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ALSUntangled 40: Ayahuasca

The ALSUntangled Group

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ARTICLE

ALSUntangled 40: Ayahuasca

THE ALSUNTANGLED GROUP

ALSUntangled reviews alternative and offlabel treatments (AOTs) for people with ALS (PALS). Here we evaluate ayahuasca therapy for ALS in response to 113 requests (1). As with all our previous reviews, this article will focus on the specific possibility that ayahuasca treatment might slow, stop or reverse ALS progression. Reviews on potential symptomatic benefits (such as improved pain or energy levels) are outside the scope of our programme.

Overview

Ayahuasca (a word which translates to vine of the soul or rope of death) is the most common name for the tea prepared from the vine Banisteriopsis caapi (B. caapi), sometimes in combination with other plants (2). It is a hallucinogen used in religious rituals primarily in the Amazon (2,3). Ayahuasca is suggested to work by a variety of mechanisms, including agonist activity at the sigma-1 receptor (S1R), monoamine oxidase (MAO) inhibition, agonist activity at serotonin (5-HT) receptors, and reduction of excitotoxicity (2–7). Risks associated with ayahuasca use include serotonin syndrome, hypertensive crisis, hospitalisation, intubation, and even death (8). Our PubMed search yielded 199 articles about ayahuasca but no published studies in which ayahuasca was used in PALS. We did, however, find two scientific publications describing studies of components of ayahuasca or similar compounds in pre-clinical models of ALS (7,9).

Mechanisms

Beta-carbolines, including harmine, tetrahydroharmine (THH), and harmaline, are hypothesised to be the active ingredients in ayahuasca (2,3,10). Harmine increased levels of the glutamate transporter GLT-1 (EAAT2 in humans) in the cortex of SOD1 mutant mice compared to mice treated with saline (7). Higher levels of EAAT2 could decrease excitotoxicity in patients with ALS by reducing synaptic glutamate. Unfortunately, another method attempting to increase EAAT2 (ceftriaxone treatment) failed to slow the progression of human ALS (11); since EAAT2 levels were not tested in this trial, it is unclear whether the trial failed because the concept was wrong or because the dosing was not optimised.

Some data also suggest that beta-carbolines work as MAO-A inhibitors (4). In humans, MAO-A breaks down 5-HT, norepinephrine, and tyramine (12). It is possible that this mechanism is important in promoting gut absorption of N,N-dimethyltryptamine (DMT), which is found in *Psychotria viridis* (*P. viridis* or *chacruna*) and *Mimosa tenuiflora* (*M. tenuiflora* or *jurema*), two plants commonly combined with *B. caapi* in ayahuasca (4,10,13). DMT is an agonist at the 5-HT1A and 5-HT2A serotonin receptors (5). There is conflicting evidence as to whether globally increasing serotonergic tone modifies disease progression in mouse models of ALS (14,15). However, DMT has also been shown to be an agonist at the S1R in vitro (6). Manipulation of this receptor could have therapeutic benefit in patients with ALS, as removal of the *S1R* gene in mSOD1 mice shortens lifespan. Furthermore, there is one family in which a mutation in the S1R led to juvenile ALS (16). Based on ayahuascas potential effects on EAAT2 and S1R, ALSUntangled assigns a TOE Mechanism grade of C (Table 1).

Daniel Gustafsson (D.G.) who maintains a website featuring interviews with PALS using ayahuasca, writes about other potential mechanisms of ayahuasca (17,18). While several of these proposed mechanisms act on pathways that may play a role in the pathogenesis of ALS, we did not find data

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Table 1. TOE grades for ayahuasca in ALS.

	Grade	Explanation
Mechanism	C	Components of ayahuasca can increase GLT-1 receptors, modulate serotonin and affect S1R receptors, actions which could theoretically help slow ALS progression.
Pre-Clinical	U	We found no trials of ayahuasca in ALS models.
Cases	D	We found reports of subjective improvements in patients who used ayahuasca without validated diagnoses. We also found one unpublished case of a validated ALS reversal in a patient who used ayahuasca one time. In our opinion, it is highly unlikely that a single dose of ayahuasca could have triggered a biological mechanism that could have caused this ALS reversal.
Trials	U	We found no published trials of ayahuasca in PALS.
Risks	D/F	Death and hospitalisation have been reported following ayahuasca use. It is not clear what percentage of users experienced these.

supporting the ability of ayahuasca to act on these mechanisms in ways that could plausibly modify disease progression.

Pre-Clinical Models

We found no trials of ayahuasca in recognised ALS pre-clinical models. Based on this, ALSUntangled assigns a TOE Pre-Clinical Grade of U (Table 1).

The above-described study of harmine in mSOD1 mice did not measure disease progression. We found one study of an S1R agonist (SA4503), in mSOD1 mice. Disease onset was not affected, but survival was increased in the mice treated with SA4503 every day from five weeks old to death (9).

Data in PALS

Cases

D.G. has posted interviews with two PALS using ayahuasca on his blog (17). The first, a 65-year-old male, sent us his records for review. At age 63 years, he had gradual onset of progressive arm and leg weakness. Neurological exams showed atrophy, fasciculations and weakness in his arms and legs, brisk reflexes throughout, and emotional lability. He did not have any sensory abnormalities or trouble controlling his bowel or bladder. Nerve conductions showed no sensory neuropathy or motor conduction blocks. Needle EMG showed denervation and reinnervation changes in multiple cervical and lumbosacral regions. MRI brain, MRI cervical spine, and blood tests (ANA, ANCA, ENA, tTG) failed to show any other causes for his symptoms. This information is consistent with ALS, although an independent neurological exam from a recognised expert would increase our confidence in this diagnosis. At his nadir, the patient had 4/5 strength bilaterally in shoulder flexion, shoulder extension, hip flexion, and hip extension and 3/5 strength bilaterally in finger extension on manual muscle testing. Over the course of the next seven to 11 months, he tried a number of different AOTs including a single dose of ayahuasca, as well as acupuncture, craniosacral therapy, massages, coenzyme Q10, chondroitin, goji berries, and 10–15 Chinese herbs. He was also following a lactose free diet and eating many organic fruits, vegetables, and meats. His medical records suggest that his strength improved, cramping and fasciculations decreased, and weight increased 10 pounds. On follow-up, his neurologist wrote that he has good strength and generally does not present in any way now with features of motor neuron disease. While it would be ideal to see improvement in additional outcome measures such as ALSFRS-R and FVC, this limited information is suggestive of an ALS reversal. However, in our opinion, it is highly unlikely that ayahuasca caused this reversal. A single dose of ayahuasca could not have triggered changes in EAAT2 or S1R receptors of sufficient magnitude or duration to reverse ALS. As we have previously noted, there are multiple possible explanations for ALS reversals, including failure to recognise an ALS mimic syndrome.

The second patient referenced on D.G.s blog is an 82-year-old female. She began using ayahuasca eight months before her death. Her son, who gave the interview for D.G., describes that after increasing the dose of ayahuasca, she did have some subjective improvement in strength in one of her legs. Unfortunately, we were unable to obtain records to confirm either her ALS diagnosis or reported improvement.

In his e-mails to us, D.G. states that his report includes data from interviews with 10 participants. The ALS diagnoses of these participants were not validated. In addition to the two cases described above, D.G. states that four interviewees claim to have noticed subjective improvements. None of these improvements was supported by validated, objective ALS outcome measures. We found two additional cases posted on the PatientsLikeMe (PLM) and ALS Therapy Development Institute (TDI) forums who reported subjective improvements (19,20). The PLM thread has been closed with a note from an administrator indicating that the two posters were under investigation for both being fake patients/members originating from the same IP address/computer user.

Based on the above-described information, ALSUntangled assigns a TOE Cases grade of D (Table 1).

Trials

We found no published trials of ayahuasca in PALS. Based on this, ALSUntangled assigns a TOE Trials grade of U (Table 1).

Risks, Dosing and Costs

We found 10 studies in which ayahuasca was administered to healthy volunteers. Of these, there were six studies with a total of 74 enrolled participants that reported on adverse events (21–26). Safety data do not appear to have been gathered systematically, but common side-effects reported included vomiting, high blood pressure, high heart rate, and psychosis. There are also data from 538 calls to US Poison Control Centers following exposure to ayahuasca from 2005 to 2015. In this study, the most common clinical manifestations were hallucinations (35%), high heart rate (34%), agitation (34%), confusion (18%), high blood pressure (16%), pupillary dilation (13%), and vomiting (6%). Of note, there were 12 cases with seizures, seven with respiratory arrests, four with cardiac arrests, and three deaths. Of the exposures, 28% of patients were admitted to the hospital, and 28 patients required intubation (8). Based on reported deaths and hospitalisations outside the setting of a clinical trial, ALSUntangled assigns a TOE Risks grade of D/F (Table 1).

There are four more theoretical but serious risks of using ayahuasca. The first is hypertensive crisis, a well-known side effect of MAO inhibitors, particularly MAO-A inhibitors. It occurs when patients taking these drugs ingest tyramine-containing foods, such as tap beer or aged cheeses and meats. This is because tyramine is sympathomimetic and can raise blood pressures to dangerous levels resulting in stroke, aneurysm, end organ damage, and even death when it is not metabolised by MAO (27). The second theoretical risk is serotonin syndrome. This syndrome is classically characterised by confusion, fluctuations in body temperature, pulse and blood pressure, and hyperactive reflexes or involuntary muscle jerking. These symptoms can range from mild to life threatening. This side-effect is often the result of combining two drugs that simultaneously increase serotonergic tone, as do beta-carbolines and DMT. Some PALS take other serotonergic medications for depression and/or anxiety, making this especially worrisome. Prognosis is generally favourable, but serious cases require care in the ICU. Death has been reported, particularly with use of MAO inhibitors (28). Several studies in goats and rats suggest that *M. tenuiflora* may lead to early foetal loss or cause birth defects such as abnormalities of the face, eyes, skin or colon (29–31). One study showed that pups of pregnant rats treated with DMT had higher rates of cleft palate and skeletal abnormalities than controls (32). Finally, we found one study in which harmaline competitively inhibited an NMDA channel blocker in rabbit brain. The authors of this article hypothesised that harmaline acts as an inverse agonist at this binding site, opens the NMDA cation channel, and increases excitation (33). This could theoretically increase excitotoxicity contributing to further injury of motor neurons.

D.G. tells us that the dose of ayahuasca used varies from patient to patient, but that 25g *B. caapi* with additional 2g *M. tenuiflora* or 10–20g *P. viridis*, taken one to two times per week is a representative dose. He adds that, compared with teas brewed from bark, concentrations of the active ingredients in leaves are more variable from harvest to harvest, thus making a standard dosage more difficult to achieve when brewing with leaves. D.G. posted one participants protocol on his Twitter page, which involved the use of 1–10mL of *B. caapi* extract per day (34). Based on similar products found online, this equals approximately 10–100g fresh *B. caapi* and would cost $1.10–$11 per day (35).

Conclusions

Ayahuasca has interesting mechanisms that could potentially be useful in treating human ALS. We found one person who appears to have experienced an ALS reversal following exposure to a single dose of ayahuasca and several other AOTs. We do not believe that a single dose of ayahuasca could trigger a mechanism that would reverse ALS. There are more plausible explanations for this case, including an unrecognised ALS mimic syndrome. Importantly, there are several documented harms associated with ayahuasca use, including hospitalisation, intubation, and death. There are also serious theoretical risks, including hypertensive crisis, serotonin syndrome, and birth defects. Given this information, at this time, we do not endorse the use of ayahuasca to slow, stop or reverse ALS progression.

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