CASE REPORT

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# Anxiety, panic, and hopelessness during and after ritual ayahuasca intake in a woman with generalized anxiety disorder: A case report

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*Background and aims:* Ayahuasca is a dimethyltryptamine- and β-carboline-rich hallucinogenic beverage traditionally used by indigenous groups of Northwest Amazonian for ritual and therapeutic purposes. Animal and human studies suggest that ayahuasca has antidepressant and anxiolytic potentials and has a good safety profile. However, anxiety-like reactions may also occur after ayahuasca intake, although they are rare. *Methods:* Case report. *Results:* Here, we describe a case of a non-medicated, symptom-free young female with generalized anxiety disorder, who experienced intense anxiety, panic, and hopelessness during and for 3 days after participating in an ayahuasca ritual. The symptoms appeared in the first hours after ayahuasca intake and were gradually reducing in the following hours/days, but were intense enough to cause significant suffering to her, who needed to seek psychiatric help and restarted pharmacological treatment. *Conclusions:* Although "bad/horror trips" with anxiety features may occur during the acute effects of ayahuasca and other hallucinogens, to the best of our knowledge, this is the first report of a subacute/prolonged anxiety-like reaction to this substance. Ayahuasca should be used with caution in people with a history of anxiety disorders.

**Keywords:** hallucinogens, ayahuasca, dimethyltryptamine, anxiety disorders

## INTRODUCTION

Ayahuasca is a botanical hallucinogenic beverage traditionally used by indigenous groups throughout the Northwestern Amazon for ritual and therapeutic purposes (Schultes & Hofmann, 1992). It is usually prepared by the prolonged decoction of the stems of the *Banisteriopsis caapi* vine combined with the leaves of the *Psychotria viridis* bush (Schultes & Hofmann, 1992). In the past decades, the use of ayahuasca has spread from South America to the United States, Europe, Africa, and Asia (Labate, Rose, & dos Santos, 2009). Active ingredients in ayahuasca include the tryptamine hallucinogen *N,N*-dimethyltryptamine (DMT) and β-carboline alkaloids, such as harmine, tetrahydroharmine, and harmaline (Schultes & Hofmann, 1992). DMT is as an agonist at cortical 5-$HT_{2A}$ receptors, and the β-carbolines are reversible inhibitors of monoamine oxidase type A (MAO-A; dos Santos, Balthazar, Bouso, & Hallak, 2016). Pure DMT is not psychoactive after oral administration, but in the case of ayahuasca, reversible inhibition of peripheral MAO-A by the β-carbolines allows DMT to reach systemic circulation and the central nervous system (dos Santos, Balthazar, et al., 2016).

Acute ayahuasca administration to healthy volunteers in controlled settings is well tolerated (dos Santos, Balthazar, et al., 2016). The psychoactive effects of orally administered ayahuasca begin within 30–40 min, peak around 1.5/2 hr, and gradually disappear in 4–6 hr after ingestion, and include perceptual alterations, introspection, and positive mood, although transient increases in psychotic and mania symptoms may also occur (de Araujo et al., 2012; dos Santos, Balthazar, et al., 2016). Nausea and vomiting are the most frequent adverse effects reported (dos Santos, Balthazar, et al., 2016). Dysphoric reactions, such as transient disorientation, anxiety, or suspiciousness/paranoia, are rare and short-lived, and usually respond well to verbal support and disappear completely after the expected time of action of ayahuasca without the need of medical intervention (dos Santos, Balthazar, et al., 2016; Riba & Barbanoj, 2006; Riba et al., 2001). In controlled settings, no prolonged adverse reactions of ayahuasca were ever reported (dos Santos, Balthazar, et al., 2016; Riba & Barbanoj, 2006; Riba et al., 2001).

These results are similar to previous studies involving the administration of other hallucinogens that also act as 5-$HT_{2A}$ agonists, such as psilocybin and lysergic acid diethylamide (LSD) (Cohen, 1960; Strassman, 1984; Studerus, Kometer, Hasler, & Vollenweider, 2011). Adverse reactions to these drugs can be classified along a temporal-severity-frequency continuum, from acute, short-lived reactions, involving anxiety, fear, panic, or psychotic symptoms (a "bad trip"), which are the most common adverse reactions and are often fairly benign, to subacute and chronic

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maladaptive/dysfunctional reactions with anxiety or psychotic features, which are less common but may carry a poor prognosis (Carbonaro et al., 2016; Cohen, 1960; Strassman, 1984). However, hallucinogen-related disorders (i.e., acute or prolonged reactions with anxiety, depressive, or psychotic features) are generally thought to have low incidence, low persistence, and high rates of recovery (American Psychiatric Association, 2013; Carbonaro et al., 2016; Cohen, 1960; Hendricks, Thorne, Clark, Coombs, & Johnson, 2015; Johansen & Krebs, 2015; Krebs & Johansen, 2013; Strassman, 1984), and population studies suggest that hallucinogen use could be associated with improved mental health (Hendricks et al., 2015; Johansen & Krebs, 2015; Krebs & Johansen, 2013).

Similarly, observational studies suggest that long-term ayahuasca use is not associated with increased psychopathology, cognitive deficits, or personality disorders (dos Santos, Balthazar, et al., 2016), with only few reports describing adverse psychiatric reactions (dos Santos, Balthazar, et al., 2016; dos Santos & Strassman, 2008; Lima & Tófoli, 2011; Szmulewicz, Valerio, & Smith, 2015). Moreover, a possible causal role of ayahuasca in these cases is sometimes difficult to establish, since other variables, such as previous psychiatric disorders and simultaneous use of other drugs, may confound interpretation. Long-term ayahuasca use appears to be associated with improved mental health (dos Santos, Balthazar, et al., 2016), and studies in animals and humans suggest that ayahuasca has anxiolytic, antidepressive, and antiaddictive properties (dos Santos, Osório, Crippa, & Hallak, 2016; dos Santos, Osório, Crippa, Riba, et al., 2016; Nunes et al., 2016). For instance, a recent open-label study reported fast-acting anxiolytic and antidepressive effects of a single ayahuasca dose (2.2 ml/kg, 0.8 mg/ml DMT) in 17 patients with treatment-resistant major depressive disorder, and ayahuasca administration was also associated with increased blood perfusion in brain regions involved in emotion processing (Sanches et al., 2016). Moreover, clinical trials with psilocybin and LSD also reported that these compounds have anxiolytic and antidepressive potentials (dos Santos, Osório, Crippa, Riba, et al., 2016).

Considering that acute, subacute, or chronic anxiety-related adverse reactions associated with ayahuasca are uncommon but possible, and that such reactions may improve our understanding of the relationship between hallucinogens, the 5-$HT_{2A}$ receptor, and anxiolytic/anxiogenic effects, here we report the case of a young adult female with generalized anxiety disorder (GAD), who experienced acute and subacute increases in anxiety, panic, and hopelessness symptoms during and after participation in an ayahuasca ritual. To the best of our knowledge, this is the first report of a prolonged anxiety-like reaction to ayahuasca described in the scientific literature.

## CASE PRESENTATION

Ms. A is a 25-year-old Brazilian female diagnosed with GAD and chronic insomnia when she was 20 years old. Our team did not have contact with Ms. A during these diagnoses, which were established by her psychiatrist at that time. Unfortunately, we were unable to contact the psychiatrist to confirm the diagnoses and to obtain more clinical details about Ms. A. Moreover, it was not possible for us to confirm the diagnoses using established diagnostic criteria because Ms. A was traveling abroad (United States and Australia), when she contacted us by e-mail to report her case. She contacted us after reading publications on ayahuasca and anxiety by our group, and none of the authors had previous contact with her. Ms. A was also unable to contact us by telephone, so all contact with her was made by e-mail. Although we are aware that it is problematic to describe a case report about one patient that the researchers have only established contact through e-mail, since it takes depth of analysis from the case, the description of diagnoses provided by Ms. A included sufficient clinical information to be considered by us a reliable report (except for the first author, all coauthors are experienced psychologists or psychiatrists specialized in anxiety disorders). Moreover, even considering this important limitation, we considered that the originality of the case and its possible relevance for the current expansion of ayahuasca use made its description worthwhile.

Her parents had a history of insomnia, and her mother had a diagnostic of panic disorder. She reported that her father was diagnosed "with many things during his treatment," but did not report any specific diagnosis. Before the episode, she had consumed other hallucinogens (LSD and psilocybin) on a few occasions ("not regularly, but occasionally, a few times per year") and 3,4-methylenedioxymethamphetamine (MDMA or *ecstasy*) ("occasionally, but for a year I have used it several times, every 2–3 months, in the weekends"), and had been a daily cannabis smoker for the preceding 8 years. Ms. A reported that neither the occasional use of hallucinogens/MDMA nor the daily use of cannabis was associated with significant adverse reactions or to her diagnoses (although we are aware that the absence of a careful face-to-face history-taking does not eliminate the possibility that the habitual cannabis use and previous use of hallucinogens and MDMA could have also contributed to the anxiety disorder and are confounding variables for this case report). Moreover, she was not using hallucinogens/MDMA at the time of the episode and did not consume cannabis (or other drugs) 2 days prior to or during the episode. She had never consumed ayahuasca before.

The chronic insomnia diagnosis preceded by some months the use of MDMA (which occurred when she was in Europe) and the GAD diagnosis. When Ms. A returned to Brazil (where she currently lives), she experienced a period of cultural crisis and had an intense anxiety episode, when she was diagnosed with GAD. Ms. A was treated with paroxetine, zolpidem, and alprazolam for 8 months, but tolerance developed for these drugs and although the anxiety symptoms gradually reduced her insomnia did not improve.

Shortly after this period, Ms. A reported experiencing a sudden, unexpected, and spontaneous "spiritual awakening," which was not induced by hallucinogens or religious practices. This experience was characterized by feeling of "serenity, peace, and love," which "healed" her from the anxiety symptoms, and she decided to stop taking her medications without medical advice. After a period of 4 months of a complete absence of anxiety symptoms and motivated by some of her friends, who enthusiastically

talked about the therapeutic potentials of ayahuasca, she started reading anecdotal and scientific reports describing anxiolytic effects of ayahuasca and decided to participate in an ayahuasca ritual in a place near her city in Brazil, a country that allows the religious use of ayahuasca (Labate et al., 2009). At the time of the episode, she was obtaining graduate training in a Brazilian university.

Ms. A did not provide a detailed description of the ritual setting, such as her impressions of the place, if there were experienced guides to coordinate the ceremony and help in the case of difficult experiences, or if there was some kind of preparation before (and integration after) the ritual. She just described the setting as a place where ayahuasca rituals were performed. The lack of a detailed description of the setting could reflect the fact that this was the first time that Ms. A was ingesting ayahuasca; therefore, she did not have any mark of reference how an appropriate setting and integration would look like. During the ceremony, she ingested two consecutive ayahuasca doses, separated by a 2-hr interval. Unfortunately, given the retrospective nature of the report, it was not possible to perform a chemical analysis in the ayahuasca sample used by Ms. A. Although she did not feel any psychoactive effects with the first dose, after the second dose (the exact time was not reported by her), she began to experience very intense anxiety, panic, and hopelessness, and also arrhythmia: "I was 100 times more anxious than normal," "I panicked with the idea of never being able to come back to my normal mental state again," "I was unable to stop moving around, and the feeling of hopelessness stayed with me for hours, until the end of the ritual," "I knew that I was not going to die, but the arrhythmia was worrying me so much that I asked one of the ritual organizers if there was any physician present, but there was none." Ms. A did not report the presence or emergence of complicated and anxiety-provoking psychological material during the episode.

Some of the organizers tried to make her calm and comfortable, and she even tried to take a shower in the attempt to reduce her anxiety, but the psychological suffering persisted for the next 8 hr of the ritual. After this period, anxiety symptoms began to reduce their intensity but continued to concern her. Ms. A was able to drive to the hotel where she was staying, and anxiety symptoms continued to reduce their intensity in the following hours. However, Ms. A still felt anxiety and hopelessness for the next 3 days, and resumed her psychiatric treatment when she finally felt better.

Currently, Ms. A is using mirtazapine, clonazepam, and zolpidem everyday, and her anxiety and insomnia have improved. Interestingly, despite the adverse psychiatric effects associated with ayahuasca ingestion, Ms. A also attributed some beneficial effects to her experience, such as reductions in alcohol and cannabis use and increase in yoga and meditation practices.

## DISCUSSION

Acute ayahuasca administration in controlled settings to healthy volunteers (de Araujo et al., 2012; dos Santos, Balthazar, et al., 2016; Riba & Barbanoj, 2006; Riba et al., 2001) and depressed patients (dos Santos, Osório, Crippa, Riba, et al., 2016; Sanches et al., 2016) is rarely associated with dysphoric/anxiogenic reactions. Indeed, ayahuasca administration is associated with anxiolytic and antidepressive effects in animals and in both healthy volunteers and depressed patients (dos Santos, Osório, Crippa, & Hallak, 2016; dos Santos, Osório, Crippa, Riba, et al., 2016; Sanches et al., 2016). Moreover, psychiatric adverse reactions are uncommon in the context of regular ayahuasca use in ritual/religious settings (dos Santos, Balthazar, et al., 2016; dos Santos & Strassman, 2008; Lima & Tófoli, 2011; Szmulewicz et al., 2015). Thus, this case appears to describe a rare event in the context of ritual ayahuasca use, which is in line with studies with other hallucinogens suggesting a low incidence of prolonged dysphoric/anxiogenic reactions both in controlled contexts (Cohen, 1960; Strassman, 1984; Studerus et al., 2011) and in population studies (Hendricks et al., 2015; Johansen & Krebs, 2015; Krebs & Johansen, 2013).

However, uncommon, acute reactions may occur in controlled settings involving the administration of ayahuasca (Riba & Barbanoj, 2006; Riba et al., 2001) and other hallucinogens (Cohen, 1960; Strassman, 1984; Studerus et al., 2011). Experimental research investigating the acute and long-term psychological effects of psilocybin (1–4 oral doses of 45–315 μg/kg) in 110 healthy volunteers reported significant but small increases in anxiety during psilocybin sessions, but only after high doses and in a minority of volunteers, who were not medicated and were all calmed down verbally (Studerus et al., 2011).

Regarding subacute or prolonged adverse reactions, to the best of our knowledge, there is no description of such an event associated with controlled administration of ayahuasca (dos Santos, Balthazar, et al., 2016; dos Santos, Osório, Crippa, & Hallak, 2016; dos Santos, Osório, Crippa, Riba, et al., 2016; Sanches et al., 2016). However, in the follow-up of the pooled analysis of the psilocybin experiments in healthy volunteers, 7 of the 110 subjects (8%) reported negative psychological effects following days/weeks of psilocybin administration, including concentration problems, mood swings, reactivation of old problems, memory problems, and being pensive and introverted (Studerus et al., 2011). Among these volunteers, only one reported severe symptoms, such as emotional instability, anxiety, and depressive symptoms, which needed professional help. These symptoms were experienced for a couple of weeks after psilocybin administration, and the volunteer was referred to a psychotherapist. After a few sessions, the volunteer was completely stabilized and did not relapse afterward. Therefore, uncommon, subacute/prolonged reactions with anxiety features and mood swings may occur in the context of controlled administration of hallucinogenic drugs, including healthy volunteers who were carefully screened for previous psychiatric disorders (Cohen, 1960; Strassman, 1984; Studerus et al., 2011).

Regarding the low incidence of psychopathological adverse reactions in the context of regular ayahuasca use, it must be considered that these previous studies with long-term users may be limited by a possible selection bias, since only those users adapted to ayahuasca effects would remain using it throughout the years, and novice users who suffer any adverse reaction might never use ayahuasca again and so will not be evaluated in these studies. Thus, prospective studies following novice ayahuasca users are necessary to

improve our understanding of ayahuasca and psychopathological (or therapeutic) effects.

The mechanisms involved in the anxiogenic effects described in this case are not well understood. Considering that the β-carbolines in ayahuasca are apparently not hallucinogenic at the doses commonly present in ayahuasca and are associated with sedative effects (dos Santos, 2011; dos Santos, Osório, Crippa, & Hallak, 2016), the anxiogenic or anxiolytic potential of ayahuasca seems to be related to DMT and its agonist activity at cortical 5-$HT_{2A}$ receptors, a mechanism of action shared with psilocybin and LSD (dos Santos, 2011; dos Santos, Balthazar, et al., 2016; dos Santos, Osório, Crippa, Riba, et al., 2016). These drugs act on frontal and limbic areas rich in 5-$HT_{2A}$ receptors and are involved in the regulation of mood, emotions, perceptions, and memory (de Araujo et al., 2012; dos Santos, 2011; dos Santos, Balthazar, et al., 2016; Sanches et al., 2016).

The prolonged negative reaction to ayahuasca experienced by Ms. A could have been modulated at least in part by the history of a panic disorder diagnosis in her family (mother) and her previous GAD diagnosis. Although she was not experiencing any anxiety symptoms 4 months before the ritual, she had stopped taking her medication without psychiatric advice, and maybe the uncompleted treatment could have predisposed her to an anxiety-like reaction in the presence of an environmental stressor (in this case, ayahuasca). In this regard, it is interesting to note that some drugs used for the treatment of anxiety and mood disorders, such as selective inhibitors of serotonin reuptake, may actually increase anxiety during the beginning of the treatment (Nutt, 2005; Zohar & Westenberg, 2000). Furthermore, some recreational drugs that are usually associated with calming/relaxing/anxiolytic-like subjective effects and that have different mechanisms of action compared with ayahuasca or among each other, such as cannabis/tetrahydrocannabinol (Kedzior & Laeber, 2014; Zuurman, Ippel, Moin, & van Gerven, 2009) and MDMA (Dumont & Verkes, 2006; Rogers et al., 2009), may also increase anxiety symptoms depending on dose, genetic/personality vulnerability, and other factors, even in healthy volunteers previously screened for psychiatric disorders. Therefore, future studies should investigate if variables, such as genetic vulnerability, severity of anxiety symptoms, gender, age, and other factors, are more or less associated with anxiolytic or anxiogenic reactions to ayahuasca and other hallucinogens acting as 5-$HT_{2A}$ receptor agonists/partial agonists.

There is also the possibility that the negative reaction of Ms. A could have been influenced or exacerbated by a poor preparation, guiding, and integration of her experience, the so-called "set and setting." The "set" refers to the person's personality, previous ideas about ayahuasca, and proper preparation before the ceremony, whereas the "setting" refers to the environment where the ritual is performed, the coordination of the ceremony, and the integration of the effects of ayahuasca. Set and setting are the important elements involving both ritual and experimental hallucinogen use, and the lack of a proper screening, guidance, and integration of the experience may increase the possibility of a negative reaction (Labate et al., 2009; Strassman, 1984). However, Ms. A did not provide details about any of these factors and did not report that they were especially relevant in her experience. Thus, although set and setting might not have been optimal, the lack of emphasis of Ms. A in these elements suggests that they did not have a prominent role in her reaction to ayahuasca. It is important to consider, however, that this was the first time that Ms. A was ingesting ayahuasca; therefore, she did not have any mark of reference how an appropriate setting and integration would look like, which could have influenced her negative reaction to ayahuasca.

It is also important to consider that there is a risk that we are interpreting a relatively common experience of a self-limited ayahuasca "bad trip" as a much more severe outcome. However, considering that the symptoms described by Ms. A were subacute and not acute, and that she needs to restart her pharmacological treatment due to the intensity of the symptoms, we do not think that this was a short-lived "bad trip." Moreover, it appears that the reported arrhythmia was a significant contributory factor behind the anxiety symptoms of Ms. A. Therefore, we cannot eliminate a possible role of this arrhythmia behind the reoccurring anxiety symptoms.

Considering the low incidence of adverse psychological reactions related to ayahuasca in ritual and research settings, and that even after screening volunteers with previous psychiatric or personality disorders, this kind of reaction may still occur, and it is very difficult to predict the occurrence of such events. However, given the potentially high morbidity associated with prolonged drug-induced anxiety disorders and the current investigations of the potential clinical use of hallucinogenic compounds in the treatment of mood and anxiety disorders, both research and religious use of ayahuasca should be made with caution in people with a history of anxiety disorders.

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