been touted for its benefit for centuries. There is limited evidence supporting clinical benefit in depression and substance use disorders, which makes the sacrament a promising area for future research. Approaches to minimize harm, maximize benefit, and reduce barriers to legitimate medical research are needed

to protect patients who may be desperate and looking for alternatives for treatment of psychiatric illness.

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