A Comprehensive Review of Potential Uses of Ayahuasca in Psychiatry

Adam Bertroche, DO

Abstract:
Objective: This paper aims to provide a review of primarily the human studies of the use of ayahuasca for psychiatric illness and outline the pharmacology and effects of ayahuasca.

Method: Literature review

Discussion: Ayahuasca has a unique delivery method and mechanism of action involving serotonin and sigma-1 receptors with downstream effects on dopamine and glutamate. There have been positive studies for using ayahuasca in psychiatric disorders. However, more extensive clinical trials and safety profiling are required before use in clinical practice.

INTRODUCTION

Ayahuasca is a hallucinogenic tea prepared in multiple Amazonian countries, including Brazil, Bolivia, Peru, Colombia, and Ecuador. The bitter tea has several other names, such as caapi, natema, yajé, and dapa [1]. Ayahuasca is believed to originate from Quechua meaning, "vine of the souls." It is used in shamanistic practice as well as in several Brazilian churches. Shamanistic societies use it for its visionary properties as a way to reach the divine. The ceremonies are often guided by an "ayahuasquero" to assist through the session. Typically, sessions with a shaman involve singing, chanting, and fast-paced rhythms to assist in the movement of the visions and prevent them from being stuck. As mentioned, ayahuasca is also utilized as a sacrament in several Brazilian churches. These include Santo Daime, the Uniao do Vegetal (UDV), and the Barquinia. These churches have rituals that overlap with other major religions, such as Christianity. They often involve ceremonies that involve sermons, songs, and hymns. In *Sacred Vine of the Spirits*, the distinction between churches and shamanism is made by stating, "In such ceremonies the intentional focus is not so much on healing and visioning, but on group worship and celebration." The use of ayahuasca is not limited to South America. There has been an increasing amount of ayahuasca tourism from Americans and Europeans, who travel to the Amazon to partake in an ayahuasca ceremony [2].

The preparation of the tea involves the combination of the bark from *Banisteriopsis caapi*, which is rich in the beta-carboline alkaloids harmine, harmaline, and tetrahydroharmine (TTH), and the leaves of a plant containing N, N-dimethyltryptamine (DMT). Most commonly, DMT is provided by the plant species *Psychotria viridis*, but preparations can utilize *Psychotria carthagenesis or Diplopterys cabreana* instead. DMT is the hallucinogenic component of the tea but is not absorbed orally on its own because MAO degrades it in the liver and intestine. For systemic absorption, it relies on MAO inhibition provided by harmine, harmaline, and TTH from *B. caapi.* It is uncertain if harmaline has enough concentration to have MAO-I activity to a significant degree; however, beta-carbolines are hallucinogens on their own. It is not believed that ayahuasca has enough of the beta-carbolines in the tea to be hallucinogenic [3].

Hallucinogens, including ayahuasca, are believed to have psychoactive effects due to their resemblance to neurotransmitters in our brain. In particular, 5-hydroxytryptamine (5-HT), or serotonin. Dysfunction in the brain's serotonin systems can lead to psychiatric illnesses such as anxiety, depression, substance use disorders, and PTSD. There is growing evidence that ayahuasca may be beneficial in these psychiatric illnesses [2]. This review discusses the pharmacology of ayahuasca, short-term effects, long-term effects, as well as human studies of ayahuasca for the treatment of psychiatric illness.

AYAHUASCA PHARMACOKINETICS

DMT is the hallucinogenic component of the tea, but it is not absorbed as it is degraded by monoamine oxidase (MAO) in the liver and intestine. For systemic absorption, it relies on MAO-inhibition provided by beta-carbolines harmine, harmaline, and TTH [3]. Harmaline is more potent in its activity than harmine [2]. However, it is believed that the low concentrations of harmaline in the brew make it less likely than the other beta-carbolines to have a significant effect on MAO-inhibition. As mentioned previously, DMT is commonly provided by the plant species *Psychotria viridis.* Beta-carboline alkaloids are often provided by the plant species *Banisteriopsis caapi*.[3] Following ingestion of ayahuasca, MAO-inhibition generally lasts 8-12 hours [2]. Riba et al. evaluated the metabolite excretion and pharmacokinetics of ayahuasca in a double-blind placebo-controlled study, in addition to looking at subjective effects. They measured urinary metabolites and blood samples for alkaloids present in the tea following ingestion on 18 volunteers in four ayahuasca sessions with two different doses. Urine samples obtained for urinary monoamine metabolites were collected at intervals to measure the MAO-inhibition of ayahuasca. These included vanillylmandelic acid (VMA), homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), metanephrine, and normetanephrine. With central MAO-inhibition, one would expect decreases in monoamine metabolites VMA, HVA, and 5-HIAA, resulting from the breakdown of norepinephrine/epinephrine, dopamine, and serotonin. However, when measured at intervals from 0-24 hours, there was a non-statistical increase in these metabolites.

Additionally, with central MAO-inhibition, increases in metanephrine and normetanephrine are typically seen. There was only a statistically significant increase in normetanephrine. Taken together, these results indicate that the MAO-I activity in ayahuasca is only peripheral in nature, acting only in the gastrointestinal system rather than centrally acting.

Blood samples were also drawn at regular intervals for analysis of DMT, harmine, harmaline, and THH, as well as harmol and harmalol. DMT and THH were quantified in this study, but harmine was unable to be measured in most subjects. The metabolites of harmine, harmalol, and harmol, were also measured and found to be in the samples. Taken together, it suggests that harmine is broken down by first-pass metabolism prior to reaching circulation. Tmax was calculated for DMT with a value of 1.5 hours regardless of the ayahuasca dose. The peak DMT concentrations correlated to peak subjective effects that were measured between 1.5 and 2 hours. The harmaline Tmax was 1.5 hours and 2 hours for the low dose and high dose, respectively. THH Tmax was 2.5 hours and 3 hours for the low dose and high dose, respectively [4]. These results correlate with Callaway et al., who looked at the pharmacokinetics of ayahuasca on 15 volunteers. They found a Tmax for DMT of 107.5 minutes and a Tmax of THH of 174.0 minutes [5]. Dos Santos et al., administered

ayahuasca in two repeated doses, and found a Tmax of 2 hours on both an initial dose of ayahuasca, and after administration of the second was 4 hours after the initial dose.[6] Additionally, Riba et al. looked at AUC normalized by dose for DMT. They found a statistically significant increase for DMT with AUC was normalized, indicating that the increase in DMT between doses may be non-proportional.[4] However, dos Santos et al. found linear increases in AUC of DMT when normalized for dose. This indicated a proportional increase in AUC for DMT after the second dose in a superimposed manner [6].

In a later study, Riba et al. looked at metabolism and excretion of DMT and beta-carbolines following ingestion of ayahuasca in 10 participants. 24-hour urine was collected following ingestion at various time intervals to measure potential metabolites of these constituents. Less than 1% of absorbed DMT was excreted unchanged. Metabolites of DMT was found to have multiple metabolic pathways including oxidative deamination from monoamine oxidase to indole-3-acetic acid (IAA), N-demethylation to N-methyltryptamine (NMT), N-oxidation to N, N-dimethyltryptamine-N-oxide (DMT-NO), and cyclization to 2-methyl-tetrahydro-beta-carboline (2MTHBC). They found that after 8 hours following ingestion of ayahuasca, 95-97% of all DMT had been excreted. The primary metabolic pathways were deamination from monoamine oxidase to IAA and N-oxidation to DMT-NO, as IAA made up 77.8% of excreted metabolites and DMT-NO was 20.1%.

Metabolism and excretion of the beta-carbolines were also evaluated. Only 0.1% of harmine was recovered unchanged in the urine, and 7.7% of harmaline and 6.0% of THH were recovered unchanged. This suggests that they are extensively metabolized, with harmine being the most extensively metabolized. They found that harmine, harmaline, and tetrahydroharmine are metabolized via O-demethylation. Harmine and harmaline are metabolized to harmalol and harmalol, and tetrahydroharmine is metabolized to tetrahydroharmine. However, the recovery rates were low for the parent compounds and metabolites, indicating that there may be other metabolic pathways for these beta-carbolines or effects from first-pass metabolism [7].

PHARMACODYNAMICS

Receptor Level Properties

Serotonin Receptors

Glennon et al. demonstrated the involvement of the 5-HT2 receptor as a mechanism of action in a variety of hallucinogens, including DMT. It was also found that increased affinity for these receptors is correlated with increased hallucinogenic intensity [8]. This has been further supported in that effects of hallucinogens are reduced following administration of 5-HT2 antagonists such as ketanserin during pretreatment [9,10]. DMT has been demonstrated to be a 5-HT2A and 5-HT2C agonist. Smith et al. demonstrated that immediately after administration, there was desensitization of 5-HT2C receptors but not 5-HT2A receptors [11]. DMT has also shown to have agonist activity at 5-HT1A sites as well [12]. Magnetic resonance spectroscopy has demonstrated metabolic changes in the posterior cingulate cortex, which is a region of the brain that has a high density of 5-HT2A receptors [13]. Some research also suggests that 5-HT1A agonism enhances hallucinogenic effects of DMT, as some of DMT's effects are blocked by the addition of the 5-HT1A antagonist, pindolol [14]. Callaway et al. evaluated for serotonin uptake on platelets of chronic ayahuasca users. They found an increased number of binding sites on platelets, suggesting increased production or release of 5-HT in

ayahuasca drinkers [15]. This may indicate a potential role for ayahuasca in alcohol use and depression, as the decreased density of serotonin transporters has been associated with these disorders. Additionally, agonism of 5-HT1A, 5-HT2A, and 5-HT2C has been proven to be effective for treating depression and anxiety. Agonism at 5-HT2 also results in the downstream reduction of dopaminergic activity, which may facilitate a role in the reduction of substance use [16].

Several neuroendocrine and cardiovascular changes are believed to result from serotonergic transmission secondary to DMT's actions. Prolactin, corticotropin, beta-endorphin, and growth hormone are all believed to increase due to the serotonergic activity of DMT in a dose-dependent manner. In addition, changes in heart rate, blood pressure, pupillary diameter, and temperature are believed to be due to serotonergic activity [17].

Sigma-1 Receptors

Fontanilla et al. demonstrated that DMT is an agonist of the sigma-1 receptor. Sigma-1 receptors are present throughout the nervous system and act in the inhibition of sodium ion channels [18]. Sigma-1 receptors are chaperones located on the endoplasmic reticulum membranes associated with mitochondria and are involved in signaling between these structures. These receptors have been implicated in diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, ALS, stroke, neuropathic pain, schizophrenia, anxiety, and depression [19]. They are also believed to be involved in the function of neurotransmitters in the brain [20]. Classes of antidepressants have been found to have agonism on sigma receptors, sigma-1 receptors [21]. Furthermore, sigma-1 receptors are located in brain regions associated with depression, such as the prefrontal cortex and hippocampus. Wang et al. also demonstrated antidepressant effects of sigma-1 receptor agonists in mice [22]. It has been postulated that future treatments for major psychiatric disorders, such as anxiety and depression could target sigma-1 receptors [23]. Additionally, ayahuasca may have a potential benefit in anxiety and depressive disorders due to its action at these receptors [16].

Glutamate Receptors

Another area of interest includes ayahuasca's effect on glutamate. A magnetic resonance spectroscopy and functional connectivity study was performed to assess neurologic changes in the post-acute period following ayahuasca ingestion. This found reduced glutamate levels. Generally, glutamate levels are elevated during increased perceptual stimulation. These results suggest a decrease in glutamate levels in the post-acute period following an increase during acute psychoactive stimulation after ingestion. These changes may partially explain the improvement in depression following ayahuasca use, as elevated glutamate levels in the parieto-occipital cortex are associated with depression [13]. It has been demonstrated that the previously discussed sigma-1 receptors are involved in NMDA receptor function [20]. Harmine, a beta-carboline found in ayahuasca, increases the expression of genes involved in the uptake of glutamate into cells as well. Glutamate is an excitatory neurotransmitter, and excess may lead to toxicity [24].

Neurocircuitry Effects:

Ayahuasca has a modular effect on the Default Mode Network (DMN). The DMN is a group of connected brain regions with increased activity at rest, and internally-oriented rather than externally oriented cognitive processes [25]. The network is activated during non-task-oriented thought, lacking focus on the goal at hand, and

described as "mind-wandering [26]." It is believed to have roles in memory consolidation and episodic memory [27]. A rise or decline in DMN activity has been associated with multiple psychiatric illnesses and mental states, including depression, anxiety disorders, schizophrenia, autism, meditative states, THC intake, and psilocybin intake. DMN competes with a contrasting brain network called the Task-Positive Network (TPN), which is involved in externally-oriented or goal-oriented tasks.

The effects of ayahuasca on the DMN in members of the Santo Daime church were assessed in a study using fMRI techniques. They examined the effects on the DMN and the connectivity between the DMN and task-positive network (TPN). They found that ayahuasca caused a reduction in activity in brain regions associated with DMN. These regions included the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and precuneus. They found no difference in the connectivity between the DMN-TPN. Researchers hypothesized that these results reflect the high level of focus and effort required for the ayahuasca experience or that it induces a state similar to meditation which requires increased introspection. Additionally, the intake of ayahuasca results in reduced DMN activity and mind-wandering [25].

Sanches et al. used single-photon emission tomography (SPECT) to evaluate changes in blood perfusion in the brain following ayahuasca ingestion in 17 participants with depression. Eight hours following intake, they found increased perfusion in regions associated with mood and emotions, including the left nucleus accumbens, right insula, and left subgenual region. Increased activity in these areas is associated with antidepressant properties [28]. Riba et al. also utilized SPECT to map changes in regional cerebral blood flow 100-110 minutes following ingestion of ayahuasca in 15 volunteers. SPECT revealed no significant decreases in cerebral blood flow, but there were increases in cerebral blood flow in multiple brain regions. Increased blood flow was found in the right anterior cingulate/medial frontal gyrus, the right anterior insula, and the left amygdala/parahippocampal gyrus. These structures are involved in processing self-awareness, interoception, and emotional state processing [29].

Araujo et al. utilized Blood Oxygenation Level Dependent (BOLD) fMRI to assess the neurologic changes from visual imagery as a result of ayahuasca ingestion in 10 participants. Participants had a baseline fMRI when subjected to varied imagery, such as natural images (viewed pictures of people, animals, or trees), imagery task (they closed their eyes and generate the image they just looked at), and scrambled image (looked at a scrambled version of the image they previously looked at). They found that the imagery task (eyes closed) had a similar level of activation in Brodmann area 17 (BA17) as the natural image (eyes open) following ayahuasca ingestion. BA17 is a primary visual area in the occipital cortex. The activation of this region of the brain was also associated with scores on the Brief Psychiatric Rating Scale (BPRS). They also found brain regions associated with memory, processing of internally generated information, contextual associations, and self-awareness activated. These include BA10, BA30, and BA37. A connectivity analysis was performed that suggested that the primary visual cortex leads other areas during imagery tasks following ayahuasca ingestion. The authors conclude that the imagery elicited by ayahuasca ingestion results in activating a network of brain regions involved in memory and vision [30].

SHORT-TERM PSYCHOLOGIC AND SUBJECTIVE EFFECTS

The effects of IV dimethyltryptamine fumarate (IV DMT) were studied on 12 volunteers in a double-blind, saline placebo-controlled, randomized study. The effects on the participants were monitored with the Hallucinogen Rating Scale (HRS) with subcategories of affect, cognition, intensity, perception, somaesthesia, and volition. They found the effects of IV DMT were almost immediate and peaked between 90-120 seconds. The effects resolved after 30 minutes following administration. The effects of IV DMT were dose-dependent, and hallucinogenic effects were seen with 0.2 and 0.4 mg/kg doses. The 0.05 and 0.1 mg/kg doses did not elicit hallucinogenic effects, but subjects at this dose did have emotional and somaesthetic effects. Participants reported a "rush" that progressed to dissociation. Some described the somaesthesia as "my body dissolved" and "I no longer had a body." As far as emotional change, it was described as anxiety during the subjective rush that was experienced. Often people described euphoria as affective change. Some described fluctuating emotions, such as going from fear or anxiety to euphoria.

The lowest dose for perceptual effects was 0.2 mg/kg. Perceptual changes were visual at the 0.2 mg/kg dose. They were described as geometric patterns, quickly changing visual images, and increased color saturation/brightness. Changes in auditory perception occurred at the highest (0.4 mg/kg) dose and were less frequent at the 0.2 mg/kg dose. Participants experienced high-pitched noises. In regards to the cognitive subscale, some participants reported increased speed of thought processes, but many believed it did not change. The experience was described as being in a dream and increased intelligence with new perspectives. Volition changed as well, with patients sensing a loss of control or helplessness. Overall, the intensity of the experience increased with the increased dose. There was a statistically significant difference between the 0.1 mg/kg and 0.2 mg/kg dose for the subscales of intensity, affect, perception, and cognition. There was a statistically significant difference between 0.2 mg/kg and 0.4 mg/kg doses for intensity, affect, perception, and cognition. This indicates a dose-response of IV DMT [17].

Riba et al. evaluated the subjective effects of ayahuasca on 6 participants using freeze-dried ayahuasca tea. Similar to IV DMT, they found changes in perceptual, cognitive, affective, and somatic domains when assessed. Scores on the Hallucinogen Rating Scale in this study were compared to those of the IV DMT study. Overall, ayahuasca's duration of effects was longer than IV DMT and was less intense. The scores of high-dose ayahuasca were comparable to moderate doses of IV DMT [31].

Riba and colleagues explored the subjective effects of ayahuasca on 18 participants in a slightly larger human study. They found statistically significant increases in all six scales of the HRS, previously mentioned. In addition to HRS, they utilized visual analog scales (VAS) and the Addiction Research Center Inventory (ACRI). The ACRI has five different scales designed to measure euphoria, sedation, somatic-dysphoric, intellectual energy or efficiency, and amphetamine-like effects following use. The ACRI scored significantly increased euphoria (measured by MBG scale), somatic symptoms (measured by LSD scale), and amphetamine-like effects (measured by A scale). The VAS evaluated for having any effect, liking the effects, dizziness/lightheadedness, changes in thought speed and content, perceived positive effects, and changes in visual perception. All seven of the measured VAS parameters were significantly increased as well. These items

were maximally increased between 90 and 120 minutes and slowly returned to baseline at 360 minutes. The largest scale increases in the VAS were for "liking," "any effect," and "high,"; with the least increased scale being "drunken." Overall, ayahuasca ingestion induced feelings of activation, euphoria, somatic effects, and perceptual changes [4].

Mindfulness and Decentering: The subjective effects of ayahuasca have been described as similar to a state of mindfulness. Mindfulness is a state of present-centered awareness of one's current situation, and users of ayahuasca have reported a subjective detached view of their current experience and emotions. Mindfulness interventions have been utilized in the treatment of psychiatric disorders. Decentering is a related ability that allows individuals to take a detached view of their current emotional state. Soler et al. evaluated the effects of a single dose of ayahuasca on mindfulness and decentering capacities in 25 individuals. They utilized the Five Facets Mindfulness Questionnaire (FFMQ) and the Experiences Questionnaire (EQ) 24 hours prior to and 24 hours after ingestion of ayahuasca. FFMQ was intended to measure mindfulness capabilities, and EQ was to measure decentering capabilities. They found statistically significant increases in two facets of the FFMQ, including Non-React and Non-judge, suggesting a relatively acute improvement in mindfulness capacities following ayahuasca ingestion. Additionally, ayahuasca's significant effect on the EQ suggested an increase in decentering capabilities [32].

Creative Divergent Thinking: Divergent thinking represents the ability to think of alternate ideas and solutions to a problem, whereas convergent thinking represents a solitary solution, rigid solution to a problem. Creative divergent thinking can be beneficial in that it allows creative, adaptable solutions to a particular issue. Kuypers et al. evaluated the effect of ayahuasca on convergent/divergent thinking on 26 participants. They utilized the pattern/line meanings test (PLMT) and the picture concept test (PCT) to assess these thinking patterns before and after ayahuasca use. There was a statistically significant increase in creative divergent thinking and reduction of convergent thinking following ayahuasca ingestion, as demonstrated on the PCT. There was no statistically significant change on the PLMT [33].

AYAHUASCA ADVERSE EFFECTS

Short-Term

Cardiovascular

The cardiovascular effects of ayahuasca are known and well documented for both ayahuasca ingestion [5, 42] as well as DMT infusion [17]. The cardiovascular effects of ayahuasca were evaluated in a double-blind placebo-controlled crossover clinical trial on 18 volunteers. They measured systolic BP (SBP), diastolic BP (DBP), and heart rate following ayahuasca ingestion at two different doses in regular intervals up to 240 minutes. Statistically significant differences between the ayahuasca group and placebo were found for DBP, but increases were present for all three cardiovascular parameters. The maximum increase of DBP following the low dose of ayahuasca was 7 mmHg at 60 minutes, and 9 mmHg for the higher dose at 15 minutes. The maximum increase in SBP was 4 mmHg for the low dose and 6 mmHg for the high dose, both at 75 minutes after ingestion. Regarding HR, the maximum increase from baseline was 60 minutes for both doses and was four beats per minute increase [4]. The cardiovascular side effects following administration of ayahuasca in two repeated doses have also been evaluated. They found a statistically significant difference in regards to SBP compared to placebo. DBP was elevated

beyond statistical significance following the second dose of ayahuasca administered four hours after the first dose. In this particular study, SBP increased to >140 mmHg in three participants after the first dose and two participants after the second dose. HR increased over 100 bpm in one participant. However, they concluded that the changes in the cardiovascular parameters were not increased following the second dose compared to the first. But rather, there was a trend toward a statistically significant reduction of SBP and HR following the second dose, which could potentially indicate acute tolerance to ayahuasca from a cardiovascular standpoint [34].

Autonomic

Callaway et al. demonstrated pupillary dilation, increased respiratory rate, and increased oral temperature in addition to the cardiovascular effects above. Pupillary dilation increased from 3.7 mm to a maximum of 4.9 mm at 180 minutes after ingestion. Pupils remained dilated for 6 hours. Respiratory rate increased from 18.4 breaths/min to a maximum of 21.5 breaths/min. Oral temperature was increased from 37.0 to a maximum increase of 37.3 on average [5]. Other studies on both ayahuasca in repeated doses [6] and on DMT have demonstrated an increase in temperature and pupillary dilation [17].

Gastrointestinal

Nausea, vomiting, and diarrhea are some of the more frequently reported side effects following ayahuasca ingestion. A review of clinical trials of ayahuasca determined that out of 53 study participants, four had vomited during the studies [34]. However, the frequency of this side effect has been variable, with one study having as many as 50% of participants vomit,[42] a small study where it only occurred in 1/6 participants, [31] and another study of 17 participants with a frequency of 47% [28]. In a study on ayahuasca in treatment-resistant depression in 29 participants, they found a rate of nausea of 71% and vomiting 57% [35].

Psychiatric

Ingestion of ayahuasca has caused acute anxiety and dysphoric states among participants [34]. In one study of 29 participants of ayahuasca in depression, ~50% of the 29 participants had acute anxiety following ayahuasca use [35]. Riba et al. assessed the tolerability of ayahuasca, found that one participant experienced a period of extreme dysphoria following ingestion [31]. In case studies, ayahuasca use has been associated with acute psychosis amongst UDV members. However, episodes were associated with a personal history of psychosis or other substance use, complicating the picture. Further clinical studies are necessary to assess the risk of psychosis following ayahuasca use [36].

Other Side Effects

These have been observed during clinical trials or reported by ayahuasca members and include headache, restlessness, insomnia, fatigue following the session, dry mouth, muscle spasm, tremulousness, sweating, dizziness, slurred speech, somatic sensations, and feeling hot/cold [31, 35, 37].

Serious or Life-Threatening Side Effects

There was an instance of a fatality following administration of ayahuasca and nicotine preparation. Presumably, it was from nicotine intoxication. There have also been cases of MAO-I intoxication when used with other serotonergic agents. Serotonin syndrome presents with autonomic instability, sweating, muscle spasms, rhabdomyolysis, hyperthermia, cardiovascular changes, and delirium. Although rare with ceremonial use of ayahuasca, serotonin syndrome has been reported. There have also been cases of death following ayahuasca use, but unable to be

certain if ayahuasca toxicity was the direct cause of death or if it was multifactorial due to lack of forensic information in these cases. The likelihood of severe reactions is believed to be increased in persons with liver dysfunction, neurologic dysfunction, cardiovascular dysfunction, people on CYP2D6 inhibitors, individuals taking serotonergic medications, and those eating foods containing tyramine [34].

Long-Term

Doering-Silveira et al. evaluated the neuropsychologic function of adolescent ayahuasca users to other adolescents between the ages of 15-19. Forty adolescents involved in the UDV church were compared to a control group of 40 individuals who had never used ayahuasca. The tests evaluated for attention, concentration, intelligence, language, memory, executive functioning, processing speed, visuomotor skills, and visuoconstructional abilities, among other subcategories. There were no significant differences overall between the ayahuasca users and the control group on neuropsychiatric assessment.[38] Grob et al. performed personality testing, psychiatric interview, and neuropsychiatric testing in 15 long-term ayahuasca using participants compared to 15 controls with no history of ayahuasca use. They found no statistically significant difference in cognitive function of the ayahuasca-using group, and the ayahuasca group outperformed the control in some testing. They did find non-pathologic differences in personality between the two groups, however. These differences included statistically significant higher scores in stoic rigidity compared to exploratory excitability and greater regimentation compared to disorderliness in the ayahuasca group [39]. Barbosa et al. took a prospective look at personality traits and quality of life in ayahuasca-naïve patients that were reassessed after six months. Previous studies had assessed similar measures in participants involved in ritual ayahuasca use over a long time rather than naïve participants. They found no reduction in quality of life among ayahuasca-users during this 6-month follow-up according to their metric, and increased social and emotional functioning amongst regular ayahuasca users [40]. Persistent psychosis has been documented with other hallucinogens. A prolonged psychosis, defined by a psychosis >48 hours, was found with LSD to be 0.8 per 1000 in experimental participants and 1.8 per 1000 in participants undergoing psychotherapy [41]. In regards to ayahuasca and DMT, the rate of prolonged psychosis is not well documented. However, as discussed previously, a history of personal psychosis, family history of psychosis, and or drug use appears to increase the risk of psychosis [36].

HUMAN STUDIES OF AYAHUASCA IN PSYCHIATRY

Depression

The department of Neurosciences and Behavior at the University of Sao Paulo in Brazil conducted a small open-label study of ayahuasca in major depressive disorder. Six participants participated in the study on an inpatient psychiatry unit, and the severity of their depression ranged from mild to severe. All participants were naïve to ayahuasca use and illicit drugs and were not taking psychotropic medications at the time. Santo Daime members in the community prepared the brew for the participants and performed individual-based sessions with participants. Various scales were employed, including the MADRS, HAM-D, YMRS, and BPRS scores were recorded at different time points. They were evaluated with the scales at baseline, 40 minutes, 80 minutes, 140 minutes, and 180 minutes after administration. The scales were

also completed on days 1, 7, 14, and 21 after administration. There was a statistically significant reduction in the HAM-D scale at Day 1 (62% reduction), Day 7 (72% reduction), and Day 21. On the HAM-D and MADRS scales, there were significant reductions from baseline at days 1, 7, and 21. In addition, there was a statistically significant decrease in the MADRS at 180 minutes after administration. Categories that were reduced on these scales included classic depressive symptoms such as suicidal ideation, guilt, pessimistic thinking, and sadness [42].

The Department of Neurosciences at the University of Sao Paulo conducted a subsequent study on the antidepressant effects of ayahuasca in patients with depression. This was also a smaller study but slightly larger than the previous one with 17 participants. Most of the participants were classified as a moderate major depressive episode, but the severity ranged from mild to severe. Similar to the previous study, participants were all naïve to ayahuasca use or illicit drug use. The participants completed the scales HAM-D, MADRS, YMRS, and BPRS at various points following administration. There was also a statistically significant reduction in HAM-D and MADRS scores from 80 to 180 minutes and days 1 and 21 following administration. For reference, the mean HAM-D score was 19.24 at baseline for participants and reduced to a mean score of 7.56 by day 21. Subscales that were decreased included pessimistic thinking, depressed mood, sadness, anxiety, feelings of guilt, suicidal ideation, and concentration difficulty. These studies, although small, demonstrate a possible rapid reduction in depression following ayahuasca administration. In addition, the reduction in depression was maintained over the course of 21 days. However, there were limitations to these studies, including no placebo group, lack of randomization, and was not double-blind [28].

Some of these limitations were mitigated in a study conducted at The Hospital Universitário Onofre Lopes (HUOL) in Brazil. They conducted a double-blind, randomized, placebo-controlled trial on the rapid antidepressant potential of ayahuasca in treatment-resistant depression. In this study, treatment resistance was defined as an inadequate response to at least two antidepressants belonging to different classes. The twenty-nine participants that were selected were all in a current moderate or severe major depressive episode. Fourteen patients were placed in the treatment group, and fifteen patients were in the placebo group. Similar to the previous two studies concerning ayahuasca in depression, participants were excluded with a prior use of ayahuasca, history of bipolar disorder or schizophrenia, family history of bipolar disorder or schizophrenia, and substance use. For the placebo to simulate ayahuasca, a liquid preparation was made to imitate the taste, color, and even some side effects of ayahuasca. The liquid prepared was brown, bitter to taste, and caused mild gastrointestinal distress and anxiety. In preparation, participants were informed that both ayahuasca or the placebo could produce some or no effects. Depressive symptom monitoring with the MADRS and HAM-D scales at baseline and after administration was conducted.

MADRS was completed at baseline, day 1, day 2, and day 7 after administration, while the HAM-D was completed at baseline and at day 7. There was a statistically significant reduction in both MADRS and HAM-D at day 7 after administration. The response rate on the HAM-D was 57% in the ayahuasca group and 20% in the placebo group at day 7, which was a statistically significant difference. There was a remission rate on the HAM-D of 43% in the ayahuasca group and

13% in the placebo group at day 7 but was a not statistically significant difference. The response rate on the MADRS was 64% in the ayahuasca group and 27% in the placebo group at day 7, which was statistically significant. There were no statistically significant differences between placebo and the ayahuasca group on the MADRS on days 1 and 2, as response rates in both groups were high on these days. The remission rate on the MADRS in the ayahuasca group was 36% and 7% in the placebo group but was not statistically significant.[35] A secondary analysis was conducted from the randomized placebo-control trial just discussed assessing suicidality. Suicidality was assessed using the MADRS-SI, an item in the MADRS ranked in severity from 0-6. This was assessed at baseline, day 1, day 2, and day 7 after administration of ayahuasca. The study results demonstrated a decrease in suicidality over time, but the effect of ayahuasca trended toward significance but did not reach significance. It was theorized that the small sample size could be attributed to this result, supported by the fact that they found medium between-group effect sizes for the reduction in suicidality and large effect sizes for the ayahuasca group at days 1, 2, and 7 [43]. These studies have been limited by the number of participants. In addition, blinding of participants is a challenge due to the psychoactive effects of ayahuasca [43].

Santos and colleagues studied the effects of ayahuasca on hopelessness scales in Santo Daime members. They found a statistically significant reduction in hopelessness and often a significant and debilitating component of depression [44].

The effects of ayahuasca on depression with comorbid substance use disorders have also been assessed. Giovannetti and colleagues evaluated the effects of ayahuasca on 31 male inpatient participants undergoing substance use treatment. They utilized the Beck Depression Inventory and found a statistically significant reduction of the scale from a mean of 18.7 to 7.5 following ayahuasca use. This indicates a potential use for ayahuasca in isolated depression and comorbid depression with substance use disorders [45].

Barbosa et al. assessed the psychological impact of ayahuasca first-time ritual users in both UDV and Santo Daime churches. There were 19 participants from Santo Daime and nine from UDV in Brazil. Participants were evaluated using the Clinical Interview Schedule-Revised Edition (CIS-R) for anxiety and depression, among other psychopathologic symptoms, 1-4 days prior to ayahuasca use as a baseline. They were reassessed with the CIS-R 7-14 days after ritual ayahuasca use. At baseline, CIS-R scores were significantly higher in Santo Daime participants than in UDV participants. They found a statistically significant reduction in the CIS-R at the reassessment in the Santo Daime participants but not the UDV participants. Presumably, these results were due to a low score on CIS-R at baseline in the UDV group. The results suggest a possible reduction of anxiety and depression with ayahuasca use after 7-14 days following ayahuasca use [46].

Grob et al. assessed 15 long-term uses of ayahuasca amongst the UDV church. Participants lived in the Brazilian Amazon and were required to have participated in rituals involving ayahuasca use twice monthly at a minimum. The participants in the UDV church were compared against 15 controls that had no history of ayahuasca use. In addition to personality testing and neuropsychiatric testing, Grob et al. conducted interviews that included psychiatric diagnostic interviews. Two participants had a previous history of major depressive disorder that had resolved after joining the church, and had not recurred since involvement in the church.[39]

Bouso et al. evaluated differences in psychopathology, along with other measures, between ayahuasca-using Brazilian church participants and members of other religious churches that do not use ayahuasca. Participants in the ayahuasca group had to be using ayahuasca for 15 years and use it at least two times per month. Participants were recruited from both jungle and urban settings. Fifty-six ayahuasca users were selected from a community in the Amazon rainforest for the jungle group and were compared to 56 controls selected from the jungle town of Boca do Acre. There were 71 urban ayahuasca users selected in Rio Branco for the urban group compared to a control group of 59 participants from Rio Branco. Participants completed the SCL-90-R questionnaire at baseline and one year after the initial assessment to assess for psychopathology. It included assessment of somatization, obsessive-compulsive pathology, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Compared to the control group, ayahuasca users scored significantly lower on all categories of psychopathology at the first assessment, including depression. At the second assessment, ayahuasca scored significantly lower on 7 of the 9 categories of psychopathology, which did not include depression [47].

Anxiety and Related Disorders

In a study investigating ayahuasca and hopelessness, the effects of ayahuasca on state-anxiety and panic were assessed in a placebo-controlled study on nine Santo Daime members following ingestion. Santo Daime members prepared the ayahuasca in this study compared to an ayahuasca-flavored solution as a control. State-anxiety and trait-anxiety were analyzed using the state-trait-anxiety inventory (STAI), and panic-like states were measured using the anxiety sensitivity index (ASI-R). Participants were all administered the control solution at the first session, and baseline questionnaires were completed 1 hour after consumption. A week later, the second session took place in which five participants consumed ayahuasca, and the other four participants consumed the control. Questionnaires were distributed 1 hour after consumption. In the final session, the participant groups switched, and those that consumed ayahuasca in the week before consumed the control and vice versa. Questionnaires were completed 1 hour after consumption again. The results demonstrated a reduction in hopelessness, as mentioned previously, and panic-like parameters demonstrated in the ASI-R. There was no reduction in trait-anxiety and state-anxiety in the STAI. However, this study had many limitations, including that participants were not ayahuasca-naïve and a small sample size [44].

In a cross-sectional study, Da Silveira et al. evaluated differences in depression, anxiety, alcohol abuse, attention deficits, and body dysmorphic disorder amongst adolescent religious ayahuasca users compared to controls. There were 40 participants in the ayahuasca group and 40 in the control group, all between 15 and 19 years old. In the ayahuasca group, the average length of use was 4.05 years of at least once/month use. Ayahuasca-using adolescents underwent a 20-day period of abstinence prior to being assessed. Screening instruments used to assess anxiety included the Beck Anxiety Inventory and the State-Trait Anxiety Inventory (STAI), in addition to other screening instruments mentioned previously. There were no statistically significant differences between these two groups, but there was a trend towards reduction in anxiety in the ayahuasca-using group [38].

Bouso et al., whose methods were discussed and described previously, compared psychopathology between ayahuasca-using Brazilian church participants and members of other religious churches that do not use ayahuasca. Compared to the control group, ayahuasca users scored significantly lower on all categories of psychopathology at the baseline assessment including anxiety and phobic anxiety. At the second assessment which was one year after the baseline, ayahuasca using participants scored lower on 7 of the 9 categories of psychopathology which included anxiety and phobic anxiety [47].

Substance Use Disorders and Addiction

A large, longitudinal study was conducted on the effect of ayahuasca on the recidivism rate among substance users convicted of a felony in the Southeastern US. Individual data from a database of over 25,000 individuals enrolled in a case management program, Treatment Accountability for Safer Communities (TASC), was obtained between the years 2002-2007. Hallucinogen use among enrollees in TASC was determined during a structured interview on the intake into the program. This particular study looked into hallucinogen use and supervision failures amongst individuals in the TASC program. Supervision failures included failure to report to the program, failing other requirements, incarceration, and not appearing in court. They found that individuals with hallucinogen use were associated with a decreased supervision failure. The use of other drugs such as amphetamines, opioids, alcohol, and cocaine demonstrated an increased supervision failure. This suggests the possible role of hallucinogens among substance users involved in the criminal justice system. However, this study did not differentiate ayahuasca from other hallucinogens but rather grouped all hallucinogens into one category [48].

Fábregas et al. assessed for reduction of other substance use amongst long-term ayahuasca users compared to non-users of ayahuasca. This study assessed differences in both small Amazonian towns and larger urban areas in two separate studies. The significance of drug use among these groups was assessed using the Addiction Severity Index (ASI), which involves an interview that assesses the impact of drug use on an individual. ASI has several categories it assesses, including Employment and Support, Drug and Alcohol Use, Medical Status, Family and Social Relationships, Legal Status, and Psychiatric Status. Participants in both groups were assessed at baseline and at a 1-year follow-up. The ayahuasca group had a statistically significant reduction in Alcohol Use and Psychiatric Status subscales in urban and rural settings. In both urban and rural settings, ayahuasca users scored significantly higher on Drug Use subscales, as ayahuasca use was included in that subscale. At the one-year follow-up, the ayahuasca group maintained a statistically significant lower score on Alcohol Use and Psychiatric Status subscales. The reduction in the Alcohol Use subscale indicates a possible reduction in use amongst ayahuasca users. However, the ayahuasca group had an increase in the Drug Use subscale in this study, as ayahuasca use was included in that subscale. Overall, this study demonstrated a reduced amount of alcohol use in ayahuasca and demonstrated that ayahuasca use possibly does not have the detrimental psychosocial problems associated with other drugs which was the primary focus of the study [49].

In Brazil, some who suffer from crack cocaine dependence have turned to ayahuasca to help with abstinence. Researchers in the Department of Preventative Medicine at the Universidade

Federal de São Paulo performed a study on the use of ayahuasca in the context of religious ceremonies to aid in crack cocaine recovery. They interviewed 40 former or current crack cocaine users in a semi-structured format that utilizes ayahuasca to help resolve their dependency on the substance. Participants generally cited failing classical treatments of substance dependence as a reason for seeking out ayahuasca, and only 8 of the participants had reported a relapse on crack cocaine after ayahuasca administration. Many of the participants attributed their success to not only ayahuasca alone but also the religious and community aspect of the treatment. This qualitative study provided good insight into the potential for ayahuasca in crack cocaine dependence [50].

A Canadian retreat, "Working with Addiction and Stress," is a program that incorporates ayahuasca into the treatment of addiction. Researchers at the University of British Columbia studied the effect of ayahuasca-assisted treatment on the reduction of substance use, quality of life, and several behavioral states associated with substance use in an observational study. The behavioral states that were monitored were hopefulness, mindfulness, empowerment, and emotional regulation. Emotional regulation is a protective factor against substance use, mindfulness is a technique used at reducing substance use (as seen in ACT, DBT, CBT, and mindfulness-based relapse prevention), hopelessness is associated with substance use, and empowerment has been associated with substance use prevention. Substance use was measured by the 4WSUS, which measures the level of substance use, among other measures related to a pattern of use. There were 12 participants, and all were of the First Nations band. They were assessed at baseline as well as at a 6-month follow-up. The results showed an improvement in mindfulness, empowerment, and hopefulness following the "Working with Addiction and Stress" retreat. These behavioral states are associated with recovery from problematic substance use. There was also an improvement in the quality of life measures following the retreat as well. On the 4WSUS measuring severity of substance use, scores decreased for alcohol, tobacco, and cocaine but had no change in the use of cannabis. These results suggest a possible use for ayahuasca-assisted group therapy in the future for substance use disorders [51].

Barbosa et al. explored levels of tobacco and alcohol use amongst religious ayahuasca users of the União do Vegetal (UDV) compared to a control group in a cross-sectional study. A total of 1,947 UDV members were assessed compared to 7,939 participants in the control group used as the "Brazilian norm." Within UDV, ayahuasca is ingested by its members in ceremonial practice. In this particular study, the mean number of years of membership was 9.44 in the UDV group, with a mean number of 34.99 ceremonies attended. The control group was recruited from varying regions of brazil. Both current and lifetime alcohol and tobacco use were assessed using the Substance Abuse and Mental Health Services (SAMHSA) and the sections of the WHO Research and Reporting Project on the Epidemiology of Drug Dependence for alcohol and tobacco. They found a statistically significant increase in lifetime alcohol and tobacco use in the UDV sample compared to the control, but a significantly reduced amount of current alcohol and tobacco use. In addition, they also found that there was an even more significant reduction in current use correlated with a membership of greater than three years, as well as ceremonial attendance in the last 12 months. This is indicative of possible benefit in reduction of tobacco and alcohol use with ayahuasca use, despite a higher incidence of lifetime alcohol and tobacco use [52].

Lawn et al. aimed to evaluate problematic alcohol use and well-being amongst ayahuasca users in another cross-sectional survey. Ayahuasca users were compared to both a non-psychedelic using control group as well as other psychedelic users. A total of 527 ayahuasca users, 18,138 users of other non-ayahuasca psychedelics, and 78,236 non-psychedelic using participants were evaluated in this study. Participants were divided into categories based on the response of whether they have taken ayahuasca in the last year, other psychedelics but not ayahuasca in the last year, and no psychedelics in the last year. Problematic alcohol use was assessed using the Alcohol Use Disorder Identification Test, and well-being was assessed using the Personal Wellbeing Index. Although well-being was reported to be higher in the ayahuasca user group compared to the other two control groups, ayahuasca users reported increased problematic drinking compared to the non-psychedelic users. These results contrast with the previously mentioned cross-sectional study that demonstrated reduced current alcohol use amongst ayahuasca users. Another variable they assessed was lifetime mental illness. Ayahuasca users had increased lifetime mental illness diagnosis when stratified to countries without historical use of ayahuasca, compared to both controls. However, there was not an increased lifetime incidence of mental illness in the ayahuasca compared to controls when stratified in countries with historic ayahuasca use alone [53].

Halpern et al. conducted interviews and evaluations of members of the Santo Daime Church to assess the long and short-term health effects of ayahuasca. Participants were 34 members of the Santo Daime Church in Oregon. Among demographic information and other psychological measures, the interviews consisted of a thorough timeline of substance use history. Many individuals reported a history of drug use, but no participants reported re-activation or worsening of other substance use after initiation in Santo Daime. Twenty-Four of the 34 interviewees reported past drug or alcohol use, and all but two were in sustained remission at the time of the interview. The two individuals that were not in sustained remission had recent or active cannabis use. Of note, five participants had a history of alcohol dependence and reported that their involvement in the Santo Daime Church was influential in their recovery [37].

Velder et al. also conducted interviews in an exploratory study to obtain subjective experiences in ayahuasca-assisted therapy for substance dependence. Individuals interviewed about their experiences included therapists, healers, and mental health professionals that have utilized ayahuasca in their treatments and patients that have undergone ayahuasca-assisted treatment for addiction. They also interviewed experts in the field of ayahuasca-assisted treatments. The therapists interviewed were from a wide range of practice settings and countries, including Peru, Brazil, Argentina, Spain, Canada, and the United States. Individuals interviewed who had completed ayahuasca-assisted treatment varied in background and included Peru, Argentina, Mexico, Colombia, Spain, and America, and came from urban and rural backgrounds. These individuals all had a history of severe substance dependence in the past, with a mean length of use of 14 years. Participants reported that ayahuasca was crucial to their recovery, and therapists reported ayahuasca as being of high value in regards to a treatment modality.

Interestingly, participants reported that they had a reduction in cravings following ayahuasca use. Many of them felt they were better able to understand their addiction following sessions with ayahuasca. Although a qualitative study with the potential for

significant bias, the exploratory findings of this study may indicate that ayahuasca may have a place in the appropriate context [54].

Grief

González et al. evaluated the possible therapeutic potential of ayahuasca in grief in a cross-sectional study. Participants were recruited through an online survey. There were 30 participants in the ayahuasca-using group compared to 30 participants that had attended a peer-support group which served as the control. Participants in both groups had lost a first-degree relative within the last five years. There were no significant differences in the number of losses and time since the losses in between both groups. The Texas Revised Inventory of Grief was used to assess both past grief and present grief. The Past Feelings Scale of the questionnaire was utilized to assess the level of grief following the loss, and the Present Feelings Scale was utilized to measure current levels of grief between groups. It was found that both groups had similar levels of grief following the death, but the ayahuasca group scored lower on the Present Feelings Scale than the control group [55].

Personality Disorders

Domínguez-Clavé et al. assessed ayahuasca's effect on emotional dysregulation, mindfulness, and borderline personality-like traits. They conducted an observational study conducted on 45 participants. They utilized instruments such as the Difficulties in Emotion Regulation Scale (DERS) to assess emotional dysregulation and the Five Facet Mindfulness Questionnaire (FFMQ) to assess mindfulness traits. Participants were divided into subgroups based on the McLean Screening Instrument of BPD (MSI-BPD) at baseline into BPD-like traits and non-BPD-like traits. The FFMQ and DERS were completed at baseline as well as 24 hours after an ayahuasca session. They found a statistically significant reduction in four subscales of the FFMQ, including acting with awareness, non-judging, observing, and non-reaction. On the DERS, they showed a statistically significant reduction on subscales of emotional interference, lack of control, and emotional non-acceptance. The BPD-like trait group also had a statistically significant reduction in the subscale of emotional interference and lack of control compared to the non-BPD-like traits group [56].

CONCLUSION

Ayahuasca has a very complex pharmacologic profile, which causes psychoactive effects mediated by its serotonergic properties [2,3]. It has effects on various neurotransmitters and receptors in the brain that may be found to be beneficial in various psychiatric disorders [11, 16, 18, 23, 24]. Furthermore, ayahuasca ingestion has resulted in a decrease in activity in the default mode network, increased mindfulness and decentering capabilities, and divergent creative thinking which also may make ayahuasca a candidate therapy in psychiatry [25, 32, 33]. The tolerability of ayahuasca may be a significant barrier of use in practice, as it causes autonomic, cardiovascular, gastrointestinal, and psychiatric side effects at varying rates [3, 31, 34, 35, 36]. Severe and fatal responses have been reported as well [34]. Initial studies regarding ayahuasca for depression, anxiety, substance use, and other psychiatric disorders have been positive and suggest a possible role for ayahuasca as an alternative treatment. However, more robust clinical trials involving ayahuasca are required to better characterize the safety and efficacy of South American tea prior to its use in psychiatric practice.

AUTHOR INFORMATION

Send correspondence to Adam Bertroche, DO (Bertad01@luther.edu)

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