Brief report

Long-term effects of ayahuasca in patients with recurrent depression: a 5-year qualitative follow-up

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Abstract

Background: Ayahuasca is a botanical hallucinogenic preparation traditionally used by indigenous populations of Northwestern Amazonian countries for ritual and therapeutic purposes. It is rich in β-carboline alkaloids and *N,N*-dimethyltryptamine (DMT). Preclinical, observational, and experimental studies suggest that ayahuasca and its alkaloids have anxiolytic and antidepressive effects. We recently reported in an open-label trial that ayahuasca administration was associated with significant decreases in depression symptoms for 2-3 weeks after the experimental session in 17 patients with treatment-resistant major depressive disorder. **Objectives:** To investigate if the experiment had any long-lasting effects on patients **Methods:** Eight patients were interviewed 4 to 7 years after ayahuasca intake. **Results:** Our results suggest that ayahuasca was well tolerated and that symptom reductions were limited to a few weeks. Importantly, most patients believed that the experience was among the most important of their lives, even 4-7 years later. **Discussion:** To the best of our knowledge, this is the first long-term follow-up of a clinical sample that participated in an ayahuasca trial. Further studies with different and repeated dosing should be designed to further explore the antidepressive and anxiolytic effects of ayahuasca.

dos Santos RG et al. / Arch Clin Psychiatry. 2018;45(1):22-4

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Introduction

Ayahuasca is a botanical hallucinogenic preparation traditionally used by indigenous populations of Northwestern Amazonian countries for ritual and therapeutic purposes[1], and also as a sacrament and therapeutic tool by Brazilian syncretic religions such as the *Santo Daime*, *Barquinha* and *União do Vegetal*[2,3]. It is usually prepared by the prolonged concoction of the bark of the vine *Banisteriopsis caapi* together with the leaves of the shrub *Psychotria viridis*. The vine is rich in *β*-carboline alkaloids such as harmine, tetrahydroharmine (THH), and harmaline, and *P. viridis* contains *N,N*-dimethyltryptamine (DMT). The *β*-carbolines act as reversible inhibitors of monoamine oxidase (MAO)-A, and DMT act as a 5-$HT_{1A/2A/2C}$ agonist[4]. DMT by itself is not orally active due to degradation by peripheral MAO-A, but MAO-A inhibition by the *β*-carbolines renders DMT active by allowing it to reach the brain[4-6]. The neural basis of the effects of ayahuasca seem to involve modulation of frontal and midline brain structures, such as the default mode network (DMN)[5-9].

Preclinical, observational, and experimental studies suggest that ayahuasca and its alkaloids have anxiolytic, antidepressive, and antiaddictive effects[2,3,10-14], and studies with healthy volunteers[2-8] and psychiatric patients[10,11] show that it is well tolerated. Previous observational studies assessing the mental health of members of Brazilian ayahuasca churches described the potential effects of regular ayahuasca use on anxiety, depression and dependence symptoms[2,14]. Moreover, the first double-blind, controlled study showing that a single ayahuasca dose induced significant reductions on panic-like and depressive symptoms was conducted among *Santo Daime* members[3].

We recently reported that administration of a single oral dose of ayahuasca (dose: 2.2 mL/kg; alkaloid content in the sample: 0.8 mg/mL DMT, 0.21 mg/mL harmine, no harmaline was detected, and THH was not analyzed due to a lack of analytical requirements) in an open-label trial to 17 patients with treatment-resistant major depressive disorder (MDD) was associated with significant decreases in depression symptoms assessed with the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Åsberg Depression Rating Scale (MADRS) from 80 minutes to day 21[10,11]. Average baseline score in the HAM-D scale was 19.24 (SD = 5.52), and at day 21 the average score was 7.56 (SD = 4.7). We recently replicated these results in a parallel arm, double-blind, randomised, placebo-controlled trial with 35 patients with treatment-resistant MDD[15]. Compared to placebo, HAM-D scores at day 7 were significantly lower in patients treated with ayahuasca (Cohen's d = 0.98), and MADRS scores were significantly reduced in the ayahuasca group at days 1, 2 and 7.

After the publication of the open-label study[10,11]; we were interested in interviewing the volunteers after a long-time period to ask if the experiment had any long-lasting effects on them. To the best of our knowledge, this is the first long-term follow-up of a clinical sample that participated in an ayahuasca trial.

Methods

An experienced psychiatrist that was closely involved with the volunteers during the study (RFS) tried to contact the volunteers by telephone. At least three attempts, in three different times of the day, were made to try to contact the volunteers. The contacted volunteers were then asked the following questions by a telephone interview:

#1. *Do you classify your experience with ayahuasca as negative, neutral, or positive?*
#2. *Did the experience bring any significant changes (positive or negative) to your life in general?*
#3. *Did the experience bring any significant changes (positive or negative) to your daily life?*
#4. *Did the experience bring any significant changes (positive or negative) to your relationship with other people (friends, family, or in your work)?*
#5. *Did the experience bring any significant changes (positive or negative) to your spirituality/religiosity or in your way to see the world and nature?*

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#6. *Did the experience bring any significant changes (positive or negative) in the way you perceive music or art in general?*
#7. *After the experiment, did you have desire to drink ayahuasca again?*
#8. *After the experience, have you used ayahuasca? If yes, how many times? Briefly describe the experience.*
#9. *How did your symptoms evolved since the experience? They improved, got worse, or remained stable?*
#10. *Have you changed your medications after the experience? Did you stop taking your medications, returned to the same medications, or increased the dose or number of medications?*
#11. *Did you observe any kind of changes in your behavior or symptoms during or after the experience that you believe is important to mention?*
#12. *Would you classify the experience among the 10 most important experiences of your life? In which position, from 1 to 10?*
#13. *If you passed for a difficult and challenging experience during the study, do you think it was positive anyway?*
#14. *Did you observe something negative or positive during the experience that you think is important to mention?*

Questions #1 to #13 could be answered as positive (+), negative (-), or neutral/stable (=). Question #14 could be answered more freely.

Results

The results of the interview are described in Table 1.

Of the 17 patients that participated in the study, we could contact only eight (seven women; mean age 39.87 years; range 28-54). The other nine patients could not be contacted after several attempts. All the non-participant subjects were not able to be located, thus, there were no subjects that refused to participate in the study.

The contacted patients had a mean baseline HAM-D score of 20.37 (range 17-24) and a mean baseline MADRS score of 27.12 (range 21-32). Means HAM-D and MADRS scores on D21 were 6.75 (range 2-15) and 8.75 (range 1-19), respectively. Patients have participated in the experiment from October 2010 (patient #1) to January 2013 (patient #8), and the follow-up interviews were conducted from January to May 2017. Therefore, patients were interviewed after a mean of 56.37 months (range 49-76), or 4.7 years.

As can be observed in Table 1, although volunteers had difficult experiences, most of them reported that participation on the study was positive and had a positive impact on their general and daily lives, and that they would like to experiment ayahuasca again (although none did). Furthermore, six patients reported that the experience was among the 10 most important experiences of their lives, with four patients reporting that the experience was among the five most important experiences of their lives.

However, four patients reported neutral effects or that their symptoms remained stable, nine reported that their medications were unchanged (one reported that the medication was changed, and none have stopped the medication), and almost all patients that reported positive effects also noted that they were short-lived. Furthermore, only three patients reported improvements in their relationships with friends, family, or at work, and only one described a positive effect of the experiment on music and art perception and on spirituality/religiosity or in the way one sees the world and nature. Negative effects included mostly nausea and vomiting.

Discussion

Previous observational studies in members of the Brazilian ayahuasca churches reported the potential effects of ayahuasca on anxiety and mood regulation[3,14]. Moreover, a controlled study in members of these groups also reported anxiolytic and antidepressive effects[3], which were corroborated in recent open-label and controlled studies with depressed patients[10,11,15]. In the present work, the first long-term follow-up of those depressed volunteers[11], we found that ayahuasca was well tolerated and associated with antidepressive effects.

The main limitations of this follow-up are the long time that passed since the experimental session was conducted and that not all volunteers were contacted. The first limitation could have increased the chances of recollection bias in the sample, and the second makes it impossible to know if the other volunteers had the same kind of responses, thus limiting the extrapolation of the results for the whole sample. Nevertheless, to the best of our knowledge, this is the first study long-term follow-up of depressed patients that have ingested ayahuasca.

Even considering the above-cited limitations, our results suggest that ayahuasca was well tolerated by these patients and that the reductions in depressive symptoms attributed to ayahuasca intake were limited to a few weeks. Moreover, most patients that participated in the interview believed that the experience was among the most important of their lives, even 4-7 years later. This last observation could be related to the fact the patients had been suffering with their depressive symptoms for a long time, and a significant (although limited in time) improvement in their symptoms could have a great significance for them.

The results and limitations of this qualitative study suggest that future studies involving administration of ayahuasca should try to perform follow-ups after shorter periods of time to try to observe any effects that could appear a few months of the experiments and to try to avoid losing contact with the volunteers, so that a clearer image of the results can be achieved. Furthermore, the present results and the data from our open-label and controlled studies suggest that

Table 1. Depressive symptoms assessed with the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Åsberg Depression Rating Scale (MADRS) and results from the follow-up questions

	Age at the time of the experiment	Time since the experiment (months)	HAM-D / MADRS (baseline)	HAM-D / MADRS (D1)	HAM-D / MADRS (D7)	HAM-D / MADRS (D14)	HAM-D / MADRS (D21)	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13
Patient 1	31	76	20 / 27	14 / 12	3 / 6	3 / 3	2 /1	=	=	=	=	=	=	-	-	=	=	×	-	=
Patient 2	36	67	20 / 32	9 / 17	11 / 7	4 / 2	2 / 3	+	+	+	+	+	+	+	-	+	≠	+	+ (6)	+
Patient 3	38	52	20 / 32	3 / 1	7 / 11	2 / 2	4 / 2	=	=	+	+	=	=	-	-	+	=	+	+ (4)	+
Patient 4	46	55	17 / 21	10 / 12	8 / 15	10 / 15[1]	13 / 15	=/-	+	=	=	=	=	-	-	=	=	+/=	-	+
Patient 5	39	51	20 / 28	17 / 20	18 / 22	15 / 18	15 / 19	+	+	+	=	=	=	+	-	+	=	=	+ (8)	+
Patient 6	54	51	19 / 23	6 / 3	10 / 9	16 / 14	5 / 8	+	+	+	=	=	=	-	-	=	=	=	+ (5)	+
Patient 7	28	50	23 / 25	5 / 7	5 / 5	6 / 6	5 / 5	=	+	=	+	=	=	-	-	=	=	=	+ (3)	+
Patient 8	47	49	24 / 29	13 / 17	20 / 23	16 / 19	10 / 17	+	=	=	=	=	=	+	-	+	=	=	+ (4)	+

Ayahuasca intake for these eight patients occurred between October 2010 and January 2013. Interviews were conducted between January and May 2017.
+: positive, -: negative, =: neutral/stable; ≠: changed medication; ×: do not remember.
The numbers in parenthesis on question #12 are the position from 1 to 10 reported by those volunteers that had a positive answer to that question.
[1] Missing data: mean of D7 and D21.

ayahuasca holds some promise as a viable treatment for refractory depression. Nevertheless, future studies designed to further explore the antidepressive and anxiolytic effects of ayahuasca should be performed with more volunteers, different doses and also with repeated dosing for longer periods of time.

Declaration of conflicting interests and source of funding

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