Research Report: Study Finds Ayahuasca Administration Associated with Antidepressant Effects
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Depressive disorders are highly prevalent, and are associated with increased mortality and high morbidity (Ebmeier et al., 2006; Andrade et al., 2012). An important proportion of depressive patients do not benefit from currently available medications, which often produce significant side-effects and may take as long as two to three weeks to produce therapeutic effects (Pacher and Kecskemeti, 2004). Therefore, new pharmacological tools for the treatment of depressive disorders should be explored.

Ayahuasca is a hallucinogenic botanical preparation traditionally used by indigenous groups of Amazonian countries such as Brazil, Colombia, Peru and Ecuador for ritual and therapeutic purposes (Schultes and Hofmann, 1992). The main ingredient in ayahuasca is the jungle vine *Banisteriopsis caapi*. In Brazil, Peru and Ecuador, ayahuasca is usually prepared by boiling the steams of the liana together with the leaves of the shrub *Psychotria viridis*, whereas the leaves of other liana, *Diplopterys cabrerana*, are used in Colombia and Ecuador (Schultes and Hofmann, 1992). *B. caapi* contains beta-carboline alkaloids (harmine, tetrahydroharmine and harmaline) and *P. viridis* and *D. cabrerana* are rich in the hallucinogenic tryptamine dimethyltryptamine (DMT). When taken orally, DMT is not psychoactive, since it is metabolized in the liver and gut by the enzyme monoamine oxidase (MAO). However, the beta-carbolines in ayahuasca are reversible inhibitors of this enzyme, allowing DMT to reach systemic circulation and the brain (Riba et al., 2003; Riba et al., 2015).

In the beginning of the 20th century, syncretic religions that mixed indigenous, African and Christian beliefs, and that centered their religious practices on the ritual and therapeutic use of ayahuasca, were created in the Brazilian Amazon (Labate et al., 2009; Labate and Jungaberle, 2011; Labate and Cavnar, 2014). In the following decades, these religions remained restricted to the Amazon cities, but in the late 1970’s groups like the Santo Daime and the União do Vegetal slowly expanded to the Brazilian urban centers. In the last two decades, the use of ayahuasca has expanded from South American cities to Europe, the United States, and Asia (Labate et al., 2009; Labate and Jungaberle, 2011; Labate and Cavnar, 2014).

The expansion in the number of people interested in the ritual and religious aspects of ayahuasca was accompanied by several studies describing anxiolytic and antidepressive effects associated with the ingestion of ayahuasca (Grob et al., 1996; dos Santos et al., 2007; Labate et al., 2009; Labate and Jungaberle, 2011; Barbosa et al., 2012; Bouso et al., 2012; Labate and Cavnar, 2014; dos Santos et al., in press). Moreover, our group reported that harmine produces antidepressive effects in rats (Fortunato et al., 2009; Fortunato et al., 2010a; Fortunato et al., 2010b; dos Santos et al., in press). Furthermore, studies with other hallucinogenic compounds like psilocybin and LSD, which share chemical and pharmacological properties with DMT, have described that these compounds produce anxiolytic and antidepressive effects in patients with life-threatening diseases (Grob et al., 2011; Gasser et al., 2014). However, there is no clinical trial that investigated the possible antidepressive effects of ayahuasca in depressive patients.

Our group just published an open-label study that assessed the antidepressive potential of ayahuasca in patients with a diagnosis of recurrent major depressive disorder (Osório et al., 2015). A single dose of orally administered ayahuasca (2.2 mL/kg) was administered to six volunteers with a current depressive episode. Volunteers were
admitted to an inpatient psychiatric unit for two weeks prior to ayahuasca administration, and during this time they did not take any psychiatric medication or recreational drugs. In line with previous clinical trials that investigated the potential therapeutic effects of psychedelic compounds without including some form of psychotherapeutic intervention (Moreno et al., 2006; Grob et al., 2011), volunteers in our study only received information on the effects of ayahuasca, and there was no formal preparation sessions prior to drug administration or integrative sessions afterwards. Thus, non-drug factors that are commonly present in ritualized and religious contexts, such as singing or listening to music (Labate et al., 2009; Labate and Jungaberle, 2011; Labate and Cavnar, 2014), were excluded. Ayahuasca was administered in a quiet dimly lit room, where volunteers remained seated in a comfortable reclining chair. The session was performed individually and lasted four hours.

Ayahuasca administration was associated with statistically significant reductions of up to 82% in depressive scores between baseline and one, seven, and 21 days after drug intake, according to the Hamilton Rating Scale for Depression (HAM-D), the Montgomery–Åsberg Depression Rating Scale (MADRS), and the Anxious–Depression subscale of the Brief Psychiatric Rating Scale (BPRS). Ayahuasca was well tolerated by all patients and vomiting was the only adverse effect recorded (reported by 50% of the volunteers), although patients did not consider this emetic effect as causing severe discomfort.

Although the described results are promising, we cannot conclude that the observed changes were in fact caused by ayahuasca, since treatment was not randomized or double-blind, and there was no placebo or other comparator group. Moreover, it is important to note that the controlled clinical setting is different from the typical ritual context of ayahuasca consumption, which may limit the generalizability of our findings.

From a psychopharmacological perspective, the effects of ayahuasca, psilocybin and LSD on mood appear to be mediated by the agonism of these compounds on 5-HT2A receptors expressed in brain regions associated with emotional processing (Vollenweider and Kometer, 2010; Baumeister et al., 2014). For instance, psilocybin enhanced positive mood, attenuated recognition of negative facial expression, and reduced amygdala reactivity, which was correlated with increases in positive mood (Kometer et al., 2012; Kraehenmann et al., in press). Furthermore, ayahuasca (Palhano-Fontes et al., 2015) and psilocybin (Carhart-Harris et al., 2012) reduce brain activity in key regions of the default mode network (DMN), and increased activity of the DMN is associated with intensification of rumination, an important depressive symptom.

We recently replicated the results of the original open-label, proof-of-concept study, but including 17 volunteers and single-photon emission computed tomography (SPECT). Results suggest that the antidepressive properties of ayahuasca may be associated with increased blood perfusion in brain regions related to depressive symptoms.
(unpublished observations). Furthermore, our group is currently performing randomized, double-blind, placebo-controlled studies assessing the antidepressive and anxiolytic potentials of ayahuasca (Frood, 2015).

Further studies are urgently needed to better understand the potential therapeutic effects of classic tryptamine psychedelics in the treatment of psychiatric disorders.

REFERENCES


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