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Acute Psychological Adverse Reactions in First-Time Ritual Ayahuasca Users

A Prospective Case Series

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Background: In recent decades, ritualistic use of ayahuasca has spread throughout the world. Retrospective studies have suggested a good psychological safety profile, but prospective studies involving ceremony ayahuasca-naïve participants are lacking.

Methods: We conducted the study using a subsample from a previous study, for which first-time ceremony ayahuasca participants were recruited. The subsample consisted of 7 subjects who experienced acute and challenging psychological reactions. The semistructured Mini-International Neuropsychiatric Interview and psychometric questionnaires were administered before participants attended the ayahuasca ceremony and at 1 and 6 months after exposure. Subjective experiences were also recorded.

Results: Seven subjects from a sample of 40 reported having experienced intense challenging psychological effects during the ayahuasca ceremony. Four of those 7 subjects met the diagnostic criteria for 1 or more psychiatric disorder before the ayahuasca ceremony. One month after the ceremony, 2 of those subjects no longer showed psychiatric symptoms, whereas the symptoms of the other 2 were reduced considerably. Those results persisted at the 6-month follow-up. Inappropriate setting/context (poor guiding skills and screening) contributed to some of the challenging reactions. Most of the participants (6 of 7) did not take ayahuasca again during the study period.

Conclusions: Based on the cases reported here, we suggest that although it is possible that participating in ayahuasca ceremonies may entail acute psychological negative reactions, those challenging experiences can also have positive long-term effects. Prospective research on the safety profile of ayahuasca and how it is affected by the context of different practices and safety strategies is therefore necessary.

Key Words: adverse events, ayahuasca, psychedelic drugs, safety

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Ayahuasca refers to any decoction containing the *Banisteriopsis caapi* vine, which is rich in β -carboline compounds (harmine, harmaline, and tetrahydroharmine). For many Amazonian cultures and communities, ayahuasca plays a central role in their spiritual and medical systems.¹ In recent decades, ceremonies involving ayahuasca have spread globally to the extent that both psychiatrists² and pastoral counselors³ have called for their colleagues to be prepared to discuss its spiritual and healing properties with those they counsel.

Although there are countless recipes for preparing ayahuasca in the Amazonian context, the one that has been popularized in Western cultures contains *B. caapi* stalks mixed with the leaves of the *Psychotria viridis* shrub or of the *Diplopterys cabrerana* vine. Both are rich in *N,N*-dimethyltryptamine (DMT), a psychoactive compound with psychedelic properties. *N,N*-dimethyltryptamine is inactive when orally ingested mainly because of its degradation by peripheral monoamine oxidase type A (MAO-A), as human experimental research has shown.^{4,5} The β -carbolines in *B. caapi* (especially harmine) inhibit MAO-A peripherally, allowing DMT to reach the brain.⁶ However, it is possible that, although in a lesser degree, central MAO also modulates the effect of DMT.⁶

The psychedelic experience induced by ayahuasca in its original cultural settings, far from being a pathological phenomenon, is central to the complex worldviews of these cultures.⁷ Indeed, it is considered a functional tool that improves the knowledge of reality.⁸ Retrospective observational studies performed on hundreds of regular ritualistic ayahuasca practitioners have failed to find long-term neuropsychiatric deficits,⁹ and clinical trials performed on healthy volunteers have shown that single or few ayahuasca doses have an acceptable tolerability profile.^{10,11} A recent study conducted by our group failed to find public health issues concerning long-term ayahuasca ceremony participants when evaluated using a wide range of health indicators.¹² Other studies have reported therapeutic effects in individuals with drug dependence^{13,14} and those experiencing grief,¹⁵ and it has been proposed as a promising treatment for people with mental disorders, such as posttraumatic stress disorder¹⁶ and borderline personality disorder.¹⁷ Open-label^{18,19} and randomized controlled clinical trials²⁰ have shown that a single dose of ayahuasca induced rapid and sustained reductions in depressive symptoms in patients with treatment-resistant major depression.

Despite this preliminary evidence, there is a lack of prospective studies that use clinical interviews and follow the evolution of subjects after they participate in ayahuasca ceremonies. Barbosa et al^{21,22} evaluated a group of 28 subjects 4 days before their first ayahuasca experience and at 1 to 2 weeks and 6 months (when 23 participants remained) after their experience. The results showed improvements in minor psychiatric symptoms after one to 2 weeks and 6 months, as assessed by the Clinical Interview Schedule—Revised Edition. Reductions in physical pain assessed using the Short

AQ2

Form-36 Health Survey (SF-36) questionnaire were also reported. No data regarding the content of the experiences were collected. Subjects were not selected by the researchers but were indicated by spiritual leaders. Thus, selection might be somewhat biased because leaders were not using systematic procedures or validated screening methods when accepting people to the ceremonies. We found similar results in our original study from where the cases presented here were selected,²³ where a sample of 40 first-time ayahuasca ceremony participants was followed until 6 months after their first session. Nearly half of the sample (45%) was found to meet the diagnostic criteria for some psychiatric disorder, but most of them (80%) showed clinical improvements that persisted until 6 months.

Among the controlled studies published regarding the acute effects of ayahuasca, there is only 1 report of a challenging psychological experience. This case involved a brief but intense moment of disorientation, for which verbal support was sufficient to help the individual overcome the temporary state.¹¹ Other non-controlled studies have shown acute increases in scales measuring psychotomimetic and dissociative symptoms, but these effects were mild and transitory without eventual clinical consequences.^{18–20,24}

A case report described the case of a young female with generalized anxiety disorder (GAD) who experienced intense anxiety, panic, and hopelessness during an ayahuasca ritual and for 3 days after participating in it.²⁵ Gable,²⁶ supported with ethnographic studies, suggested that adverse psychological reactions of ayahuasca would be more frequent when it is administered outside ceremonial settings. He also noted that the medical studies section of the UDV registered between 13 and 24 cases of adverse events in a period of 5 years, in which a total of 25,000 servings were estimated to be given. Additionally, an analysis of data coming from US Poison Control Centers showed that in a period of 10 years, 538 cases were reported involving ayahuasca intoxications.²⁷ Notably, among those cases, 206 (38%) consisted in intoxications involving ayahuasca and other nonreported substances. Psychological reactions were among the most common clinical effects (hallucinations, 35%; agitation, 34%; confusion, 18%), but tachycardia (34%) and hypertension (16%) were also common. Finally, a recent review collected several case reports of psychotic reactions associated with DMT and ayahuasca,⁷ noting that this would be one of the main risks of ayahuasca exposure.

The important role that the setting/context in which the ayahuasca ceremony takes place has on the experience is worth mentioning, a topic that has not been adequately addressed in most studies. These conditions include the space, the available facilities, or the skills of the guides and are commonly grouped under the concept “setting.” While it is obvious that these aspects will determine to some extent the outcome of the experience, available research tends to focus on individualistic variables or on the beverage itself. In summary, although psychiatric reactions are uncommon, they do occur. Thus, given the growing phenomenon of ayahuasca ceremonies being conducted in nontraditional contexts, it is necessary to better understand the potential psychiatric consequences of participating in those ceremonies.

This article provides a case series of challenging psychological experiences found in a subsample of subjects from a previously published study in which we recruited ayahuasca-naive participants and followed them for 6 months after their first ayahuasca use.²³ Among our sample, we found that some participants met the criteria for psychiatric disorders such as major depressive disorder, GAD, or panic disorder, among others. Thus, we were interested in collecting qualitative data regarding challenging psychological experiences likely associated with the ayahuasca ceremony and their short- and long-term consequences, at 1 and 6 months, respectively.

MATERIALS AND METHODS

Sample, Measures, and Procedure

We selected a subsample of 7 participants from an initial sample of 40 ayahuasca-naive subjects. These participants experienced acute adverse psychological effects from ayahuasca use. Acute effects of ayahuasca and other psychedelic drugs may involve anxiety or feelings of fear to some extent.^{9,28} Thus, only the experiences that were clearly negative and distressful were selected, according to the research team experience performing observational and controlled studies with ayahuasca. The semistructured Mini-International Neuropsychiatric Interview 5.0 (MINI)²⁹ was administered. With the MINI, some psychometric questionnaires were also administered (Hamilton Depression Rating Scale [HAM-D])³⁰ as a measure for depression; Community Assessment of Psychic Experiences [CAPE])³¹ as a measure of psychotic-like experiences; Symptom Checklist-90—Revised [SCL-90-R])³² as a measure of general psychopathology; Acceptance and Action Questionnaire II [AAQ-II])³³ as a measure of psychological flexibility; SF-36³⁴ as a measure of general health; and World Health Organization Quality of Life [WHOQOL-Bref])³⁵ as a measure of quality of life; see Jiménez-Garrido et al²³ for a detailed description). All measures were administered before participants attended the ayahuasca ceremony and during follow-ups at 1 and 6 months following exposure. During each interview, subjects were asked about their subjective experience and any challenges/difficulties related to their ayahuasca use. If the experience was challenging, they were encouraged to explain this with as much detail as possible. Reports were manually recorded in writing.

Statistical Analysis

Descriptive statistics were used to describe the demographic data of the subjects.

Ethics

This study was approved by the Research Ethics Committee of the Autonomous University of Madrid, Spain. Informed consent was obtained in writing from all volunteers. All experimental procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

RESULTS

Sample

Figure 1 shows the flowchart of participant recruitment, including the number of subjects who had challenging experiences and the number of dropouts. From 40 initial subjects (28 women) included at baseline, 26 subjects (20 women) completed the 1-month follow-up, and 15 subjects (9 women) completed the 6-month follow-up. The original publication of this study²³ addressed in detail the dropout issue, finding few differences in the variables analyzed except for the scores of CAPE-depression and SCL-90-R depression. In these measures, subjects who dropped out scored less (they were less depressed) than did the subjects who remained in the study. Thus, because it took too much time to fill all the questionnaires and the interview, and participants were not economically compensated to participate in the study, we concluded that they would just choose to not present at the follow-ups because of lack of time/motivation. At the 1-month follow-up, subjects informed about their first ayahuasca experience. In this case, 5 challenging experiences were reported (by 1 man and 4 women). Among those 5 subjects, 2 (women) quit the study for unknown

AQ3

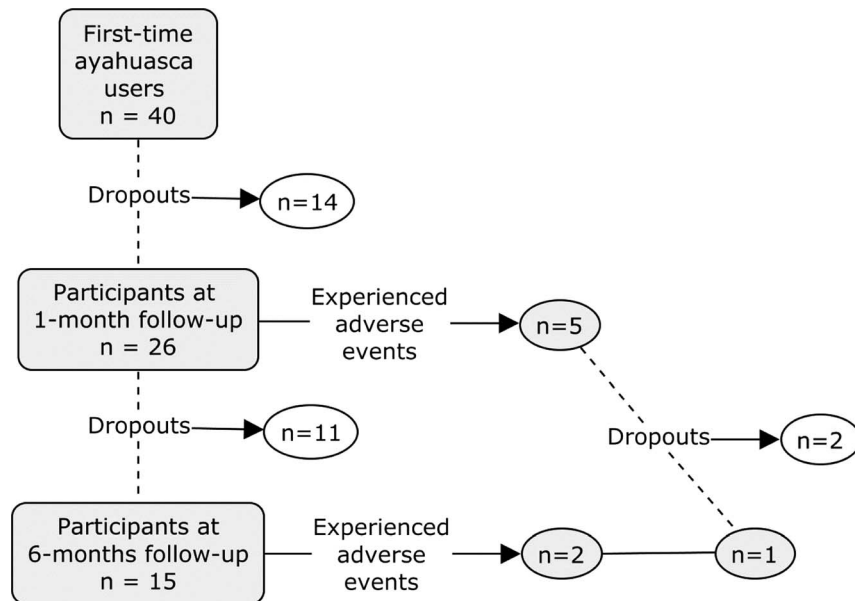


FIGURE 1. Flowchart of sample recruitment.

reasons. At the 6-month follow-up, subjects reported whether acute adverse reactions occurred or not in subsequent ceremonies, in case they participated in other ones. Three challenging experiences were reported (by 3 women), including a report from a subject who had also reported a challenging experience at the 1-month follow-up. Thus, 2 subjects (both women) did not report any challenging experiences at the 1-month follow-up but did so at the 6-month follow-up.

T1 Table 1 shows the demographic characteristics of the sample, previous use of other psychedelic drugs and prescription medications, and psychiatric diagnosis according to the MINI at baseline and at 1 and 6 months for subjects who reported challenging experiences. The most common effects concerned “losing control” or acute feelings of fear and distress. The challenging experiences are described in the following section.

Regarding the psychiatric assessment conducted with the MINI, 4 (women) of 7 subjects met some diagnostic criteria before attending the ayahuasca ceremony. No subjects experienced new psychiatric symptoms except by one (patient 1), who despite having reduced other symptoms met the criteria for hypomanic disorder. Additionally, 2 subjects (patients 2 and 6) scored significantly higher in some psychopathology scales at both follow-ups. All subjects who met the diagnostic criteria showed a reduction in some or all their psychiatric symptoms. At 1 month, 2 subjects (women) no longer had psychiatric symptoms, and in 2 others (women), they were reduced considerably. Subjects who did not meet the diagnostic criteria for psychiatric disorders at baseline still did not meet them at the 1-month follow-up. At 6 months, only 1 subject still met the diagnostic criteria reported at baseline. That subject was 1 of the 2 subjects who showed a considerable reduction in their psychiatric symptoms at 1 month, maintaining the “low risk of suicide” at the 6-month follow-up. In summary, 7 subjects described challenging effects during the experience, 4 of whom had previous psychiatric symptoms. At the 6-month follow-up, 2 subjects showing psychiatric symptoms at baseline no longer had them; another subject had reduced psychiatric symptoms; another 2 did not show psychiatric symptoms at any assessment; and 2 others had dropped out the study.

The scores obtained in different psychological questionnaires were also included. For 1 subject, most questionnaires could not

be used because of a high number of unanswered items, so only the questionnaires for the remaining 6 cases are presented. The scores of these questionnaires are reported in Table 2. **T2**

Case Reports

Patient 1 met the diagnostic criteria for a major depressive episode, melancholic symptoms, and dysthymic disorder at baseline. She reported drinking much more alcohol after taking ayahuasca. Before using ayahuasca, she tended to drink a daily glass of wine, but afterward, she drank an entire bottle on a daily basis. She reported eating a lot more as well. Fluoxetine was prescribed to her long before her ayahuasca experience. In addition to her negative experience and increased use of alcohol, at 1 month, she was found to meet the diagnostic criteria for hypomanic disorder. At the 6-month follow-up, she had attended 5 further ayahuasca ceremonies in addition to her first experience. She reported feeling much better and that ayahuasca had changed her life in a positive manner. She reported a lack of sleeping problems, which she had previously experienced and feeling much more peaceful. Psychometric questionnaires of this subject are missing.

Patient 2 met the criteria for major depressive disorder, melancholic symptoms, dysthymic disorder, low risk of suicide, panic disorder, bulimia, and substance dependence (lorazepam) at baseline. She reported feelings of being observed in the street after taking ayahuasca. At the 1-month follow-up, she only met the diagnostic criteria for “low risk of suicide.” She never took ayahuasca again, but was assessed again at month 6, at which time she still met the diagnostic criteria for “low risk of suicide.”

Patient 3 did not meet the criteria for any psychiatric disorder at baseline. She had previous experience with psychedelic drugs, having used “magic mushrooms.” She reported losing consciousness while under the effect of ayahuasca. She was unconscious for approximately 2 minutes. However, the following day, she reported feeling more relaxed and having gained useful insights. She wanted to use ayahuasca again, which she did between month 1 and month 6, reporting another challenging experience at month 6. She had an intense “bad trip” according to her. The psychoactive effects were described as very strong. She mentioned finding herself inside a terrifying loop that represented the whole universe.

TABLE 1. Available Data for the Patients Who Experienced Challenging Effects

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex	Female	Female	Female	Male	Female	Female	Female
Age	36	38	38	26	25	36	43
Previous experience with psychedelic drugs	No	NR	Psilocybin mushrooms	<i>Cannabis</i> , mescaline, <i>S. divinorum</i>	NR	NR	Peyote
Previous use of prescription drugs	Fluoxetine	Lorazepam	No	No	Depakene (due to past history of seizures)	No	No
MINI Interview	Baseline	Major depression episode, melancholic symptoms, dysthymic disorder, low risk of suicide, panic disorder, dysthymic disorder	No criteria met	No criteria met	Dysthymic disorder, obsessive-compulsive disorder; GAD	No criteria met	Low risk of suicide
	1 mo	Hypomanic disorder	No criteria met	No criteria met	No criteria met	No criteria met	No criteria met
	6 mo	No criteria met	No criteria met	No criteria met	—	No criteria met	No criteria met

NR, not reported; AYA, ayahuasca.

She thought that the whole world was actually an illusion, and she lost control of herself. Then, she physically assaulted one of the caregivers present at the ceremony, demanding to return to a normal state. She mentioned that before participating in this last ceremony, she had experienced the appearance of some kind of spiritual entity that led her to choose when to drink ayahuasca. After the ceremony, she adopted the belief that humans are “infinite beings,” an idea that terrified her because she associated it with the loop that she experienced in her first ceremony, which still scared her. She also reported learning that she had to quit “theoretical” activities (reading books, watching videos, etc.) and focus on “practical” ones (such as meditation and speaking with “superior angels”). She experienced increased anxiety as well. However, during the interview, she insisted that ayahuasca use had not changed her for the better or the worse, but only the experience of the loop affected her strongly. She did not use ayahuasca again. She did not meet any diagnostic criteria at either of the follow-up assessments.

Patient 4 did not meet the criteria for any psychiatric disorder at baseline. He had previous experience with psychedelic drugs, having used cannabis, mescaline, and *Salvia divinorum*. He experienced distressing visual hallucinations while under the acute effects of ayahuasca. The hallucinations involved modifications of the faces of other participants, which turned malicious. During the ceremony, when he looked at a mirror, he did not recognize himself. The situation was not well managed because the “guide” went to sleep while people were still experiencing psychoactive effects. The subject did not meet any diagnostic criteria at the 1-month follow-up, but he did not take ayahuasca again. At the 6-month follow-up, he did not meet any diagnostic criteria either.

Patient 5 met the diagnostic criteria for dysthymic disorder, obsessive-compulsive disorder, and GAD. During the MINI interview, she reported a history of epilepsy and that she had been prescribed Depakene. Although this was an observational study, making it unusual to interfere in a subject's decisions, in this case we advised the subject that ayahuasca could induce seizures and that it is contraindicated if there is a history of epilepsy. However, the subject decided to attend the ayahuasca ceremony nonetheless. We were told by the subject that she also informed to the ceremony guides about her condition but that they allowed her to assist to the ceremony either way. It is important to note that this practice is totally risky and irresponsible from a medical point of view, so the screening process of the organizers of the ceremony completely failed. She reportedly lost consciousness for a matter of minutes while she was experiencing seizures. She then reportedly lost her sense of reality for the rest of the ceremony. She reported an intense feeling of fear in relation to things that could happen inside her head. She thought that her body could not handle the experience. When psychoactive effects were no longer present, she felt as if her head was not “entire,” as if she had lost some part of it because of the psychoactive effects. She was in an anxious state for 2 days, until she received assistance from a psychologist and finally overcame the crisis without using any prescription drugs. Despite this dramatic experience, she reported that her ayahuasca use had influenced her positively. She stopped drinking alcohol, smoked less tobacco, and started trying to take better care of herself than she had prior to using ayahuasca. She did not want to take ayahuasca again. At the 1-month follow-up, she did not meet any diagnostic criteria according to the MINI. She quit the study for unknown reasons.

Patient 6 did not meet the diagnostic criteria for any psychiatric disorder. She reported “having had enough” after her first experience with ayahuasca. She felt that she did not need this kind of experience. She was looking for something “gentler,” as she experienced very strong effects. She reported overwhelming feelings of sadness and pain. However, she also recognized some positive

TABLE 2. Scores Obtained in Psychometric Questionnaires by 6 of 7 Patients Described

	Patient 2			Patient 3			Patient 4			Patient 5			Patient 6			Patient 7		
	1	6	6	1	6	6	1	6	6	1	6	6	1	6	6	1	6	6
	Baseline	mo	mo	Baseline	mo	mo	Baseline	mo	mo	Baseline	mo	mo	Baseline	mo	mo	Baseline	mo	mo
HAM-D	25	18	5	1	4	0	0	0	2	9	1	—	8	0	—	0	0	—
CAPE																		
TFS	86	73	78	58	62	67	59	62	49	72	60	78	68	70	78	72	55	—
TDS	70	70	80	34	37	42	31	34	13	49	24	80	51	78	80	55	30	—
PSF	29	27	35	23	25	27	26	26	20	29	32	35	27	30	35	28	23	—
PSD	15	12	25	6	7	6	9	8	0	11	14	25	14	21	25	10	3	—
DSF	22	16	17	14	14	13	12	14	10	17	11	17	16	14	17	18	13	—
DSD	21	23	23	14	15	10	10	10	5	16	5	23	16	21	23	22	18	—
NSF	35	30	26	21	23	27	21	22	19	26	17	26	25	26	26	26	19	—
NSD	34	35	32	14	15	26	12	16	8	22	5	32	21	36	32	23	9	—
SCL-90-R																		
SOM	0.33	1.58	2.41	0	0.41	0.25	0.25	0.33	0.5	2.16	0.5	—	0	0.83	1.41	0	0	—
O-C	0.1	2	2.7	0.1	0.2	0.1	0.7	1.1	1.2	1.4	0	—	0.3	1.3	1.2	1.10	0	—
I-S	0.11	1.66	1.88	0.44	0.66	0.11	0.66	0.66	1.22	0.88	0	—	0	1.88	2.33	0.89	0.33	—
DEP	0	2.15	1.07	0.15	0.38	0.15	0.46	0.46	1.30	1.61	0	—	0.15	1.30	2.23	1.23	0.53	—
ANX	0	0.3	1.1	0.1	0	0	0.4	0.6	0.7	1.5	0.1	—	0.1	0.5	1	0.80	0.1	—
HOS	0	0.16	1.16	0.16	0.33	0.16	0.16	0.5	0.83	2	0.16	—	0	0.66	1.16	1.67	0	—
PHOB	0	0.14	1	0	0	0	0.42	0.57	0.57	0	0	—	0	0.42	0.57	0	0.14	—
PAR	0.33	0.5	1.66	0	0.16	0	0.66	0.5	1.16	0	0	—	0	1.33	2.5	0	0	—
PSY	0	0.3	1	0	0.1	0	0	0.4	0.3	0.3	0.1	—	0	0.2	1.8	0	0	—
GSI	0.08	1.15	1.62	0.12	0.3	0.1	0.41	0.58	0.87	1.2	0.1	—	0.06	0.93	1.57	0.66	0.15	—
PSDI	9	53	93	11	23	10	32	43	59	50	10	—	6	56	69	28	13	—
PST	0.88	1.96	1.56	1	1.17	0.9	1.15	1.23	1.33	2.16	0.9	—	1	1.5	2.05	2.11	1.07	—
AAQ-II	41	28	23	30	26	30	15	20	17	27	12	—	25	24	26	33	30	—
SF-36																		
PF	95	95	100	100	100	100	100	95	100	100	100	—	100	90	90	90	—	—
RP	12.5	100	100	100	100	100	100	100	100	100	100	—	100	100	75	100	—	—
RE	0	0	100	100	100	100	100	100	66.6	100	100	—	100	33.3	100	33.3	—	—
VIT	0	45	100	80	80	80	55	70	50	80	70	—	75	65	60	60	—	—
MH	16	52	96	76	64	72	76	72	68	56	72	—	64	60	76	36	—	—
SF	37.5	37.5	100	100	100	100	87.5	87.5	75	100	100	—	100	87.5	100	100	—	—
BP	45	90	90	100	90	100	0	70	90	70	100	—	80	32.5	90	100	—	—
GH	35	55	65.2	100	100	95	75	80	80	60	70	—	90	85	80	70	—	—
WHOQOL-Bref	7	10	27	14	13	13	13	10	14	10	22	-	19	29	28	6	5	-

ANX, anxiety; BP, bodily pain; DEP, depression; DSD, depression symptoms distress; DSF, depression symptoms frequency; GH, general health; GSI, General Severity Index; HOS, hostility; I-S, interpersonal sensitivity; MH, mental health; NSD, negative symptoms distress; NSF, negative symptoms frequency; O-C, obsessive-compulsive; PAR, paranoid ideation; PF, physical function; PHOB, phobic anxiety; PSD, positive symptoms distress; PSDI, Positive Symptoms Distress Index; PSF, positive symptoms frequency; PST, positive symptoms total; PSY, psychoticism; RE, role emotional; RP, role physical; SF, social function; SOM, somatization; TDS, total distress score; TFS, total frequency score; VIT, vitality.

effects. The experience allowed her to break unhealthy habits and to “transcend to other mental states.” At the 1-month follow-up, she did not meet any diagnostic criteria, nor had she used ayahuasca again. The same was found at the 6-month follow-up, when she reported again that the first experience was overwhelming. She thought that she could do the same “work” but without taking ayahuasca, in a gentler way. She considered that ayahuasca forces you to remain at the mud for so long, and this might not be necessary. Despite having obtained some benefits, both physically and psychologically, she did not take ayahuasca again because of the unpleasant effects.

Patient 7 met the criteria for “low risk of suicide.” She had used peyote previously. She did not consider the experience of

using ayahuasca pleasurable. After the second cup of ayahuasca, she remembered problems with her father and experienced a paranoid episode. She spoke with invisible people 4 or 5 times during the ceremony. However, she reported that the experience influenced her very positively, “bringing back” her personal and professional life. She did not use ayahuasca again and did not meet any diagnostic criteria at months 1 and 6.

DISCUSSION

In this article, we described challenging experiences that occurred among a sample of first-time ayahuasca ceremony participants who were followed up for one and 6 months after their ayahuasca

experiences. The first publication of this prospective longitudinal study reported that ayahuasca ceremonies can have some beneficial effects on mental health.²³ This is in accordance with many other observational and controlled studies.^{18–20} However, this is the first study in which first-time ayahuasca ceremony participants were prospectively followed using a validated clinical interview and were asked about their challenging experiences.

First, the relatively large proportion of the sample reporting challenging experiences is remarkable (17.5%). Because our sample was not previously screened, unlike previous clinical trials and in the prospective observational study already published,^{21,22} our results may better reflect the actual prevalence of such experiences. Of the 7 cases reported, 1 was a man and 6 were women. It is not possible to infer that women would be more at risk of suffering adverse events related to ayahuasca because the sample size is small and there was a higher presence of women in the original study, which may explain the ratio found.²³ Four subjects had previous psychiatric conditions, and one of them showed a “low risk of suicide” according to the MINI interview. None of the subjects without psychiatric conditions developed psychiatric symptoms as a consequence of their challenging experiences, and even those who met the diagnostic criteria at baseline improved their psychiatric conditions. However, it must be noted that at 1-month follow-up 1 subject (patient 1) met the criteria for a psychiatric disorder (hypomanic disorder) not present at baseline, despite no longer meeting the diagnostic criteria for the previous disorders (major depression episode, melancholic symptoms, dysthymic disorder). One case report informed about a similar outcome from a subject with a preexisting bipolar disorder.³⁶ The authors suggested that the MAO-inhibiting properties of β -carbolines present in ayahuasca could be involved. Patient 1 reported using much more alcohol after the ceremony. Thus, it is challenging to attribute the symptoms of hypomanic disorder only to the ayahuasca experience. Despite that causality could not be entirely established, our finding suggests again that people with traits potentially attributed to bipolar disorder should be aware of the risks of ayahuasca regarding the possible induction of manic episodes. Similarly, patient 2 reported “feelings of being observed,” which may indicate the presence of paranoia or paranoid delusions. Indeed, the paranoid ideation scale of SCL-90-R questionnaire showed increases through the assessments (0.33, 0.5, and 1.6, respectively). However, there were also improvements in other scales, such as in quality of life, as informed by WHOQOL-Bref, as well as in the MINI interview, in which the criteria met for different disorders clearly declined. Thus, a further evaluation would be necessary because this may possibly inform about the risk of ayahuasca and other psychedelic drugs in terms of increasing psychotic traits or inducing psychotic-like breaks, as has been already suggested.⁹

In summary, although most subjects do not seem to develop further psychiatric symptoms as informed by the MINI and the questionnaires, 2 subjects (patients 2 and 6) showed higher scores in some scales of the SCL-90-R questionnaire, despite improving in the psychiatric interview. Patient 2 scored greater than 70 (in T scale, which is considered a clinical score) in the depression (71.5) scale at 1-month follow-up and in somatization (74.1) and

obsessive-compulsive disorder (77) scales at 6-month follow-up. Patient 6 scored greater than 70 in interpersonal sensitivity (73), depression (72.3), and paranoid ideation (75) at the 6-month follow-up, after marked increases observed at 1-month follow-up. Thus, while clinical data suggest some improvements that are further supported by HAM-D and AAQ-II scores, psychopathology scores also show a tendency to increase in some cases, as observed in Figure 2 and Table 2. The results on depression [F2] scores (both the HAM-D and the depression scale of the SCL-90-R questionnaire) observed in patients 2, 5, 6, and 7 are in line with a randomized, placebo-controlled trial in which ayahuasca was administered to patients with treatment-resistant MD.²⁰ Notably, the authors of the trial also reported that most of patients experienced intense psychological distress during the session; however, the outcomes were undoubtedly positive, finding a rapid and marked antidepressant effect. De Araujo et al²⁴ also found increases in psychopathology measures while under the effects of ayahuasca that disappeared at the end of the session. However, our data suggest that certain kinds of patients might be at risk to develop complications in psychopathology status, as occurs with several other psychological or medical interventions. In this case, the well-known risks associated with other self-care practices such as meditation are actually similar to those found in ayahuasca ceremonies, consisting mainly of meditation-induced psychosis,^{37–39} mania,^{39,40} or even higher risk of seizures.⁴¹ Further studies are necessary to describe profiles at risk in order to avoid potentially adverse events.

Although no previous studies have collected data regarding the prevalence of challenging experiences in the population of ayahuasca ceremony participants, in our cumulative experience of performing observational studies and interviewing hundreds of participants, we noticed a high prevalence of these experiences. For the participants, these experiences are considered normal, to some extent, and even therapeutic. In fact, some degree of distress is inherent to every psychotherapeutic process, and this may also be true in the case of ayahuasca ceremonies. Additionally, what could be of crucial relevance is the posterior integrative process, where participants share and discuss the content of their experience with their guide.⁴² The integration process is not standardized among guides, so it is difficult to describe its effect on the outcomes. In traditional contexts, there is a series of specific rules that participants should comply with before, during, and after drinking ayahuasca, and the outcomes are inherently contextualized within the relevant cultural system.⁴³ Thus, future studies should collect data regarding the integrative processes employed by guides in order to better interpret the outcomes. The way in which the ceremony is performed is also important.⁴⁴ These processes have also been considered in clinical trials involving other psychedelic substances, such as LSD,⁴⁵ psilocybin,⁴⁶ and empathogens, such as MDMA,⁴⁷ for the treatment of several mental health conditions.

There is a lack of knowledge regarding what can predict a challenging experience that would make a person susceptible to develop a psychiatric condition. A recent systematic review of case reports in which psychotic reactions developed following ayahuasca or DMT use included subjects with and without previous psychopathological conditions, as well as people who

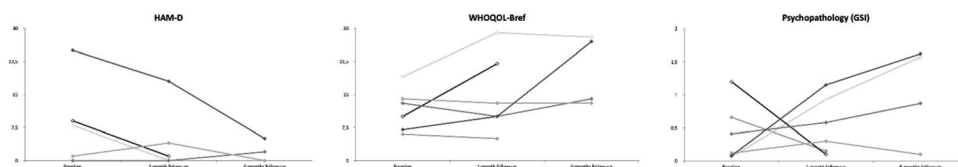


FIGURE 2. Scores of HAM-D (depression), WHOQOL-Bref (quality of life), and General Severity Index from SCL-90-R questionnaire, informing about psychopathology, at baseline, 1-month follow-up, and 6-months' follow-up.

took ayahuasca in both “controlled” (traditional, shamanic, and neoshamanic) and “uncontrolled” (recreational) settings.⁹ Thus, it seems that, regardless of the context or the previous psychiatric status of subjects, it is possible for participants to experience challenging experiences that produce persistent psychiatric outcomes. In that review, some subjects used cannabis while under the effects of ayahuasca, so cannabis may be a contributing factor. But when it comes to the context, beyond the “controlled” or “uncontrolled” categories, it should be noted that in some of the cases presented in this article, clear context deficiencies can be found. Patients 4 and 5 are especially remarkable. Patient 4 describes how the guide apparently went to sleep while there were still people under the effects, leading the whole group in a highly vulnerable situation. In patient 5, we can see how a person with a history of epilepsy, a condition clearly contraindicated, is welcomed in an ayahuasca ceremony, even when the ceremony guides were aware of that. This is possibly due to the attitude of some ayahuasca ceremony providers, who tend to think that ayahuasca is always a good choice and can benefit nearly all medical or psychiatric conditions in some way. In addition, the fact that she remained in an anxious state for 2 days, lately needing psychological support, is especially worrying. These cases raise concerns about which factors associated with the context can prevent psychological adverse reactions and enhance the safety of participants. In this sense, our team has developed for the Catalan government a good practices guide for both organizers and attendants to ayahuasca ceremonies, to avoid these unfortunate situations (see <http://drogues.gencat.cat/en/detalls/Noticia/Cap-amillors-practiques-en-lus-de-layahuasca>).

The unique study that explored the correlation between having previous psychological conditions and experiencing an adverse reaction after using psilocybin failed to arrive at consistent results.⁴⁸ However, the study was performed with a sample of healthy volunteers who used psilocybin in clinical trials, so the results are difficult to extrapolate to naturalistic settings. In modern clinical trials involving psychedelic drugs, including ayahuasca, having previously met the psychiatric diagnostic criteria has been established as an exclusion criterion. In our sample, after having suffered challenging experiences, most subjects have not developed psychiatric symptoms, whereas 1 subject met the criteria for hypomanic disorder after the ceremony. Two other subjects showed higher scores in psychopathology measures at follow-ups. Four subjects improved in psychopathology measures compared with baseline scores. Future naturalistic studies are warranted to better characterize how challenging experiences can lead to the development of a psychiatric disorder.

Beyond challenging experiences, in the case series 2 subjects experienced a transitory loss of consciousness. In our field work, we have also noticed the occurrence of such phenomenon, both with and without convulsions. Between 2005 and 2015, 12 cases of seizure supposedly related to ayahuasca were reported, although determining causality in such cases is difficult because of the lack of detailed information on the previous health condition of the individuals (including if they had epilepsy).²⁷ A neurobiological explanation might involve the liberation of glutamate when DMT binds to 5-HT_{2A} receptors.⁴⁹ This warns us of the potential negative effects of ayahuasca on individuals with epilepsy.

Finally, it is possible that the occurrence of these challenging experiences is highly dependent on cultural and ritualistic factors rather than psychological ones. It is remarkable that Westerners have largely maintained traditional ritualistic and ceremonial settings when using ayahuasca and other psychedelic substances. This can have a protective effect in relation to challenging effects,⁵⁰ and may be among the reasons why the cases we reported did not show long-term negative consequences.

Limitations

We must consider the limitations of this article. First, the 7 cases analyzed in-depth represent a small sample, limiting the generalizability of results. Second, the cases came from various groups to which ayahuasca was provided, so there was a high degree of heterogeneity regarding preparation before the experience, the ritual in which the experience took place, and the integration process. Third, it was not possible to measure the alkaloid content or the quantity of ayahuasca ingested by subjects, which could produce great variations in terms of the intensity of its effects. Fourth, we based our analyses on subjective reports and self-administered questionnaires. A systematic collection of challenging effects using validated scales was not performed. Finally, because of the observational nature of the case series, the long-term effects observed in some of the cases cannot be fully attributed to the ayahuasca ceremony, because other variables were not controlled for.

CONCLUSION

These case series aimed to describe challenging psychological effects associated with ayahuasca use and its long-term consequences, information that is lacking in the specialized literature. We note that, among our original study sample, 17.5% of subjects experienced some kind of challenging experience. Despite this, nearly half of the cases discussed here reported that the experience as a whole influenced them positively, and 4 of 7 saw their psychiatric symptoms reduced. As a counterpart, 2 subjects showed higher scores in psychopathology measures after the experience, whereas another one met the diagnostic criteria for hypomanic disorder after having reduced the symptomatology of other disorders. These 3 subjects showed improvements in the psychiatric interview and other questionnaires, so further studies should explore whether ayahuasca benefits in some areas could come with deleterious effects in others. This information can be used by ayahuasca practitioners to raise awareness regarding the need to develop harm-reduction strategies for their ceremonies. Future prospective naturalistic studies are warranted to better characterize the different factors that could predict outcomes after experiencing challenging effects related to participation in ayahuasca ceremonies.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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