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EDITORIAL

Translational evidence for ayahuasca as an antidepressant: what's next?

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Depression is among the most important contributors to global disability and suicidal deaths. Available antidepressants are usually selective inhibitors of serotonin and norepinephrine uptake, which need weeks of daily intake before therapeutic effects appear, have limited efficacy for many patients, and induce significant adverse reactions after prolonged use. Therefore, recent research has focused on finding new antidepressant compounds that are fast-acting, more effective, and less toxic.

The article recently published by da Silva et al. in the *Brazilian Journal of Psychiatry*[1] reported that ayahuasca, a psychoactive decoction containing harmine and dimethyltryptamine traditionally used by Amazonian indigenous groups and Brazilian syncretic religions, produced antidepressant effects in a juvenile primate model of depression. The antidepressive effects of ayahuasca and its alkaloids have been previously demonstrated in rodent models of depression. Harmine (5-15 mg/kg) induced behavioral and neurochemical antidepressant effects after acute and prolonged (7-14 days) administration, and acute oral administration of ayahuasca (5 mg/kg) has also induced antidepressant effects in rodents.[2] Observational studies of long-term ritual ayahuasca users also show evidence of antidepressant effects,[2] as did a controlled study with nine healthy volunteers.[3]

The antidepressant effects of a single ayahuasca dose (2.2 mL/kg) were also demonstrated in a recent open-label trial with 17 patients with treatment-resistant major depression disorder (MDD), where significant reductions in depressive symptoms were observed from the first hours after ayahuasca intake and persisted up to 21 days afterwards.[4] These results were replicated in a controlled trial with 29 patients, where a single dose of ayahuasca produced significant reductions in depressive symptoms from the experimental day until 7 days afterwards compared to placebo.[5] Importantly, both studies were performed by Brazilian scientists from the Universidade de São Paulo and Universidade Federal do Rio Grande do Norte.

Both institutions also participated in the study by da Silva et al.,[1] which complements previous rodent and human studies by showing that a single dose of ayahuasca (1.67 mL/300 g) produced significant physiological and behavioral improvements in a juvenile primate model of social isolation, which is phylogenetically closer to humans. Moreover, these effects remained significant for 14 days, corroborating previous results with MDD patients (improvements lasting 7-21 days).[4,5] Taken together, these results provide further translational evidence of the antidepressant effects of ayahuasca, adding to a body which now consists of preclinical (rodents, non-human primates), experimental (phase I), and clinical (phase II) studies.

So, what's next?

It is important to acknowledge that, although the above-mentioned results are promising, they are not conclusive evidence that ayahuasca can be used as an antidepressant. The results were observed only with single doses in few patients, and the depressive symptoms returned some weeks after ayahuasca intake. Thus, ayahuasca is not a cure for depression, and further studies using more doses in larger samples are necessary to evaluate its long-term efficacy and safety, especially with a view to use in adolescents. Future studies will also need to assess the possible advantages and disadvantages of ayahuasca in relation to traditional antidepressants, and in which specific subpopulations of patients with depression ayahuasca could be more helpful. Specifically, it would be interesting to assess the effects of ayahuasca in patients that do respond to available biological treatments (antidepressants, electroconvulsive therapy, etc.), as well as to investigate other compounds with antidepressant effects and nontraditional mechanisms of action (such as cannabidiol and ketamine). Moreover, further naturalistic studies assessing depression in large populations of regular ayahuasca users should also be performed, since the traditional use of ayahuasca involves its use in group settings that enhance community bonds, and social support can be a protective factor in mental health. Further studies are also necessary regarding the toxicology of ayahuasca and the stability and proportion of its components.

If these studies show positive results, we will need to think about the inclusion of ayahuasca in our health

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system. Considering its traditional uses to improve health in Brazil and other Amazonian countries and the need for better treatments for depression, the future seems promising.

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Disclosure

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