Journal of Psychoactive Drugs, 45 (2), 179–188, 2013

ISSN: 0279-1072 print / 2159-9777 online
DOI: 10.1080/02791072.2013.785846

A Critical Evaluation of Reports Associating Ayahuasca with Life-Threatening Adverse Reactions

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Abstract—Ayahuasca is a botanical hallucinogenic preparation traditionally consumed by Northwestern Amazonian indigenous groups. Scientific evidence suggests good tolerability after acute administration of ayahuasca and also after years or even decades of its ritual consumption. Nevertheless, some scientific and media reports associate ayahuasca or some of its alkaloids with severe intoxications. The purpose of the present text is to do a critical evaluation of these reports. The evaluation of the cases highlights the fact that some lack accurate forensic/toxicological information, while others are not directly relevant to traditional ayahuasca preparations. These limitations reduce the possibility of an accurate risk assessment, which could indicate potential contraindications and susceptibilities for ayahuasca consumption. Nevertheless, even with these limitations, the cases suggest that previous cardiac and hepatic pathologies and current use of serotonergic drugs/medications are contraindications to ayahuasca use, and that caution should be taken when using different botanical species and extracted/synthetic alkaloids to prepare ayahuasca analogues.

Keywords—ayahuasca, hallucinogens, psychopharmacology, tolerability, toxicology

RATIONALE

In the last few decades, an increase in the ritual and psychonautic uses of ayahuasca and analogue preparations has been observed in many parts of the world. This cultural phenomenon has increased the need for more scientific information regarding the human pharmacology and toxicology of ayahuasca consumption.

Current scientific evidence suggests safety and good tolerability after acute and long-term ayahuasca administration/consumption in humans. Moreover, there is no scientific published study or report of serious intoxications caused by ayahuasca *per se*. Nevertheless, there are scientific reports and media-reported histories of cases associating ayahuasca or some analogue preparations with life-threatening adverse reactions and even lethality.

The present text will briefly review the ethnobotany, phytochemistry, and pharmacology of ayahuasca in humans. Moreover, the present work will critically evaluate the possible causal role, if any, of ayahuasca or of some of its alkaloids in cases reporting severe intoxications. Possible biological mechanisms for explaining potential toxic effects will also be discussed.

MATERIAL AND METHODS

A bibliographical research was performed searching for toxicological information on ayahuasca, dimethyltryptamine, harmine, and related compounds; clinical trials of acute ayahuasca administration; and studies of long-term ayahuasca consumption; as of May 2013. The studies' languages were limited to Portuguese, English, and Spanish.

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Article research was performed using the PubMed and SciELO (Brazilian) databases, specialized books and book chapters, as well as the relevant bibliography extracted from research papers, books, and book chapters. Moreover, Internet websites specializing in ayahuasca and related themes were also consulted, as well as articles in digital magazines and newspapers.

RESULTS

Ethnobotany and Phytochemistry

Ayahuasca is a hallucinogenic botanical preparation traditionally used in magico-religious rituals by indigenous groups of Northwestern Amazonian countries like Colombia, Peru, Ecuador, and Brazil. It is commonly obtained by the decoction of the stems of the jungle vine *Banisteriopsis caapi* together with the leaves from the shrub *Psychotria viridis* or from the liana *Diplopterys cabrerana*. *B. caapi* is rich in β-carboline alkaloids, especially harmine and tetrahydroharmine (THH), while *P. viridis* and *D. cabrerana* are rich in the tryptamine hallucinogen *N*,*N*-dimethyltryptamine (DMT) (dos Santos 2011a; dos Santos 2011b; Luna 2011; Schultes & Raffauf 2004; Riba 2003; Ott 1994; Schultes & Hofmann 1992; Schultes 1986).

In many indigenous contexts of ayahuasca preparation, several other admixture plants are added to the brew (McKenna et al. 1995; Ott 1994). Some of these botanical ingredients appear to be non-psychoactive, while others contain psychoactive substances like the psychostimulants caffeine (*Illex guayusa*, *Paullinia yoco*), cocaine (*Erythroxylum coca*), and nicotine (*Nicotiana* spp.), and the anticholinergic deliriant scopolamine (*Brugmansia* spp.) (dos Santos 2011a; dos Santos 2011b; Riba 2003; McKenna et al. 1995; Ott 1994).

The ritual and therapeutic uses of ayahuasca are also present among the *mestizo* populations of Colombia, Peru, and Brazil, and also among syncretic Brazilian religions like the *Santo Daime* and the *União do Vegetal*, which today have groups present not only in the main Brazilian cities but also in other South American countries, the United States, Europe, Asia, and Africa (Labate & Jungaberle 2011; Luna 2011; Labate & MacRae 2010; Labate et al. 2009; Luna 1986).

In addition to ayahuasca *per se*, which in the present text will refer exclusively to the brew prepared by the decoction of *B. caapi* stems and *P. viridis* leaves, some preparations intended to replicate the ayahuasca formula also exist. Some of these preparations are made by the admixture of extracted compounds like harmine plus DMT (*pharmahuasca*), while others are prepared with other botanical sources of β-carbolines and tryptamines (*anahuasca*), like *Peganum harmala* [Syrian rue] seeds, a β-carbolines source, in combination with the inner bark of *Mimosa tenuiflora* [jurema], a DMT-rich plant traditionally used in indigenous and syncretic rituals in Northeast Brazil (da Mota & Albuquerque 2002; Ott 1994).

Mechanism of Action and Acute Human Pharmacology

The β-carboline harmine is a natural, reversible, and specific inhibitor of the enzyme monoamine oxidase A (MAO-A), which is involved in the metabolism of serotonin, norepinephrine, dopamine, and DMT. THH acts as a selective inhibitor of serotonin reuptake. MAO-A inhibition by harmine appears to be the main pharmacological action of the β-carbolines in ayahuasca preparations. Harmine inhibits the metabolism of DMT in the gastrointestinal tract and thereby allows it to reach the central nervous system, where it acts as a serotonin$_{2A/2C/1A}$ receptor agonist at frontal and paralimbic brain regions (dos Santos 2011a; Riba et al. 2006; Riba 2003; Riba et al. 2003; Smith et al. 1998; McKenna et al. 1984; Buckholtz & Boggan 1977a; Buckholtz & Boggan 1977b).

The acute administration of ayahuasca in randomized, double-blind, placebo-controlled clinical trials in healthy humans has shown that ayahuasca produces perceptual, cognitive, and affective modifications at the subjective level (dos Santos et al. 2012; dos Santos et al. 2011; Riba et al. 2003; Riba et al. 2001), relative power increase in the beta band of the electroencephalogram (dos Santos et al. 2012; dos Santos et al. 2011; Riba et al. 2002), increase of urinary excretion of normetanephrine, a methylated breakdown product of norepinephrine, which indicates MAO inhibition (Riba et al. 2003), moderate increases in blood pressure and heart rate (dos Santos et al. 2012; Riba et al. 2003; Riba et al. 2001), increases in the secretion of prolactin, cortisol, and growth hormone (dos Santos et al. 2012; dos Santos et al. 2011), moderate increases in autonomic variables such as body temperature, respiration rate, and pupillary measures (dos Santos et al. 2012; dos Santos et al. 2011), and modifications in lymphocyte subpopulations such as decreases in the percentages of CD4 and CD3 and increases in the percentages of natural killer cells (dos Santos et al. 2012; dos Santos et al. 2011). Moreover, blood analyses do not show any evidence of clinically relevant alterations in hematological indices or biochemical indicators of liver function or other standard analytical parameters (cellular counts, plasma bilirubin, and hepatic enzymes) (Riba et al. 2001).

Acute Safety, Tolerability, and Possible Adverse Reactions

Gastrointestinal effects. Nausea and vomiting are the most frequently reported adverse effects in clinical trials of acute ayahuasca administration (dos Santos 2013a; dos Santos et al. 2012; dos Santos 2011a; Riba & Barbanoj, 2005; Riba 2003; Riba et al. 2001). A review of the controlled clinical trials of acute ayahuasca administration published in 2005 (Riba & Barbanoj 2005) related that

actual vomiting was only observed in four of 53 occasions of ayahuasca administration (some volunteers were administered ayahuasca more than once).

Variable degrees of nausea, vomiting, and occasionally simultaneous diarrhea, are not uncommon in ayahuasca rituals. In general, these purgative effects are considered positive by participants of ayahuasca ceremonies. In *Santo Daime*, for example, vomiting and diarrhea are interpreted as a ritual "*limpeza*" (Portuguese for "cleansing"), and one of the Colombian names for ayahuasca, which in that country is commonly prepared by using *B. caapi* stems plus *D. cabrerana* leaves, is "*la purga*" (Spanish for "the purge") (dos Santos 2011b; Labate & Jungaberle 2011; Labate & MacRae 2010; Labate et al. 2009; Shanon 2002; Luna 1986).

Cardiovascular effects. Ayahuasca produces moderate cardiovascular effects in young, healthy volunteers, with few and brief cases of hypertension and/or tachycardia (dos Santos et al. 2012; Riba & Barbanoj 2005; Riba et al. 2003; Riba et al. 2001). These moderate effects may have a different impact in persons who are performing physical exercise, in older individuals, or in people with cardiovascular pathologies. From published research studies of ayahuasca in healthy subjects, there are no reported significant cardiovascular adverse events.

Psychological effects. Riba et al. (2001) reported that one volunteer experienced a brief (around 20 minutes in duration) but intensely dysphoric reaction with disorientation and anxiety symptoms that remitted after verbal support. Riba & Barbanoj (2006) related a case of a volunteer who reported feelings of suspiciousness and menace that remitted after the expected time of action of ayahuasca, requiring no medical intervention. Riba & Barbanoj (2005) reported that states of manifested agitation and panic were never observed in their studies.

Recent reviews highlight the safety and good physiological and mental health tolerability of acute ayahuasca administration (dos Santos 2013a; dos Santos 2011a; Bouso & Riba 2011; Riba & Barbanoj 2011; dos Santos 2010; Gable 2007; Riba & Barbanoj 2005; Riba 2003).

Long-term Safety, Tolerability, and Possible Adverse Reactions

The scientific literature assessing possible deleterious effects of long-term ritual ayahuasca consumption on physiological, psychological, psychiatric, and neuropsychological measures has been reviewed (dos Santos 2013a; Barbosa et al. 2012; Bouso & Riba 2011; dos Santos 2010; Gable 2007). These reviews suggest that there is no evidence of physiological or mental health toxicity in long-term consumers of ayahuasca, despite years and sometimes several decades of continuous ayahuasca consumption.

The incidence of psychopathology among long-term ayahuasca consumers appears to be low. Nevertheless, psychotic-like adverse reactions persisting after the expected effects of ayahuasca have been described (dos Santos & Strassman 2011; Lima & Tófoli 2011; Lima et al. 2002; see for review dos Santos 2013a; Bouso & Riba 2011; dos Santos 2010; Gable 2007).

AYAHUASCA AND LIFE-THREATENING ADVERSE REACTIONS

Critical Evaluation of Scientific Reports

Fatal nicotine intoxication resulting from the ingestion of "ayahuasca." Warren (2004) published a brief report that describes the unexpected death of a 7l-year-old native female who was partaking in a three-day holistic healing ritual involving ayahuasca. On the third day she was given, apparently, an enema of the ayahuasca preparation. Following this, she collapsed and died a short time later.

The preparation was made with *B. caapi* mixed with tobacco leaves, which is consistent with the chemical analysis of the ayahuasca brew that found harmine, harmaline, and nicotine. An autopsy revealed no anatomical cause of death and blood analysis revealed only the presence of nicotine. The cause of death was attributed to acute nicotine intoxication.

Warren (2004) did not document the concentration of any β-carbolines, but did report measurements of nicotine concentrations that exceeded by at least 20 times the average postmortem nicotine concentration reported in another study (Gable 2007). Since tobacco smoke inhibits human monoamine oxidase, where β-carboline alkaloids act as potent and reversible inhibitors (Herraiz & Chaparro 2005), it is theoretically plausible to speculate that the ayahuasca β-carbolines could increase the toxicity of nicotine by increasing the monoamine oxidase inhibitory effect.

Despite the fact that nicotine can be found as a component of ayahuasca (Ott 1994), the case of this woman highlights the fact that ayahuasca can be obtained not only by using *B. caapi*, but also by adding a great variety of plants to the potion. Many of these plants have unknown chemical components, and more than 120 plants are capable of, in more than 4000 different combinations, producing ayahuasca analogues (McKenna et al. 1995; Ott 1994). Caution must be taken regarding "homemade" ayahuasca analogues, since different methods of preparation may increase toxicity. Swallowing Syrian rue seeds (*P. harmala*) or the root bark of jurema (*M. tenuiflora*) could be more toxic than consuming aqueous infusions of these botanical species (Ott 1996).

From the available information, including the absence of information regarding the previous heath condition of this woman, it can be affirmed that ayahuasca *per se* did not cause the death, which was probably caused by nicotine. The title of the report by Warren wrongly associated the death with ayahuasca *per se*.

Monoamine oxidase inhibitor poisoning resulting from Internet misinformation on illicit substances. In another report, Brush et al. (2004) described a case of a 17-year-old adolescent who had a severe, non-fatal intoxication caused by the combination of an extract of three Syrian rue seeds with smoked and snorted 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT). The authors argue that the combination of a MAO inhibitor with another centrally active serotonergic agent poses significant health risks from MAO inhibitor poisoning or serotonin syndrome. Next, they argue that MAO toxicity is initially characterized by hyperthermia, tachycardia, agitated delirium, and rhabdomyolysis as a consequence of muscle activity (see also Yamada & Yasuhara 2004). Widely fluctuating vital signs and depression of mental status would also occur. The recovery period would be typically of several days. Brush et al. argued that with the exception of hypertension, the adolescent demonstrated all aspects of MAO inhibitor intoxication.

Anecdotal and self-experimentation reports, as well as clinical studies in healthy volunteers, suggest that administration of harmine and related compounds demonstrate an absence of any serious adverse reactions. Adverse reactions to these substances are mostly somatic-dysphoric effects, nausea and vomiting, tremor, body numbness, dizziness, bradycardia, trouble focusing the eyes, hypotension, and cold extremities, even with high doses (dos Santos 2011a; Riba 2003).

Poisoning admissions to a Tunisian intensive care unit over a five-year period report that four (7%) of 56 cases were due to exposures to *P. harmala*, none of whom died (Yuruktumen et al. 2008). Gable (2007) reported that fatalities from harmine are extremely rare and Frison et al. (2008) argued that "there has been no report of fatalities as a direct consequence of harmala alkaloids intoxication."

Mahmoudian et al. (2002) described a case where a 35-year-old male patient experienced gastrointestinal distress, slight elevation in body temperature and pulse rate, low blood pressure, convulsion, tremor (limbs and facial muscles), visual hallucination, abdominal pain. and vomited blood after taking 150 g of seeds of *P. harmala*. Endoscopy showed a gastric ulcer and laboratory tests showed a mild anemia due to his internal bleeding. Other biochemical parameters were found to be normal. After a few hours, signs and symptoms of toxicity had resolved and he left the hospital.

Another case reported the intoxication of a 27-year-old woman with *P. harmala* seeds. This person presented hallucinations and neuro-sensorial syndromes, bradycardia, nausea, and vomiting. Liver, kidney, and hematological tests were normal, and the patient was discharged from the hospital a few hours later after signs of intoxication had disappeared. She had consumed 50 g of *P. harmala* seeds in a cup of coffe (Mahmoudian et al. 2002).

Frison et al. (2008) described a case where an 18-year-old male was admitted to an emergency unit due to *P. harmala* intoxication. He presented psychomotor agitation, visual hallucinations, diffuse tremors, ataxia, vomiting, nystagmus, was "unable to stand upright," and "sleepy though responding to verbal stimulus." The patient rapidly and fully recovered and was discharged the following day. Tests for the presence of other psychoactive drugs in both the seed extract brought by the patient and in his urine yielded negative results. In particular, no trace of DMT, 5-MeO-DMT or hallucinogenic tropane alkaloids (atropine, scopolamine) were detected. There was no information regarding the β-carboline dose used by the patient, but the authors argued that the concentrations found should be considered "unexpectedly high."

Yuruktumen et al. (2008) reported a case where a 41-year-old female experienced *P. harmala* intoxication after consumption of a hot drink made by boiling in water approximately 100 g of the seeds of the plant. Her intention was to use the preparation in order to "calm her nerves." She used no regular medications, had no significant past medical history, and had not used herbal preparations before. According to a relative, approximately three hours after drinking the preparation, "she became nauseated and vomited several times." Then "she became somnolent, experienced visual hallucinations and diaphoresis" and then was "unarousable while in a deep sleep." The next morning she was "still unarousable and was noted to be diaphoretic," so the relative called an ambulance. Upon presentation to the emergency room, she was unconscious and had hypertension, tachycardia, and tachypnea. Measures of renal function were significantly decreased and hepatic enzymes were markedly elevated. She improved with supportive care over the course of five days. When she was discharged on day 10, her renal function tests had returned to normal but her hepatic enzymes were still elevated. Upon discharge she exhibited no symptoms, and had no neurologic or other complaints.

According to Yuruktumen et al. (2008), signs of intoxication in other case reports of *P. harmala* seed ingestion received treatment within minutes-hours and resolved themselves over the course of a few hours. In contrast, this patient presented 18 hours after ingestion. The patient presented life-threatening respiratory difficulties, coma, and disturbed liver and renal function tests and, according to the authors, was the first severe poisoning due to *P. harmala* in the English medical literature. Nevertheless, when contacted by telephone three months later, she reported no symptoms or sequelae from this incident. It also must be noted that the recommended dose to make a tea from the seeds is 5-10 g (Gracie & Zarkov 1986), so the patient consumed 10-20 times this dose.

From the available information described above, the report by Brush et al. (2004) of MAO inhibitor intoxication seems inconsistent. There are some contraindications to

the use of MAO inhibitors, including severe liver and kidney impairment, severe or frequent headache, uncontrolled hypertension, cardiovascular diseases, and cerebrovascular diseases (Savinelli & Halpern 1995), but Brush et al. do not give any information about the previous health status of the adolescent. Also, in the cases of intoxication where *P. harmala* seeds were ingested, it is necessary to take into consideration that there are other alkaloids in these seeds that could contribute to some toxic effect. In particular, peganine and deoxypeganine, two quinazoline alkaloids, have a strong anticholinesterase activity (Frison et al. 2008).

Although it cannot be determined conclusively what actually happened, what Brush et al. (2004) described as MAO inhibitors intoxication could perhaps be classified as a case of serotonin syndrome, which may include mental status changes, agitation, tremor, diarrhea, autonomic instability, hyperthermia, sweating, muscle spasms, rhabdomyolysis, and possible death (Boyer & Shannon 2005; Hilton et al. 1997). In fact, there is one paper arguing that *P. harmala* could be a possible causing agent of serotonin syndrome (Boyer & Shannon 2005), although this report should be examined with caution, since the authors do not offer any reference of a concrete case of intoxication with this plant or any data regarding its possible toxic dose.

A few irreversible or non-selective MAO inhibitors (e.g., phenelzine, tranylcypromine) are associated strongly with instances of severe serotonin syndrome, but a large number of opiates, analgesics, tricyclic antidepressants, selective serotonin reuptake inhibitors and antimigraine agents have also been implicated. The combination of MAO inhibitors such as some ayahuasca β-carbolines with monoaminergic and serotoninergic substances in general, antidepressives, as well as ginseng, St John's wort, dextromethorphan, amphetamine, and 3,4-methylenedioxymethamphetamine (MDMA: "ecstasy"), could produce the serotonin syndrome (dos Santos 2013a; Pilgrim et al. 2012; Frecska 2007; Gable 2007; Silins et al. 2007; Boyer & Shannon 2005; Vuori et al. 2003; Callaway & Grob 1998; Hilton et al. 1997; Abdel-Fattah et al. 1996; Savinelli & Halpern 1995; Bonson 1994).

Nevertheless, serotonin syndrome is not commonly reported in the context of sacramental ayahuasca use, and anecdotal evidence suggests that many people use antidepressants, including selective serotonin reuptake inhibitors, in combination with ayahuasca, without presenting any toxic reaction (Lima & Tófoli 2011). Taking into account the available information described above, one possible explanation is that the ayahuasca β-carbolines are reversible inhibitors of MAO-A, and the use of these substances alone or in combination with selective serotonin reuptake inhibitors appears to present better safety and tolerability related with the occurrence of serotonin syndrome (Hilton et al. 1997). Another possibility is that the significant up-regulation in the density of the serotonin transporter in blood platelets of ayahuasca long-term consumers reported by Callaway et al. (1994) could enhance the uptake of serotonin. This might reduce the chance of accumulation of this neurotransmitter, even in the presence of a pro-serotoninergic substance.

The only published report relating ayahuasca with the serotonin syndrome is the case reported by Callaway & Grob (1998). These authors described a case study in which the concomitant use of ayahuasca and daily use of a serotonin reuptake inhibitor (fluoxetine) by an 36-year-old male led to motor tremors, sweating, shivering, confusion, and severe nausea and vomiting. These symptoms persisted for around four hours, which is approximately the time necessary for the resolution of ayahuasca effects. No long-term consequences were reported.

From the available information, it can be affirmed that serotonin syndrome may actually happen during ayahuasca consumption, especially if pro-serotonergic drugs are concomitantly consumed.

A fatal intoxication following the ingestion of 5-Methoxy-N,N-dimethyltryptamine in an ayahuasca preparation. Sklerov et al. (2005) described a case of a 25-year-old male who was found dead the morning after consuming herbal extracts containing β-carbolines and tryptamines. There is no information regarding the composition or dosage of the herbal preparation, although blood analysis found harmine, THH, harmaline, DMT and 5-MeO-DMT. No anatomic cause of death was found in the autopsy and the medical examiner ruled that the cause of death was hallucinogenic amine intoxication and the manner of death was undetermined.

The article title may be misleading because the term "ayahuasca" is being used generically. Moreover, Callaway and collaborators (2006) argued that this hallucinogenic amine intoxication could not be attributed to ayahuasca *per se*. Considering the high levels of 5-MeO-DMT measured in the study, and the fact that neither *B. caapi* nor *P. viridis* contain 5-MeO-DMT and that *D. cabrerana* contains only trace amounts of this substance (Riba 2003; Ott 1994), Callaway et al. (2006) suggested that this tryptamine may have a synthetic origin. Moreover, diphenhydramine, an antihistamine and anticholinergic drug, was also found in the victim's system, which might have contributed to the death.

From the available information, it cannot be determined that ayahuasca, as defined in the present text, was actually ingested. This case is not directly relevant for the toxicity of ayahuasca.

Critical Evaluation of Media Reports

There are some cases reported in the media that associate ayahuasca with severe and even lethal intoxications. An important limitation in most of these reports is the absence of any detailed analysis of the purported ayahuasca. An analysis of the chemical composition of the

ayahuasca can ascertain if the case did involve ayahuasca or some admixture of plants of unknown chemical composition and toxicity. Gable (2007), for example, cited a situation which involved more than 30 individuals who had an intoxication characterized by tachycardia, coma, and amnesia after drinking an herbal preparation containing harmine, atropine, and scopolamine. Although all patients recovered satisfactorily, adverse events like the need for mechanical ventilation were reported.

An important limitation of most of these media reports is that they are difficult to evaluate because they lack key evidence, like formal autopsy descriptions, and they mislead because they often provide tenuous information and create the perception that intoxication cases are more frequent than they really are.

One of these reports described the case of an 18-year-old man who died some hours after an ayahuasca ritual in Brazil (Neto 2009; UOL Notícias 2009). The case was described as a "sudden death" caused by a "fulminant heart attack" that "tore apart the aortic artery" (Gomes 2010). From the available information, it cannot be determined what role ayahuasca had, if any, in the incident. The relationship between ayahuasca and the reported case cannot be established with confidence because the reported information is controversial; i.e., the young man had been participating in the rituals for three consecutive years without any problems, which suggests that he was well adapted to ayahuasca.

Another report from Brazil described a case of an 18-year-old man who drowned several hours after an ayahuasca ritual (Gomes 2010; iG Notícias 2010). The relationship between ayahuasca and the reported death cannot be established with confidence because the young man did not know how to swim, and he could have drowned for some reason completely independent of ayahuasca ingestion. Even if it is possible to speculate that some psychological effects of ayahuasca might have distorted the young man's perception of reality, which could have potentially contributed to the drowning incident, there is no clear evidence of a causative role of ayahuasca in this case.

A recent report related the case of a 33-year-old man who died in an ayahuasca ritual in Colombia (CityTv 2010; La FM 2010; Vera 2010). According to Vera (2010), the man had already taken ayahuasca on two different occasions, but on the third one he had convulsions and died. From the available information, it cannot be determined what the actual role of ayahuasca in the incident was, since no details were given about the victim's previous health condition, if he was using some medication, or regarding the chemical composition of the ayahuasca; i.e., it cannot be determined what was actually ingested.

Another recent report described the case of a 40-year-old Swedish man who was hospitalized for several days in a comatose state after taking ayahuasca in Peru (Cárdenas 2011; La Gaceta 2011; El Comercio 2010; La Republica 2010; RPP Noticias 2010). The relationship between ayahuasca and the comatose state case cannot be easily established since, despite his hospitalization, no analysis of alkaloid disposition in body fluids or any other biological tests were reported. From the available information, it cannot be determined what the actual role of ayahuasca in the incident was, but one hypothesis suggested that after aspirating his own vomit, his lungs were obstructed, which produced convulsions and then the comatose state (Cárdenas 2011).

Also in Peru, a 39-year-old French man was found dead the morning after an ayahuasca ceremony (La Republica 2011). Several bottles of ayahuasca were found in the victim's room, and the press suggested that the man died of an ayahuasca overdose. Nevertheless, the relationship between ayahuasca and the fatality is equivocal, since no forensic analysis was performed at that time and the possible influence of previous health conditions or current medication use cannot be ruled out.

There is the case of a 43-year-old French woman who died during an ayahuasca ritual in Peru (NTN24 2013; Perú21 2011) and the case of two men (29 and 37 years old) who died during a ritual in Colombia (Colombia Reports 2011; El Espectador 2011; Vanguardia 2011). The cases are all poorly described, with little forensic information, which makes any affirmation of the causative role of ayahuasca in the incidents speculative. In the case of the French woman, a preliminary coroner's report listed the cause of death as heart attack (Perú21 2011). Nevertheless, one report suggested that the woman had a preexisting heart condition (Hearn 2013), and no information is given on medications possibly in current use by the woman. In the cases in Colombia, no forensic details were published, and the causative role of ayahuasca is difficult to determine.

Finally, there is a case of 18-year-old man who supposedly died during an ayahuasca ritual in Peru (América Noticias 2012; El Comercio 2012; Farberov 2012; Johnson 2012; Kovner 2012; La Republica 2012; Mason 2012; Perú21 2012; RPP Noticias 2012). According to the reports, the man died supposedly after exceeding the dosage of ayahuasca. To cover up his death, a Peruvian shaman later confessed that he had buried the man's body and then said that he had disappeared. No details about the death were published.

FINAL COMMENTS

As this survey has shown, many of the cases reported in the literature have been poorly described. The general paucity of forensic/toxicological information limits our ability to precisely evaluate the potential causal role that ayahuasca or its various alkaloids may have played in the intoxication reports. Some of the cases presented cannot be directly compared to traditional ayahuasca preparations

made from *B. caapi* plus *P. viridis* or *D. cabrerana*, for they contain other botanical species with different chemical compositions and sometimes with higher β-carboline or DMT concentrations. Moreover, the potential use of extracted or synthetic alkaloids highlights an additional difference between ayahuasca analogues and traditional ayahuasca potions.

One of the cases described above concerned lethal nicotine intoxication, which occurred with the administration of an ayahuasca preparation. In the indigenous practice of using several admixture plants other than *P. viridis* or *D. cabrerana* to *B. caapi*, some plants with potent psychotropic substances may be used, while other plants may contain chemicals or possess toxicological characteristics as yet unknown to science. The use of other botanical ingredients in ayahuasca preparations, even if they are traditionally used in the indigenous ayahuasca context, may present different biological, toxicological, and safety profiles from that of ayahuasca.

Persons with hepatic, neurological, and cardiovascular dysfunctions probably have more possibilities of suffering an ayahuasca-related adverse reaction. The simultaneous use of ayahuasca preparations with pro-monoaminergic and serotonergic drugs could potentially increase the chances of suffering a serotonergic syndrome. Harmine is a selective inhibitor of the human cytochrome P450 isozyme 2D6 (CYP2D6), which also metabolizes harmaline (Zhao et al. 2011; Wu et al. 2009; Callaway 2005; Riba et al. 2003; Yu et al. 2003). The addition of drugs that inhibit cytochrome isoform CYP2D6 to the therapeutic use of selective serotonin reuptake inhibitors has been associated with serotonin syndrome (Boyer & Shannon 2005). Since there is still some controversy regarding the incidence of serotonin syndrome in the context of ritual ayahuasca use, epidemiological studies, as well as animal models of the serotonin syndrome using ayahuasca or some of its isolated alkaloids, could shed light on this topic.

Drugs used for treating hepatic, neurological, and cardiovascular dysfunctions, as well as psychotropic substances like psilocybin, mescaline, and cannabis, can also produce interactions with ayahuasca (dos Santos 2011c; Ott 1994). Moreover, the combination of foods containing tyramine and MAO inhibitors could potentially lead to hypertension (dos Santos 2013b; Frecska 2007; Yamada & Yasuhara 2004; Youdim & Weinstock 2004), although there is some controversy regarding the impact of this combination on the health of ayahuasca consumers. Animal models should also contribute to further development of this topic.

CONCLUSIONS

There remains a limited body of knowledge from which to draw definite conclusions on the potential causal role of ayahuasca *per se* on severe, life-threatening intoxications. Considering the limitations of the reports just described, these cases do not offer strong evidence to refute the idea that ayahuasca presents good acute and long-term tolerability. Nevertheless, some especially susceptible sub-groups of consumers may present idiosyncratic characteristics that could predispose them to higher possibilities of suffering adverse reactions. If severe intoxications following ayahuasca preparations are again described in the future, the forensic/toxicological data should be of better quality.

Although limited, the data reviewed present suggestions for recommendations on preventive interventions, like avoidance of concomitant use of serotonergic agents together with ayahuasca, and identification of potential susceptible individuals or groups of individuals with liver, kidney, or brain disorders. The information may also be useful for informing about the adverse effects of ayahuasca preparations and the contraindications associated with these substances.

Limitations aside, the consolidation and synthesis of what is currently known about the toxicology of ayahuasca is important to advance practice, stimulate further debate, and provide direction for further research which will, hopefully, prevent or reduce the occurrence of possible serious adverse reactions following ayahuasca ingestion.

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