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The current state of research on ayahuasca: A systematic review of human studies assessing psychiatric symptoms, neuropsychological functioning, and neuroimaging

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Abstract

Rationale: In recent decades, the use of ayahuasca (AYA) – a β -carboline- and dimethyltryptamine-rich hallucinogenic botanical preparation traditionally used by Northwestern Amazonian tribes for ritual and therapeutic purposes – has spread from South America to Europe and the USA, raising concerns about its possible toxicity and hopes of its therapeutic potential. Thus, it is important to analyze the acute, subacute, and long-term effects of AYA to assess its safety and toxicity.

Objectives: The purpose of this study was to conduct a systematic review of human studies assessing AYA effects on psychiatric symptoms, neuropsychological functioning, and neuroimaging.

Methods: Papers published until 16 December 2015 were included from PubMed, LILACS and SciELO databases following a comprehensive search strategy and pre-determined set of criteria for article selection.

Results: The review included 28 full-text articles. Acute AYA administration was well tolerated, increased introspection and positive mood, altered visual perceptions, activated frontal and paralimbic regions and decreased default mode network activity. It also improved planning and inhibitory control and impaired working memory, and showed antidepressive and antiaddictive potentials. Long-term AYA use was associated with increased cortical thickness of the anterior cingulate cortex and cortical thinning of the posterior cingulate cortex, which was inversely correlated to age of onset, intensity of prior AYA use, and spirituality. Subacute and long-term AYA use was not associated with increased psychopathology or cognitive deficits, being associated with enhanced mood and cognition, increased spirituality, and reduced impulsivity.

Conclusions: Acute, subacute, and long-term AYA use seems to have low toxicity. Preliminary studies about potential therapeutic effects of AYA need replication due to their methodological limitations.

Keywords

Hallucinogens, ayahuasca, dimethyltryptamine, harmine, safety, toxicity, psychopathology, cognition, neuroimaging, antidepressant

Introduction

Ayahuasca (AYA) is a botanical hallucinogen that has been used for centuries in ritual contexts by Amazonian indigenous groups in countries such as Brazil, Peru, Colombia and Ecuador (Labate and Araújo, 2004; Schultes and Hofmann, 1992). In Brazil and worldwide, AYA is used as a sacrament in syncretic religions such as the *Santo Daime*, *União do Vegetal* (UDV), and *Barquinha*, which blend elements of Amazonian shamanism, Christianity, Spiritualism, and African-Brazilian religions such as Umbanda (Labate and Araújo, 2004; Labate et al., 2009; Schultes and Hofmann, 1992). It is estimated that nearly 20,000 people worldwide are members of some of the Brazilian AYA religions, but epidemiological data on recreational use is scarce (Cakic et al., 2010; Labate and Araújo, 2004; Labate et al., 2009; United Nations Office on Drugs and Crime, 2010).

AYA is usually obtained by boiling the pounded stalks of the vine *Banisteriopsis caapi* (popularly called *mariri* or *jagube* in Brazil) and the leaves of the bush *Psychotria viridis* (*chacrona* or

queen) (Labate and Araújo, 2004; Labate et al., 2009; Schultes and Hofmann, 1992). *B. caapi* contains β -carboline alkaloids

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such as harmine, tetrahydroharmine (THH), and harmaline, that are reversible inhibitors of monoamine oxidase A (MAO-A), while *P. viridis* is rich in the tryptamine hallucinogen dimethyl-tryptamine (DMT), an agonist of serotonin (5-HT)_{1A/2A/2C} receptors (McKenna et al., 1984; Schultes and Hofmann, 1992; Riba et al., 2003). When ingested alone, DMT is metabolized by peripheral MAO-A and does not produce psychoactive effects (Riba et al., 2003, 2015). In the case of AYA, the β -carbolines (especially harmine), temporarily inhibit MAO-A, allowing DMT to reach systemic circulation and the Central Nervous System (Riba et al., 2003).

Acute AYA administration produces significant psychoactive effects that peak around 1.5–2 h and last for 4–6 h, involving perceptual modifications, somatic effects, changes in thought content, increased emotional lability, and increased positive mood and activation (Dos Santos, 2013a; Dos Santos et al., 2011, 2012; Riba et al., 2001, 2003). AYA is well tolerated in healthy volunteers, producing moderate and short-lived cardiovascular, autonomic, neuroendocrine, and immunological effects (Dos Santos, 2013a; Dos Santos et al., 2011, 2012; Riba et al., 2001, 2003). Nausea and vomiting are the main side-effects observed in ritual and experimental settings (Dos Santos, 2013a; Dos Santos et al., 2012; Gable, 2007; Labate and Araújo, 2004; Labate et al., 2009; Riba et al., 2001).

Case-control and cross-sectional studies of experienced AYA consumers also suggest that the ritual consumption of this hallucinogen is safe and not associated with psychopathology or neuropsychological deficits (Barbosa et al., 2012; Bouso and Riba, 2011; Dos Santos, 2013a; Gable, 2007). However, most of these studies were performed among long-time members of AYA religions, who were already well adapted to prolonged exposure to AYA and, thus, less likely to have experienced negative reactions to the brew. This may have produced a selection of individuals who were more likely to be chosen because they were better adapted to AYA, possibly biasing the results and limiting extrapolation to non-experienced individuals.

Finally, although previous reviews suggest that both acute AYA administration in the experimental setting and the long-term ritual consumption of the brew are relatively safe, one of these reviews was published eight years ago (Gable, 2007), one is a narrative overview (Bouso and Riba, 2011), another made a succinct description of long-term studies (Dos Santos, 2013a), and the most recent review did not discuss neuroimaging studies (Barbosa et al., 2012). Thus, considering the above reasons, the increasing number of studies reporting anxiolytic, antidepressive, and antiaddictive properties of AYA (Dos Santos et al., 2016; Labate and Cavnar, 2014), and the apparent increase of AYA consumption (Cakic et al., 2010; Labate et al., 2009), the objective of this article was to extend previous reviews by conducting a systematic literature search of human studies assessing the acute, subacute, and long-term effects of AYA on psychiatric symptoms, neuropsychological functioning and neuroimaging.

Method

Data for this systematic review were collected in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009).

Data acquisition

We attempted to identify all human studies available to review up to 16 December 2015 in which the effects of AYA on psychiatric symptoms, neuropsychological functioning, and neuroimaging were analyzed.

Search strategy

Electronic searches were performed using PubMed (1 January 1966–16 December 2015), LILACS (1 January 1982–16 December 2015) and SciELO (1 January 1998–16 December 2015) databases. The following keywords were used: *ayahuasca* AND *subjective effects* OR *psychological effects* OR *psychiatry* OR *psychiatric symptoms* OR *psychiatric disorders* OR *psychopathology* OR *cognition* OR *neuropsychology* OR *neuropsychological tests* OR *neuropsychological performance* OR *neuroimaging* OR *single-photon emission computed tomography* OR *SPECT* OR *functional magnetic resonance imaging* OR *fMRI*. References were retrieved through searching electronic databases and manual searches through reference lists of identified literature. All the studies published up to 16 December 2015 in English were included.

Eligibility criteria

The following inclusion and exclusion criteria were established prior to the literature search.

Article type. For purposes of this review, only experimental studies in healthy volunteers, observational studies of experienced AYA consumers, and clinical trials published in peer-reviewed journals were included. Animal studies, review papers, qualitative studies, case reports, opinion pieces or comments, letters or editorials, conference abstracts or posters, books or book chapters, and published abstracts were excluded.

Study design. The review included (a) experimental studies of AYA administration to healthy volunteers that assessed neuroimaging and psychiatric symptoms and neuropsychological functioning with validated scales; (b) observational studies of AYA consumers that assessed neuroimaging and psychiatric symptoms and neuropsychological functioning with validated scales; and (c) clinical trials involving patients with a diagnosis based on a structured diagnostic interview (using the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM (American Psychiatric Association, 2000 and early versions))).

Participants/sample. Healthy volunteers (including AYA consumers) and patients with a diagnosis based on a structured diagnostic interview (using the DSM criteria) were included.

Interventions. All designs evaluating the effects of AYA on psychiatric symptoms, neuropsychological functioning and neuroimaging were included.

Comparisons. The main comparators considered, when available, were placebo (experimental studies and clinical trials) and a control group or normative data (observational studies).

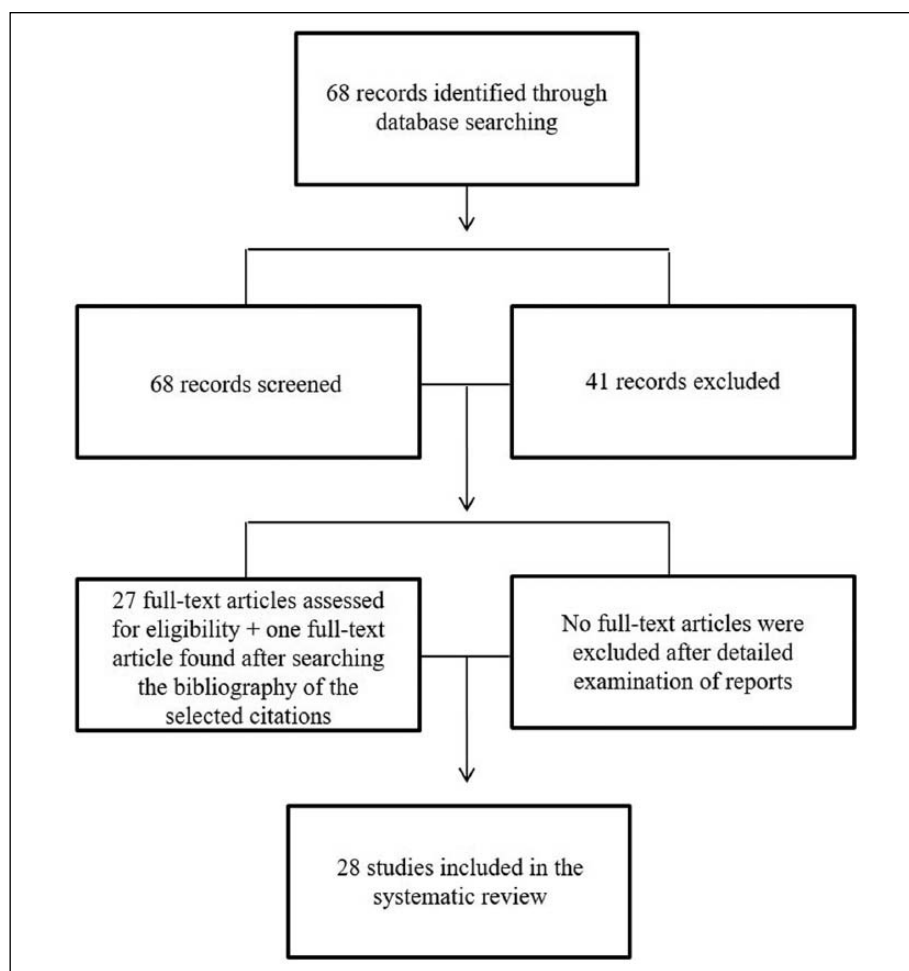


Figure 1. Flow diagram illustrating the different phases of the systematic review.

Outcomes. Studies investigating the effects of AYA on psychiatric symptoms, neuropsychological functioning and neuroimaging were included.

Data extraction

All studies were screened by two independent reviewers with discrepancies resolved by a third reviewer. From the articles included we recorded names of authors, year of publication, study design (experimental, observational, clinical trial), characteristics of the participants (healthy, patient, sample size), and type of outcome measure (scales, neuropsychological tests, neuroimaging parameters). The sample was divided into (a) psychiatric symptoms, (b) neuropsychological functioning, and (c) neuroimaging to allow better clarification and interpretation of results. Furthermore, the sample was also subdivided in studies assessing acute, subacute, and long-term effects.

Results

Study selection

A flow diagram illustrating the different phases of the systematic review is presented in Figure 1

The search of the literature yielded 68 separate references that were reviewed for abstract screening (first pass). Following the first pass of the citations, 27 potentially relevant references were identified. Full-text reports of these citations were obtained for more detailed evaluation. Following detailed examination of the reports, all 27 citations were included (Alonso et al., 2015; Barbosa et al., 2005, 2009; Bouso et al., 2012, 2013, 2015; Da Silveira et al., 2005; De Araujo et al., 2012; Doering-Silveira et al., 2005a; Dos Santos et al., 2007, 2011, 2012; Fábregas et al., 2010; Frecska et al., 2012; Grob et al., 1996; Halpern et al., 2008; Osório et al., 2015; Palhano-Fontes et al., 2015; Riba et al., 2001, 2002a, 2002b, 2003, 2004, 2006; Sanches et al., 2016; Soler et al. 2015; Thomas et al., 2013). Another reference was included after searching the bibliography of the selected citations (Schenberg et al., 2015). Thus, 28 citations were included in the systematic review.

The studies included comprised 25 studies that assessed subjective/psychological effects or psychiatric symptoms (Alonso et al., 2015; Barbosa et al., 2005, 2009; Bouso et al., 2012, 2015; Da Silveira et al., 2005; De Araujo et al., 2012; Dos Santos et al., 2007, 2011, 2012; Fábregas et al., 2010; Frecska et al., 2012; Grob et al., 1996; Halpern et al., 2008; Osório et al., 2015; Riba et al., 2001, 2002a, 2002b, 2003, 2004, 2006; Sanches et al., 2016; Schenberg et al., 2015; Soler et al. 2015; Thomas et al.,

2013), five that evaluated neuropsychological functioning (Bouso et al., 2012, 2013, 2015; Doering-Silveira et al., 2005a; Grob et al., 1996), and five that employed neuroimaging techniques (Bouso et al., 2015; De Araujo et al., 2012; Palhano-Fontes et al., 2015; Riba et al., 2006; Sanches et al., 2016). The main information of each citation is presented in Table 1.

Despite the small number of studies and small sample sizes in most of them, high degree of heterogeneity, and lack of placebo and control groups in many of the selected citations, the reported results consistently show that acute administration of AYA to healthy volunteers in experimental settings, or to patients with depression or substance dependence in a controlled environment, appears to be safe. Likewise, the results also suggest that the subacute effects of AYA in ritual and controlled contexts, as well as long-term consumption of AYA in ritual contexts, are not associated with psychopathologies or neuropsychological deficits.

Regarding therapeutic potentials, although the described results are promising, we cannot conclude that the observed changes were in fact caused by AYA since treatment was not randomized or double-blind and there was no placebo or other comparator group. These findings will be further discussed in detail below.

Psychiatric symptoms/status: personality, psychopathology and other psychological measures

Acute effects. Grob and co-workers (1996) assessed the subjective effects of a 2 mL/kg oral AYA dose (0.24 mg DMT/mL) within one hour following the close of an AYA ritual in 15 long-term members of the UDV (membership in the UDV for at least 10 years). Subjective effects were measured with the Hallucinogen Rating Scale (HRS). The HRS includes six subscales: somesthesia (somatic effects), affect (emotional responses), volition (capacity to interact with his/her “self” and/or the environment), cognition (modifications in thought processes or content), perception (perceptual effects), and intensity (strength of the experience). Grob et al. reported that scores on all subscales were in the mild end of the spectrum and were comparable to a 0.1–0.2 mg/kg intravenous (i.v.) DMT dose, while somesthesia scores were below the lowest DMT dose measured by the scale (0.05 mg/kg).

The effects and tolerability of AYA were measured in six healthy volunteers in a single-blind placebo-controlled clinical study that included administration of three increasing doses of encapsulated freeze-dried AYA (0.5, 0.75, and 1 mg DMT/kg) (Riba et al., 2001). AYA produced significant dose-dependent increases in five of the six HRS subscales (except “volition”) and in the morphine-benzedrine (measuring euphoria), lysergic acid diethylamide (LSD) scale (measuring somatic-dysphoric effects), and amphetamine (A; measuring stimulation) scales of the Addiction Research Center Inventory (ARCI). These findings were subsequently corroborated in a non-controlled study (Schenberg et al., 2015) and in several double-blind crossover placebo-controlled studies (Dos Santos et al., 2011, 2012; Riba et al., 2002a, 2002b, 2004, 2006). No clear-cut tolerance or sensitization was observed for AYA subjective effects after administration of two consecutive oral doses of 0.75 mg DMT/kg 4 h apart (Dos Santos et al., 2012).

A double-blind study with nine members of the *Santo Daime* showed that AYA administration (oral dose of 50 mL; DMT and β -carbolines were detected but not quantified) was associated with significant reduction in hopelessness and panic symptoms as measured by the Beck Hopelessness Scale (BHS) and the Anxiety Sensitivity Index – Revised (ASI-R), respectively (Dos Santos et al., 2007). De Araujo et al. (2012) assessed the acute effects of AYA in nine frequent AYA users in an open-label neuroimaging study and reported that all subjects experienced transient increases in psychotic and mania symptoms following AYA ingestion, according to the Brief Psychiatric Ratings Scale (BPRS) and the Young Mania Rating Scale (YMRS), respectively.

Alonso et al. (2015) assessed the subjective acute effects of a single dose of encapsulated freeze-dried AYA (0.75 mg DMT/kg) in 10 healthy volunteers in a double-blind, randomized, crossover study. Acute AYA administration was associated with significant increases in the visionary restructuring (Visionäre Umstrukturierung (VUS)) subscale of the Altered States of Consciousness Questionnaire (Aussergewöhnliche Psychische Zustände (APZ)), which measures illusions, hallucinations, and synesthesia.

Subacute effects. Barbosa and collaborators (2005) investigated the short-term psychological and psychiatric after-effects induced by the first time use of AYA in 28 subjects that participated in the rituals of the UDV and *Santo Daime*. They assessed psychiatric symptoms with the Clinical Interview Schedule-Revised Edition (CIS-R) one to four days before AYA intake and one to two weeks afterwards. AYA ingestion was associated with a significant reduction in the intensity of minor psychiatric symptoms in the week after the ayahuasca experience.

A naturalistic study assessed visual creativity in 40 individuals participating in AYA rituals in Brazil using the visual components of the Torrance Tests of Creative Thinking (Freckska et al., 2012). The test was completed before and on the second day after the end of a series of AYA ceremonies, which involved AYA ingestion on every second or third day within a two-week timeframe (total of 4–5 times). A control group of 21 subjects who did not participate in recent psychedelic drug use completed the test twice, two weeks apart. AYA administration was associated with significant increases in the number of highly original solutions, suggesting increased visual creativity. However, since the number of AYA users is twice that of control subjects, the statistical significance of these results should be interpreted with caution.

In a non-controlled study, Soler et al. (2015) used the Five Facets Mindfulness Questionnaire (FFMQ), the Experiences Questionnaire (EQ), and the MINDSENS Composite Index to measure mindfulness-related capacities in a group of 25 individuals (14 females) with prior experience with AYA, before and 24 h after an AYA intake. Twenty-three participants had consumed AYA on average 79 times (range 1–500), and two were ingesting it for the first time. During the session, participants ingested on average 43.6 mg DMT (range 28.82–69.81). AYA intake was associated with significant increases in the MINDSENS composite index, in two subscales of the FFMQ (Non-judging the inner experience, and Non-reacting to the inner experience), and in the EQ. Overall, these results suggest a non-judgmental approach towards the present experience, thoughts, and emotions. Moreover, scores were in the range of those observed after extensive mindfulness practice.

Table 1. Main results of the citations included in the systematic review.

Sample	Study design/drug	Significant results	References
Subjective/psychological effects or psychiatric symptoms (acute)			
15 Long-term (≥ 10 years) UDV members	Open-label, no placebo or control group Oral dose of AYA (0.48 mg DMT/kg)	Increases in all HRS subscales (<i>somaesthesia, affect, volition, cognition, perception, and intensity</i>)	Grob et al., 1996
6 Healthy volunteers	Single-blind, placebo-controlled 3 Oral doses of encapsulated freeze-dried AYA (0.5, 0.75, and 1 mg DMT/kg)	Dose-dependent increases in all HRS subscales (except <i>volition</i>) and in the <i>morphine-benzedrine, LSD, and amphetamine</i> scales of the ARCI	Riba et al., 2001 ^a
18 Healthy volunteers	Double-blind, cross-over, placebo-controlled 2 Oral doses of encapsulated freeze-dried AYA (0.6 and 0.85 mg DMT/kg)	Dose-dependent increases in all HRS subscales (except <i>volition</i>)	Riba et al., 2002 ^a
18 Healthy volunteers	Double-blind, cross-over, placebo-controlled 2 Oral doses of encapsulated freeze-dried AYA (0.6 and 0.85 mg DMT/kg)	Dose-dependent increases in all HRS (except <i>volition</i>) and APZ subscales (<i>oceanic boundlessness, dread of ego dissolution, and visionary restructuring</i>)	Riba et al., 2002 ^b
18 Healthy volunteers	Double-blind, cross-over, placebo-controlled 2 oral doses of encapsulated freeze-dried AYA (0.6 and 0.85 mg DMT/kg)	Dose-dependent increases in all HRS subscales (except <i>volition</i>) and in the <i>morphine-benzedrine, LSD, and amphetamine</i> scales of the ARCI	Riba et al., 2003 ^a
18 Healthy volunteers	Double-blind, cross-over, placebo-controlled Oral dose of encapsulated freeze-dried AYA (0.85 mg DMT/kg)	Increases in all HRS subscales	Riba et al., 2004 ^a
15 Healthy volunteers	Double-blind, cross-over, placebo-controlled Oral dose of encapsulated freeze-dried AYA (1 mg DMT/kg)	Increases in all HRS subscales and in the <i>morphine-benzedrine, LSD, and amphetamine</i> scales of the ARCI	Riba et al., 2006
9 Long-term (≥ 10 years) STD members	Double-blind, cross-over, placebo-controlled Oral dose of AYA (DMT and β -carbolines detected but not quantified)	Lower scores in ASI-R and BHS scales	Dos Santos et al., 2007
10 Healthy volunteers	Double-blind, cross-over, placebo-controlled Oral dose of encapsulated freeze-dried AYA (1 mg DMT/kg)	Increases in all HRS subscales and in the <i>morphine-benzedrine, LSD, and amphetamine</i> scales of the ARCI	Dos Santos et al., 2011
10 Experienced AYA users (duration of AYA use was not informed)	Open-label, no placebo or control group Oral dose of AYA (1.76 mg DMT/kg)	Increases in the BPRS and YMRS scales	De Araujo et al., 2012 ^b
9 Healthy volunteers	Double-blind, cross-over, placebo-controlled 2 Consecutive doses of encapsulated freeze-dried AYA (0.75 mg DMT/kg)	Increases in all HRS subscales and in the <i>morphine-benzedrine, LSD, and amphetamine</i> scales of the ARCI	Dos Santos et al., 2012
10 Healthy volunteers	Double-blind, cross-over, placebo-controlled Oral dose of encapsulated freeze-dried AYA (0.75 mg DMT/kg)	Increases in all HRS subscales and in the <i>visionary restructuring</i> scale of the APZ	Alonso et al., 2015
20 Experienced AYA users (mean number of occasions 96.7 (SD 135.2, range 5–500))	Open-label, no placebo or control group Oral dose of AYA (1.39 mg DMT/kg)	Increases in all HRS subscales (only mean $\pm$ SD was reported, no statistical analysis performed)	Schenberg et al., 2015
Subjective/psychological effects or psychiatric symptoms (subacute)			
28 Volunteers participating in STD/UDV rituals for the first time	Observational, no placebo or control group Assessments 1–4 days before AYA intake and 1–2 weeks afterwards Unknown AYA/DMT dose	Improvements in the CIS-R scale a week following AYA intake	Barbosa et al., 2005 ^c
40 Healthy volunteers	Observational, no placebo Assessments before and 2 days after a series of AYA ceremonies (AYA ingestion on every second/third day within a 2-week timeframe; total of 4–5 times) Control group of 21 subjects who did not participate in recent psychedelic drug use assessed twice, 2 weeks apart Unknown AYA/DMT dose	Increases in the number of highly original solutions (TTCT)	Frecska et al., 2012

(Continued)

Table 1. (Continued)

Sample	Study design/drug	Significant results	References
25 Experienced AYA users (23 participants had consumed AYA on average 79 times (range 1–500), and 2 were ingesting it for the first time)	Open-label, no placebo or control group Assessments before and 24 h after AYA intake Oral dose of AYA (average 43.6 mg DMT, range 28.82–69.81)	Increases in the MINDSENS Composite Index, in the <i>non-judging the inner experience</i> and <i>non-reacting to the inner experience</i> subscales of the FFMQ, and in the EQ	Soler et al., 2015
6 Volunteers with MDD	Open-label, no placebo or control group Assessments before and 7, 14 and 21 days after AYA intake Oral dose of AYA (1.76 mg DMT/kg)	Reductions in the HAM-D and MADRS scales and in the <i>Anxious-Depression</i> subscale of the BPRS between baseline and 1, 7 and 21 days after AYA intake	Osório et al., 2015 ^d
17 Volunteers with MDD	Open-label, no placebo or control group Assessments before and 7, 14 and 21 days after AYA intake Oral dose of AYA (1.76 mg DMT/kg)	Reductions in the HAM-D and MADRS scales; increases in the CADSS scale, and reductions in the <i>Anxious-Depression</i> , <i>Thinking Disorder</i> and <i>Withdrawal-Retardation</i> subscales of the BPRS between baseline and 1, 7 and 21 days after AYA intake	Sanchez et al., 2016 ^d
Subjective/psychological effects or psychiatric symptoms (long-term)			
15 Long-term (≥ 10 years) UDV members compared with 15 matched controls with no prior history of AYA use	Observational, inclusion of a control group	UDV group: past psychiatric diagnoses (ICD-10, DSM-III-R) of drug abuse ($n=5$), major depression ($n=2$), and phobic anxiety ($n=3$), but all remitted after starting participation in UDV rituals (absence of current psychiatric diagnosis (CIDI)), and lower scores on the <i>Novelty Seeking</i> and <i>Harm Avoidance</i> temperament dimensions of the TPQ UDV adolescents were overall comparable to controls in terms of psychopathological profile (SRQ, CES-D, BAI, STAI, DUST, CASRS, BSQ)	Grob et al., 1996
40 Long-term (4.05 $\pm$ 2.28 years) UDV adolescent members compared with 40 matched controls with no prior history of AYA use	Observational, inclusion of a control group		Da Silveira et al., 2005 ^e
32 Long-term (lifetime 269 $\pm$ 314.7 ceremonies; range 20–1300) STD members	Observational, no control group	Absence of psychological (SCID, SCID-II, HAM-A, SCL-90-R, UHSCF, WURS) and physical (neurology-focused physical exam) problems, and lower SCL-90-R scores compared with the normative scores for the general population	Halpern et al., 2008
Six-month follow-up of 23 subjects (out of 28) from the study by Barbosa et al. (2005)	Observational, no control group, inclusion of follow-up	Lower scores in the <i>Harm Avoidance</i> and <i>Reward Dependence</i> temperament dimensions of the TCI and reduction in minor psychiatric symptoms (CIS-R, SF-26)	Barbosa et al., 2009 ^e
Jungle- ($n=56$) and urban-based ($n=71$) long-term (≥ 15 years) STD/BRQ members compared with rural ($n=56$) and urban ($n=59$) matched controls with no prior history of AYA use, including a 1-year follow-up	Observational, inclusion of a control group and follow-up	AYA users showed lower scores on the <i>Alcohol Use</i> and <i>Psychiatric Status</i> subscales of the ASI, and while the jungle-based AYA users showed significant previous illicit drug use, this was not observed at the time of the assessment (except for cannabis); abstinence from illicit drug use was maintained in both AYA groups a year later (except for cannabis), but differences on ASI scores were still significant only for the jungle-based group. A time-dependent worsening was observed only in the <i>Family/Social Relationships</i> ASI subscale among the urban AYA users	Fábregas et al., 2010 ^f

Table 1. (Continued)

Sample	Study design/drug	Significant results	References
Jungle- ($n=56$) and urban-based ($n=71$) long-term (≥ 15 years) STD/BRQ members compared with rural ($n=56$) and urban ($n=59$) matched controls with no prior history of AYA use, including a 1-year follow-up	Observational, inclusion of a control group and follow-up	AYA users showed higher scores in the <i>Reward Dependence</i> and <i>Self-Transcendence</i> temperament dimensions of the TCI, and lower scores in the <i>Harm Avoidance</i> and <i>Self-Directedness</i> dimensions: AYA users also showed higher scores in the SOI, PLT, and BIEPS, and lower scores on the SCL-90-R; overall differences with controls were maintained one year later	Bouso et al., 2012 ^f
12 Participants with a problematic substance use pattern	Observational, no placebo or control group Assessments before and 6 months after a retreat including 4 days of group counseling and 2 AYA ceremonies Unknown AYA/DMT dose	Improvements in the HS, ES and PHLMS scales and in the <i>meaning</i> and <i>outlook</i> subscales of the MQL survey, and decreases in the 4WSUS for cocaine	Thomas et al., 2013
22 Long-term (average 5.3 years, range 2–13) STD members compared with 22 matched controls with no prior history of AYA use	Observational, inclusion of a control group	Absence of psychopathology (SCL-90-R) in AYA users, which showed higher scores in the <i>Self-Transcendence</i> temperament dimension of the TCI, and lower scores in the <i>Harm Avoidance</i> and <i>Anticipatory Worry</i> dimensions	Bouso et al., 2015
Neuropsychological functioning (acute) 11 Long-term (average 179 occasions, range 70–352) and 13 occasional (average 33 occasions, range 8–60) AYA users	Open-label, no placebo or control group Oral dose of AYA (DMT and β -carbolines detected but not quantified)	Lower scores in the Sternberg test and a reduction in the response latency time during the Stroop test for both groups, while only occasional users showed increased execution and resolution times and number of movements in the Tower of London test, which was inversely correlated with lifetime AYA use	Bouso et al., 2013
Neuropsychological functioning (long-term) 15 Long-term (≥ 10 years) UDV members compared with 15 matched controls with no prior history of AYA use 40 Long-term (4.05 ± 2.28 years) UDV adolescent members compared with 40 matched controls with no prior history of AYA use	Observational, inclusion of a control group Unknown AYA/DMT dose Observational, inclusion of a control group	No evidence of cognitive deterioration among UDV members, and AYA users performed better than controls on the number of words recalled (WHO/UCLA AVLT) Overall, no significant difference in performance between AYA users and controls (Trailmaking test, Stroop test, ROCF, CPT-II, WHO/UCLA AVLT, WAIS-III), but lower scores in the WHO/UCLA AVLT were reported for the AYA group, although mean scores did not significantly differ from adolescent normative data	Grob et al., 1996 Doering-Silveira et al., 2005a ^e
Jungle- ($n=56$) and urban-based ($n=71$) long-term (≥ 15 years) STD/BRQ members compared with rural ($n=56$) and urban ($n=59$) matched controls with no prior history of AYA use, including a 1-year follow-up	Observational, inclusion of a control group and follow-up	No evidence of neuropsychological impairment in the AYA group (Stroop test, WCST, LNS, FrSBe), and AYA users scored better than controls on almost all measures, with most of these differences maintained one year later	Bouso et al., 2012 ^f
22 Long-term (average 5.3 years, range 2–13) STD members compared with 22 matched controls with no prior history of AYA use	Observational, inclusion of a control group	AYA users scored better than controls (two-back test, switching test)	Bouso et al., 2015

(Continued)

Table 1. (Continued)

Sample	Study design/drug	Significant results	References
Neuroimaging (acute)			
15 Healthy volunteers	Double-blind, cross-over, placebo-controlled Oral dose of encapsulated freeze-dried AYA (1 mg DMT/kg) SPECT	Bilateral activation of the anterior insula/inferior frontal gyrus, activation of the anterior cingulate/medial frontal gyrus of the right hemisphere and of the amygdala/parahippocampal gyrus in the left hemisphere During an imagery task, activation in the primary visual area was comparable to the activation levels of a natural image with the eyes open, and AYA administration was also associated with activation of the cuneus and lingual gyrus and parahippocampal, retrosplenial, and frontopolar cortices, and with altered fronto-occipital connectivity Decreased activation of key hubs of the DMN (posterior cingulate cortex/precuneus and medial prefrontal cortex) and decreased functional connectivity within the posterior cingulate cortex/precuneus Increased blood perfusion in the left nucleus accumbens, right insula and left subgenual area	Riba et al., 2006
10 Experienced AYA users (duration of AYA use was not informed)	Open-label, no placebo or control group Oral dose of AYA (1.76 mg DMT/kg) fMRI		De Araujo et al., 2012 ^b
10 Experienced AYA users (duration of AYA use was not informed)	Open-label, no placebo or control group Oral dose of AYA (1.76 mg DMT/kg) fMRI		Palhano-Fontes et al., 2015 ^a
17 Volunteers with MDD	Open-label, no placebo or control group Assessments before and 7, 14 and 21 days after AYA intake Oral dose of AYA (1.76 mg DMT/kg) SPECT		Sanches et al., 2016 ^d
Neuroimaging (long-term)			
22 Long-term (average 5.3 years, range 2–13) STD members compared with 22 matched controls with no prior history of AYA use	Observational, inclusion of a control group	Regular AYA use was associated with cortical thinning in mesiotemporal and inferior frontal gyri, precuneus, superior frontal gyrus, posterior cingulate cortex and superior occipital gyrus, while increased thickening was observed in precentral gyrus and anterior cingulate cortex	Bouso et al., 2015

ARCI: Addiction Research Center Inventory; ASI-R: Anxiety Sensitivity Index – Revised; AVA: ayahuasca; BAI: Beck Anxiety Inventory; BHS: Beck Hopelessness Scale; BIEPS: Psychosocial Well-Being Test; BPRS: Brief Psychiatric Ratings Scale; BRQ: *Barquinha*; BSQ: Body Shape Questionnaire; CASRS: Comer's Adolescent Self-Rating Subscale; CES-D: Center for Epidemiological Studies Depression Scale; CIDI: Composite International Diagnostic Interview; CIS-R: Clinical Interview Schedule – Revised Edition; CPT-II: Conner's Continuous Performance Test-II; DMN: default mode network; DMT: dimethyltryptamine; DSM-III-R: *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised*; DUST: Drug Use Screening Inventory; EQ: Experiences Questionnaire; ES: Empowerment Scale; FFMQ: Five Facets Mindfulness Questionnaire; fMRI: functional magnetic resonance imaging; F5Be: Frontal Systems Behaviour Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; HS: Hope Scale; HRS: Hallucination Rating Scale; ICD-10: *International Classification of Diseases, Revision 10*; LNS: Letter-Number Sequencing task from the WAIS-III; LSD: lysergic acid diethylamide; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; MQL: McGill Quality of Life Survey; PHLMS: Philadelphia Mindfulness Scale; PLT: Purpose in Life Test; ROCI: Rey-Osterrieth complex figure Test; SCID: Structured Clinical Interview for DSM-IV Disorders; SCID-II: Structured Clinical Interview for DSM-IV Axis II Personality Disorders; SCL-90-R: Symptom Check List 90 Revised; SD: standard deviation; SF-26: Short Form-36 Health Survey; SOI: Spiritual Orientation Inventory; SPECT: single photon emission computed tomography; SRQ: Self Report Questionnaire; STAI: State-Trait Anxiety Inventory; STD: *Santo Daime*; TCI: Temperament and Character Inventory; TPQ: Tridimensional Personality Questionnaire; UDV: *União do Vegetal*; UHSCF: Uplifts, Hassles, Stresses, and Cognitive Failures Questionnaire; WAIS-III: Wechsler Adult Intelligence Scale-III; WCST: Wisconsin Card Sorting Test; WHO/UCLA AVLT: World Health Organization/University of California at Los Angeles Auditory Verbal Learning Test; WURS: Wender Utah Rating Scale; YMRs: Young Mania Rating Scale; 4WSUS: 4 Week Substance Use Scale; APZ: Altered States of Consciousness Questionnaire. See text for details and description of scales and subscales.

^aThese citations report data from the same group of volunteers. Riba et al. (2001) is the pilot study, and the other references report data from the final sample of participants.

^bThese citations report data from the same group of volunteers.

^cThese citations report data from the same group of volunteers. Barbosa et al. (2009) is the follow-up study of Barbosa et al. (2005).

^dThese citations report data from the same group of volunteers. Osório et al. (2015) is the pilot study, and Sanches et al. (2016) report data from the final sample of participants.

^eThese citations report data from the same group of volunteers.

^fThese citations report data from the same group of volunteers.

A recent open-label study performed by our group has shown rapid and sustained antidepressant and anxiolytic effects associated with administration of a single 2.2 mL/kg oral AYA dose (0.8 mg DMT/mL) to six volunteers with a current depressive episode (Osório et al., 2015). AYA administration was associated with statistically significant reductions of up to 82% in depressive scores between baseline and 1, 7, 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 BPRS.

A subsequent study by our group with a bigger sample ($n=17$, including the six volunteers of the pilot study) showed that AYA administration increased psychoactivity (Clinician Administered Dissociative States Scale (CADSS)) and was associated with significant score decreases in the HAM-D, MADRS, and BPRS from 80 min to day 21 (Sanches et al., 2016). In both studies AYA was well tolerated by all patients and vomiting was the only adverse effect recorded, being reported by 47–50% of the volunteers. However, patients did not consider this emetic effect as causing severe discomfort.

Long-term effects. Grob and collaborators (1996) evaluated 15 long-term users of ayahuasca – members of the UDV – in comparison to 15 matched controls with no prior history of AYA ingestion regarding long-term psychological and psychiatric health. According to the Composite International Diagnostic Interview (CIDI), none of the UDV subjects had a current psychiatric diagnosis. However, before membership in the UDV, some of the participants had past psychiatric diagnoses – according to *International Classification of Diseases, Revision 10* (ICD-10) and *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised* (DSM-III-R) criteria – of drug abuse ($n=5$), major depression ($n=2$), and phobic anxiety ($n=3$). All of these psychiatric diagnoses remitted after starting participation in UDV rituals. Moreover, UDV members scored lower on the Novelty Seeking and Harm Avoidance temperament dimensions of the Tridimensional Personality Questionnaire (TPQ), suggesting reduced impulsivity and shyness, respectively. The results also suggested that UDV subjects were more reflective, confident, gregarious, and optimistic compared to the control group. However, considering the small sample size, these results should be interpreted with caution.

Da Silva et al. (2005) evaluated the mental health of 40 adolescents from three different cities in Brazil that had consumed AYA within the UDV context at least 24 times during the last two years prior to the assessment. The study compared the mental status of these adolescents with a control group ($n=40$) that had never used AYA and that was matched regarding sex, age, and education. Mental status was assessed by means of the Self Report Questionnaire (SRQ; measuring overall psychic condition), the Center for Epidemiological Studies Depression Scale (CES-D; measuring depression), the Beck Anxiety Inventory (BAI; measuring anxiety), the State-Trait Anxiety Inventory (STAI; measuring anxiety), the Drug Use Screening Inventory (DUSI; measuring drug misuse), the Conner's Adolescent Self-Rating subscale (measuring attention deficit disorder), and the Body Shape Questionnaire (BSQ; measuring self-image related disorders). The study reported that adolescents drinking AYA were overall comparable to controls in terms of psychopathological profile. Moreover, the AYA group showed considerable

(although non-significant) lower frequencies of anxiety symptoms, body image dysmorphia, and attentional problems.

Halpern et al. (2008) evaluated 32 North American members of the *Santo Daime*, using a neurology-focused physical exam and psychological test scores (Structured Clinical Interview for DSM-IV Disorders (SCID), Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II), 14-item Hamilton Anxiety rating Scale (HAM-A), 21-item Hamilton Depression rating Scale (HAM-D), Symptom Check List 90 Revised (SCL-90-R), Uplifts, Hassles, Stresses, and Cognitive Failures questionnaire (UHSCF), and Wender Utah Rating Scale (WURS)). Results showed that 19 subjects met lifetime (past or present) criteria for a psychiatric disorder, with six in partial remission, 13 in full remission, and eight reporting induction of remission through church participation: one subject still met criteria for panic disorder and another for bipolar I disorder; five for a single major depressive episode that predated church membership; six for recurrent major depressive disorders with four in remission and two in partial remission; four for simple phobia with two in remission and two in partial remission; three of bulimia nervosa in remission; six for post-traumatic stress disorder or panic disorder, all in full remission; and 24 for drug or alcohol abuse or dependence with 22 in full remission, where all five with prior alcohol dependence and one with a history of alcohol abuse described church participation as the turning point in their recovery. According to the majority of the symptom dimensions of the SCL90R, participants presented lower rates of symptomatology, overall complaints, and intensity and severity of complaints compared with the normative scores for the general population – but there was no control group. Participants considered that side-effects (nausea, vomiting, bad taste, exhaustion) were transient, manageable, and rarely persisted beyond a day or two.

Barbosa and collaborators (2009) conducted a six-month follow-up study with 23 subjects from their original sample (Barbosa et al., 2005). They found that continuous AYA intake was significantly associated with lower scores in the Harm Avoidance and Reward Dependence temperament dimensions of the Temperament and Character Inventory – 125 items (TCI-125) compared to baseline scores, suggesting that AYA users were less dependent of social approval. Also, AYA was associated with a change in attitude towards more confidence, optimism and independence, decrease in physical pain, and reduction in minor psychiatric symptoms such as somatic symptoms, fatigue, difficulties in concentration, sleep problems, irritability, preoccupation with body functions, depression, depressive ideas, worry, anxiety, compulsions, obsessions and panic, according to the CIS-R and the Short Form-36 Health Survey (SF-26).

Fábregas et al. (2010) assessed the addiction potential of AYA in experienced members of AYA religions using the Addiction Severity Index (ASI). Jungle- ($n=56$) and urban-based ($n=71$) AYA users were compared with rural ($n=56$) and urban ($n=59$) controls, respectively, and a follow-up assessment was performed one year later. Jungle- and urban-based AYA users scored significantly lower than controls on the ASI Alcohol Use and Psychiatric Status subscales, and although the jungle-based AYA users showed significant previous illicit drug use, this was not observed at the time of the assessment (except for cannabis). Abstinence from illicit drug use was maintained in both AYA groups one year later (except for cannabis), but differences on ASI scores were

still significant only for the jungle-based group. A time-dependent worsening was observed only in the Family/Social Relationships ASI subscale among the urban AYA users.

In the same sample of regular AYA users ($n=127$) and controls ($n=115$), Bouso et al. (2012) assessed the impact of repeated AYA use on general psychological well-being and mental health by evaluating personality, psychopathology, and life attitudes at baseline and one year later. Regarding personality traits assessed with the TCI, AYA users showed higher scores in the Reward Dependence and Self-transcendence temperament dimensions, and lower scores in the Harm Avoidance and Self-directedness dimensions. Self-transcendence is a personality trait associated with religiousness, transpersonal feelings and spirituality, and AYA users also showed higher scores on the life attitudes scales Spiritual Orientation Inventory (SOI), Purpose in Life Test (PLT), and Psychosocial Well-being test (BIEPS). Moreover, AYA users scored significantly lower on all psychopathology measures assessed with the SCL-90-R. Overall differences with controls were maintained one year later.

Thomas et al. (2013) conducted a preliminary observational study of a retreat in a rural First Nations community in British Columbia, Canada, involving alternative treatments for problematic substance use and stress such as sweat lodges and AYA. The retreat included four days of group counseling and two AYA ceremonies, and data were collected pre-treatment and after six months for 12 participants with a problematic substance use pattern. Significant improvements were observed in scales measuring hopefulness (Hope Scale (HS)), empowerment (Empowerment Scale (ES)), mindfulness (Philadelphia Mindfulness Scale (PHLMS)), and quality of life “meaning” and “outlook” subscales (McGill Quality of Life survey (MQL)). Although scores of the Four Week Substance Use Scale (4WSUS) decreased for all substances (alcohol, tobacco, and cocaine) except cannabis and opioids during the study, significant reductions were observed only for cocaine.

Bouso et al. (2015) assessed personality (Temperament and Character Inventory-Revised (TCI-R)) and psychopathology (SCL-90-R) in the context of a neuroimaging study in a group of 22 Spanish members of the *Santo Daime* and 22 controls matched for age, sex, years of education, verbal IQ, and fluid IQ. AYA users scored significantly lower than controls in terms of Harm Avoidance, which was associated with lower scores in the Anticipatory Worry dimension. Furthermore, AYA users scored significantly higher than controls on Self-Transcendence, which was associated with higher scores in all subscales comprising this character dimension (Self-forgetfulness, Transpersonal Identification, and Spiritual Acceptance). Regarding the psychopathology assessment, no significant differences were found between groups.

Neuropsychological functioning

Acute effects. Bouso et al. (2013) conducted a study comparing the neuropsychological performance of occasional and long-term AYA users under the acute effects of the brew. Eleven experienced users and 13 occasional users were assessed in their habitual setting on working memory (Sternberg working memory task) and executive function (Stroop color and word test and Tower of London) following intake of a single AYA dose (oral dose of 100 mL; DMT and β -carbolines were detected but not

quantified). AYA ingestion was significantly associated with lower scores in the Sternberg test for both groups compared with baseline scores. However, under the influence of AYA both groups had a significant reduction in the response latency time during the Stroop test, which evaluates inhibitory control. This result suggests a certain performance improvement, since answer accuracy was not reduced. Interestingly, only occasional AYA users showed significantly increased execution and resolution times and number of movements in the Tower of London test, which evaluates strategic planning. Moreover, impaired performance in the Tower of London was inversely correlated with lifetime AYA use.

Long-term effects. In the study conducted by Grob and coworkers (1996) assessing the mental health of experienced members of the UDV, verbal learning and memory were measured with the World Health Organization/University of California at Los Angeles (WHO/UCLA) Auditory Verbal Learning Test. In this test, subjects are read a list of 15 items for five consecutive trials (I–V), each followed by a free recall test. These first trials are associated with learning and encoding abilities and strategies, and are followed by an interference trial (VI) of 15 items from another list and three subsequent memory trials (VII–IX) (Doering-Silveira et al., 2005a; Grob et al., 1996). There was no evidence of cognitive deterioration among UDV members. However, AYA users performed significantly better than controls on the number of words recalled on the 5th learning trial.

Doering-Silveira et al. (2005a) did a neuropsychological evaluation of the same group of 40 UDV and control adolescents assessed by Da Silveira et al. (2005). Neuropsychological functioning was evaluated by tests of attention, concentration, intelligence, language, memory, executive functioning, processing speed, visuomotor skills, and visuoconstructional abilities. The following tests were administered: Trailmaking test, Stroop-Victoria version, Rey–Osterrieth complex figure Test (ROCF), Conner’s Continuous Performance Test-II (CPT-II), WHO/UCLA Auditory Verbal Learning Test, and the following subtests of the Wechsler Adult Intelligence Scale–III (WAIS–III): Digit Span; Digit Symbol; Symbol Search; and Object Assembly. Overall, no significant difference in performance was observed between AYA users and controls. The only significant difference observed was the lower score of the AYA group in trials II and IV and on the total score of the initial trials (I–IV) of the WHO/UCLA Auditory Verbal Learning Test. However, mean raw scores of the initial trials (II and IV) of both groups did not significantly differ from adolescent normative data.

In the study with the sample of regular Brazilian AYA users, Bouso et al. (2012) also assessed the impact of repeated AYA use on neuropsychological functioning at baseline and one year later using the Stroop color and word test (assessing resistance to interference), the Wisconsin Card Sorting Test (WCST; measuring executive function), the Letter-Number Sequencing task (LNS) from the WAIS–III (assessing working memory), and the self-report instrument Frontal Systems Behaviour Scale (FrSB; measuring behaviors associated with frontal lobe damage). No evidence of neuropsychological impairment was found in the AYA group. Moreover, AYA users scored significantly better than controls groups on almost all measures, and most of these differences were maintained one year later.

In the study evaluating the Spanish sample of experienced AYA users, Bouso et al. (2015) also assessed neuropsychological function using the two-back test (assessing working memory), the WCST, and the switching task (assessing set-shifting). AYA users scored significantly better than controls in several variables. In the two-back test, with the exception of the percentage of false alarms and correct rejections, comparisons for all other variables were significant. In the task-switching test, the percentage of correct responses was significantly higher and the percentage of errors was lower for non-switch trials. No other significant differences were found. Moreover, no correlations were found between scores in neuropsychological tests and cortical thickness measures (see below).

Neuroimaging

Acute effects. Riba et al. (2006) used Single Photon Emission Computed Tomography (SPECT) to assess the acute effects of AYA in 15 volunteers who received a single oral dose of encapsulated freeze-dried ayahuasca (1.0 mg DMT/kg) and a placebo in a randomized double-blind clinical trial. AYA administration was associated with bilateral activation of the anterior insula/inferior frontal gyrus, with greater intensity in the right hemisphere, and increased blood perfusion in the frontomedial wall of the right hemisphere, especially in the anterior cingulate/medial frontal gyrus, areas associated with somatic awareness, subjective feeling states, and emotional arousal (Damásio, 2000). A smaller cluster was found in the ventral anterior cingulate/subcallosal gyrus. In the left hemisphere, AYA administration was associated with activation of the amygdala/parahippocampal gyrus, which is also involved in emotional arousal (Damásio, 2000). No significant activation of occipital areas involved in visual perception was observed. The absence of activation in this area is particularly intriguing, since subjects scored positively compared with placebo in the perception subscale of the HRS. There was no significant decrease of blood flow in any area.

A study using functional magnetic resonance imaging (fMRI) explored the neural basis of the visual imagery produced by AYA (De Araujo et al., 2012). Nine frequent AYA users participated in a study using an imagery task where each subject drank a single oral AYA dose (2.2 mL/kg, 0.8 mg DMT/mL). AYA administration was associated with increased activation in the precuneus, cuneus, lingual, fusiform, middle occipital, parahippocampal, posterior cingulate, superior temporal, superior middle, and inferior frontal gyri. In this study, after passively seeing images of people, animals, or trees with the eyes opened, subjects were asked to close their eyes and mentally generate the images they had just seen. After AYA administration, the activation in the primary visual area (Brodmann area 17) during the imagery task was comparable in magnitude to the activation levels of a natural image with the eyes open, and was specifically correlated with the occurrence of individual perceptual changes measured by psychiatric scales (BPRS and YMRS). During the imagery task, AYA administration was also associated with activation of non-primary areas of vision (cuneus and lingual gyrus, which are related to the peripheral visual field, typically activated during dreams, psychopathological hallucinations, and rapid eye movement (REM) sleep), and regions involved in episodic and working memory and in

the processing of contextual associations (parahippocampal cortex and the retrosplenial cortex), and in imagery (frontopolar cortex). Thus, activation of occipital, temporal, and frontal cortical areas by AYA may boost imagery to the same level of natural image, even with the eyes shut, lending a status of reality to inner experiences. Moreover, a connectivity analysis showed that AYA significantly altered fronto-occipital relationships by increasing the capacity of the primary visual cortex to lead other cortical areas during imagery. Therefore, these results suggest that an imbalance in the direction of information flow in these brain regions could be associated with psychotic symptoms or disorders in susceptible individuals.

In a subsequent study with the same group of volunteers, Palhano-Fontes et al. (2015) used fMRI to assess the acute effects of AYA on the activity of the default mode network (DMN), which has been associated with internal mentation, the sense of “self”, and states of mind-wandering and rest (Mason et al., 2007). Ten experienced AYA users ingested an oral AYA dose of 2.2 mL/kg (0.8 mg DMT/mL). AYA administration was associated with decreased activation of key hubs of the DMN, including the posterior cingulate cortex/precuneus and the medial prefrontal cortex. Moreover, AYA administration was also associated with decreased functional connectivity within the posterior cingulate cortex/precuneus. According to the authors, these results are consistent with the idea that the experiences with AYA require mental effort and concentration. In other words, as the authors point out, the internally-generated activity could be compared to a cognitive demand, when users are dealing with AYA effects. Another possible explanation is that AYA increases self-perception and introspection, which directs attention to mental states, similarly to what happens with meditation, which also decreases the DMN activation.

The single dose study performed by our group with 17 patients with recurrent depression (Sanches et al., 2016) used SPECT imaging to assess blood perfusion and showed that AYA administration was associated with significant increases in blood perfusion in the left nucleus accumbens, right insula and left subgenual area, brain regions implicated in the regulation of mood and emotions (Damásio, 2000; Vollenweider and Komater, 2010).

Long-term effects

Bouso et al. (2015) used MRI to investigate cortical thickness in 22 Spanish members of the *Santo Daime* and 22 controls matched for age, sex, years of education, verbal IQ, and fluid IQ. Regular AYA use was significantly associated with cortical thinning in mesotemporal and inferior frontal gyri, precuneus, superior frontal gyrus, posterior cingulate cortex, and superior occipital gyrus, while increased thickening was observed in precentral gyrus and anterior cingulate cortex. This study also found inverse correlations between cortical thickness values in the posterior cingulate cortex and age of onset and intensity of prior AYA use and scores on the Self-transcendence temperament dimension of the TCI-R, a personality trait measuring religiousness, transpersonal feelings and spirituality. As previously described, psychopathology was also assessed in this study using the SCL-90-R. No significant differences were found between AYA users and controls in all the SCL-90-R subscales, suggesting that the observed alterations in cortical thickness do not seem to be associated with psychiatric symptoms.

Discussion

The reviewed studies show that acute AYA administration to healthy volunteers in controlled settings produces significant subjective effects, peaking between 1.5 and 2 h and subsiding around 4 h later, involving perceptual modifications, enhanced introspection, intense emotional modifications, and increases in ratings of positive mood and activation (De Araujo et al., 2012; Dos Santos, 2013a; Dos Santos et al., 2011, 2012; Riba et al., 2001, 2003, 2006; Schenberg et al., 2015; Soler et al., 2015). These effects are similar to those described for other classic hallucinogens that act as 5-HT_{2A}-receptor agonists, such as mescaline (Hermle et al., 1992; Hollister and Sjöberg, 1964), psilocybin (Carhart-Harris et al., 2012a, 2012b; Hollister and Sjöberg, 1964; Komater et al., 2012; Kraehenmann et al., 2015; Studerus et al., 2011; Vollenweider et al., 1997), LSD (Hollister and Sjöberg, 1964; Schmid et al., 2015), and DMT (Strassman et al., 1994).

In the case of patients, AYA was administered only to volunteers with depression (Osório et al., 2015; Sanches et al., 2016) in two open-label trials and to patients with drug-related disorders in an observational study (Thomas et al., 2013). Acute AYA administration was associated with acute and subacute symptom improvement in all three studies, including fast-acting and enduring antidepressive effects (Osório et al., 2015; Sanches et al., 2016) and significant reductions in cocaine use (Thomas et al., 2013). Although participants reported positive and lasting changes from participating in these studies, these trials have several important limitations such as small sample sizes and absence of matched controls.

However, these preliminary data corroborate the results from non-controlled human studies reporting that regular AYA use is associated with remission of mood and anxiety disorders (Barbosa et al., 2009; Bouso et al., 2012; Da Silveira et al., 2005; Grob et al., 1996; Halpern et al., 2008) and drug abuse/dependence (Bouso et al., 2012; Fábregas et al., 2010; Fernández and Fábregas, 2014; Fernández et al., 2014; Grob et al., 1996; Halpern et al., 2008; Labate et al., 2014; Loizaga-Velder and Loizaga Pazzi, 2014; Loizaga-Velder and Verrer, 2014; Winkelman, 2014). These studies also corroborate the results from recent clinical trials describing antidepressive, anxiolytic, and antiaddictive effects of psilocybin (Bogenschutz et al., 2015; Grob et al., 2011; Johnson et al., 2014; Moreno et al., 2006) and LSD (Gasser et al., 2014). Moreover, Oliveira-Lima et al. (2015) showed that AYA inhibited and prevented the onset and recurrence of alcohol-related behaviors in mice.

Lieber and Prickett (2012) suggested four hypotheses to explain the mechanisms of AYA's action in the cases of successful treatment of drug-related disorders, including (a) the biochemical perspective (i.e. AYA could inhibit dopamine levels in the mesolimbic pathway and reduce activity in the reward center, therefore it could reduce the effects of addictive drugs in this circuit), (b) the physiological perspective (i.e. reduced dopamine levels could interfere with the synaptic plasticity associated with dependence), (c) the psychological perspective (i.e. by helping to resolve traumas and to understand the potential outcomes of choices and by improving decision-making, since it enhances insights into personal concerns), and (d) the transcendental perspective (i.e. by facilitating transcendent experiences in a model similar to psychedelic therapy with LSD).

It is necessary to emphasize that controlled trials have not been carried out to separate or distinguish these factors from each other and test them. Additionally, the subjective effects of AYA, as of other psychedelic substances, vary significantly among users. Thus, while AYA could be therapeutic to some people, it could be quite uncomfortable for others. However, animal studies with AYA and its alkaloids do show that these substances have antiaddictive (Aricioglu-Kartal et al., 2003; Brierley and Davidson, 2013; Glick et al., 1994; Liester and Prickett, 2012; Oliveira-Lima et al., 2015; Owaisat et al., 2012) and antidepressive (Fortunato et al., 2009, 2010; Pic-Taylor et al., 2015) potentials.

The neural correlates of the subjective and therapeutic effects of AYA and other hallucinogens such as psilocybin and LSD seem to involve agonism at 5-HT_{2A} receptors expressed in frontal and paralimbic brain areas implicated in emotional processing, interoception, memory, and the sense of "self" (Alonso et al., 2015; Carhart-Harris et al., 2012a, 2012b, 2014; De Araujo et al., 2012; Hermle et al., 1992; Komater et al., 2012; Kraehenmann et al., 2015; Palhano-Fontes et al., 2015; Riba et al., 2006, 2004, 2006; Sanches et al., 2016; Schenberg et al., 2015; Vollenweider and Komater, 2010; Vollenweider et al., 1997). For instance, acute psilocybin administration was associated with enhanced autobiographical recollection (Carhart-Harris et al., 2012b), increased positive mood and attenuated recognition of negative facial expression (Komater et al., 2012), and reduced amygdala reactivity, which was correlated with increases in positive mood (Kraehenmann et al., 2015). Moreover, increased DMN activity is associated with rumination, and both AYA (Palhano-Fontes et al., 2015) and psilocybin (Carhart-Harris et al., 2012a) reduce brain activity in key areas of the DMN, such as the posterior cingulate cortex. Furthermore, the fast-acting antidepressive effects of AYA were associated with increased blood perfusion in brain regions implicated in the regulation of mood and emotions, such as the left nucleus accumbens, right insula, and left subgenual area (Sanches et al., 2016).

Agonism at cortical 5-HT_{2A} receptors also seems to be involved in the cognitive effects induced by acute AYA intake, which was associated with impaired working memory (Bouso et al., 2013; Damásio, 2000), sustained attention (Bouso et al., 2013) and planning (Alonso et al., 2015), but also with improved inhibitory control (Damasio, 2000). Acute administration of psilocybin can induce several effects on cognitive processes including deficits in spatial working memory (Vollenweider et al., 1998; Wittmann et al., 2007), motion perception (Carter et al., 2004), visual-spatial attention (Carter et al., 2005a), context-dependent (Umbricht et al., 2003) and sensory information processing (Carter et al., 2005b), sustained attention (Hasler et al., 2004), and time perception and temporal control (Wittmann et al., 2007). Acute DMT administration may induce deficits in context-dependent (Heekeren et al., 2007) and sensory information processing (Heekeren et al., 2008) and in attentional processes (Daumann et al., 2008, 2010). Moreover, acute AYA intake may also produce deficits in context-dependent information processing (Frecka et al., 2004).

Long-term AYA use was associated with structural alterations in medial parts of the brain, such as increased cortical thickness in the anterior cingulate cortex and decreased cortical thickness in the posterior cingulate cortex (Bouso et al., 2015). Furthermore, greater exposure to AYA was associated with a higher degree of

thinning of the posterior cingulate cortex, and greater scores on the Self-transcendence temperament dimension of the TCI-R, a personality trait measuring religiousness, transpersonal feelings, and spirituality, were associated with increased thinning of the posterior cingulate cortex. However, despite these structural differences there was no evidence of increased psychopathology or worse neuropsychological functioning among AYA users. In fact, results even suggest cognitive enhancement and increased religiousness and spirituality (Bouso et al., 2012, 2013, 2015).

Previous studies in humans suggest that the anterior and posterior cingulate cortices are involved in the acute effects of AYA (De Araujo et al., 2012; Palhano-Fontes et al., 2015; Riba et al., 2004, 2006) and other hallucinogens (Carhart-Harris et al., 2012b; Muthukumaraswamy et al., 2013; Studerus et al., 2011). The posterior cingulate cortex has a prominent role in the DMN, involved in internal mentation, the sense of “self”, mind-wandering, remembering, imaging, and planning; the anterior cingulate cortex is involved in cognitive functions such as attention and executive control (Alonso et al., 2015; Bouso et al., 2015; Carhart-Harris et al., 2012a, 2012b, 2014; Palhano-Fontes et al., 2015). The structural alterations observed could be induced by activation of frontocortical glutamate networks secondary to 5-HT_{2A} receptor agonism, leading to enhanced expression of transcription (egr-1, egr-2) and neurotrophic (brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF)) factors involved in synaptic plasticity and also to increases in the size of dendritic spines on cortical neurons, thus enhancing neuroplasticity and neurogenesis (Baumeister et al., 2014; Bogenschutz and Johnson, 2016; Bogenschutz and Pommy, 2012; Moreno et al., 2013; Ross, 2012; Vollenweider and Kometer, 2010).

In line with this hypothesis, Fortunato et al., (2009, 2010) reported that acute and chronic administration of harmine to rats induced antidepressive-like behaviors in experimental models of depression and also increases in BDNF levels in the rat hippocampus. Moreover, a recent study reported that AYA administration to female Wistar rats was associated with antidepressive-like behaviors and increased neuronal activation in serotonergic brain areas (Pic-Taylor et al., 2015). Research with rats have also reported beneficial effects of *B. caapi* extracts and its alkaloids harmine and harmaline in preclinical models of Parkinson's disease, an effect that seem to depend on increased levels of serotonin and dopamine secondary to MAO-A inhibition (Samoylenko et al., 2010; Schwarz et al., 2003). However, it is important to note that animal studies should not be uncritically generalized to humans, since there are important differences in the action and metabolism of AYA alkaloids among different species (Dos Santos, 2013a), and distinct definitions of depression.

Thus, taken together, the above studies suggest that enhanced neuroplasticity and neurogenesis could be involved in the antidepressive, anxiolytic and antiaddictive effects of AYA and other hallucinogens (Baumeister et al., 2014; Bogenschutz and Johnson, 2016; Bogenschutz and Pommy, 2012; Dos Santos et al., 2016; Fortunato et al., 2009, 2010; Moreno et al., 2013; Ross, 2012; Vollenweider and Kometer, 2010). Indeed, Bouso et al. (2015) even speculated that the cognitive enhancement observed in regular AYA users (Bouso et al., 2012, 2013, 2015) could be explained by the greater cortical thickness observed in the anterior cingulate cortex, involved in attention and executive control.

Adverse events associated with AYA use

The above mentioned cognitive deficits resemble some of the symptoms of the acute phase of psychosis, and classic hallucinogens have been used as experimental models of psychosis (Carhart-Harris et al., 2013, 2014; Carter et al., 2004, 2005a, 2005b; Daumann et al., 2008, 2010; Frecska et al., 2004; Geyer and Vollenweider, 2008; González-Maeso and Seafon, 2009; Hasler et al., 2004; Heekeren et al., 2007, 2008; Hermle et al., 1992; Hollister and Sjöberg, 1964; Steeds et al., 2015; Umbricht et al., 2003; Vollenweider and Geyer, 2001; Vollenweider and Kometer, 2010; Vollenweider et al., 1997, 1998; Wittmann et al., 2007). Indeed, one of the major concerns associated with the ingestion of AYA and other hallucinogens is the possibility of suffering a prolonged psychotic reaction or disorder.

However, according to the reviewed studies there is no evidence that acute AYA administration in controlled settings is associated with prolonged psychotic reactions (Dos Santos, 2013a; Dos Santos et al., 2011, 2012; Osório et al., 2015; Riba et al., 2001, 2003; Sanches et al., 2016; Thomas et al., 2013). AYA was well tolerated by healthy volunteers and patients, producing few short-lived side-effects such as transient anxiety, nausea, and vomiting. No side-effects lasting beyond the acute effects of AYA were reported in the reviewed studies. With the exception of the significant emetic effects, which seem to be associated only with AYA, these results are in line with previous studies involving the administration of hallucinogenic compounds such as psilocybin and LSD to healthy volunteers and to patients with psychiatric disorders (Cohen, 1960; Cohen and Ditman, 1962; Frecska and Luna, 2006; Malleon, 1971; Smart and Bateman, 1967; Strassman, 1984; Studerus et al., 2011).

Furthermore, despite the fact that nearly 20,000 people worldwide are members of some of the Brazilian AYA religions (Labate and Araújo, 2004; Labate and Cavnar, 2014; Labate et al., 2009), we are aware of only a few case reports describing adverse psychiatric reactions to AYA (Dos Santos and Strassman, 2008; Gable, 2007; Lima and Tófoli, 2011; Szmulewicz et al., 2015). Gable (2007) reported that over a five-year period in the UDV context there were 13 to 24 cases in which AYA intake was associated to an undefined psychotic incident. These cases were reported from a cumulative estimated 25,000 AYA sessions, thus representing a rate less than 0.1% (0.052–0.096%), which is comparable to the incidence of transient psychoses associated with LSD administration in controlled settings (Cohen, 1960).

Dos Santos and Strassman (2008) reported the case of a young adult male who experienced two psychotic paranoid episodes (separated by one year) during and after participation in AYA rituals. He had no previous psychotic symptoms or a family history of psychosis, but he had consumed other hallucinogens (LSD and psilocybin) on several occasions and was a nearly-daily cannabis user for the preceding six years before the psychotic episodes. Moreover, he was participating in AYA rituals for about two years, sometimes using cannabis concurrently. During an AYA ritual he combined its use with cannabis and experienced paranoid and suicidal thoughts and superficially cut himself with a sharp-edged ceremonial item. Psychotic symptoms persisted for a few weeks and only resolved after treatment with risperidone (6 mg/day gradually reduced to 0.5 mg/day over one year). After risperidone treatment, he resumed participation in AYA rituals and again experienced paranoid and suicidal

ideation, which also persisted for some weeks and responded well to risperidone. Although this case is associated with AYA intake, it is difficult to establish a direct causal relationship between AYA and the emergence of psychotic symptoms because of the concurrent use of cannabis. On the other hand, the patient had been using cannabis and other hallucinogens including AYA for years without significant adverse reactions, suggesting the he was adapted to these drugs. Thus, it is not clear why he suffered a psychotic reaction in that particular ritual.

A study conducted in the context of the UDV reported that from 1994–2007 the Psychiatric Monitoring System organized by the Medical-Scientific Department of this religious group reported the occurrence of 29 cases presenting psychotic features that were possibly associated with AYA use (Lima and Tófoli, 2011). However, further evaluation of the cases showed that in only 19 of them AYA seemed to be the main onset factor. But even in these cases, an analysis of pre-morbid personality factors revealed aspects or characteristics that could also be associated with the occurrence of a psychotic behavior (Lima and Tófoli, 2011). Szmulewicz et al. (2015) reported a case of an adult who developed a manic episode after AYA consumption. Importantly, the patient had a clinical history including a previous episode of hypomania, and his father had been diagnosed with bipolar affective disorder type I. Interestingly, no significant changes in the YMRS were observed after AYA administration to depressed patients (Osório et al., 2015; Sanches et al., 2016). However, in these studies a diagnosis of bipolar disorder or a previous history of mania or hypomania induced by antidepressant or substance use were considered exclusion criteria. Thus, AYA may be contraindicated for patients with bipolar disorders.

Taken together, these results suggest that the incidence of adverse psychiatric reactions among AYA users is rare, and its causal relation with AYA is sometimes difficult to establish. Moreover, admixture plants with chemical compounds that may induce psychotic-like reactions, such as the anticholinergic deliriant scopolamine, present in *Brugmansia* varieties sometimes used in mestizo and indigenous contexts, should be looked for in cases of reported psychotic outcomes (Gable, 2007; Dos Santos, 2013b). Furthermore, some of the *Santo Daime* churches may use cannabis as a sacrament in their rituals, especially in Europe, where the laws regarding cannabis use are more permissive (in Brazil, it is officially forbidden to use cannabis within the *Santo Daime* rituals since the 1980s because cannabis is illegal in this country) (Dos Santos, 2011; Groisman, 2000; MacRae, 1998). While there is little known about this, the careful examination of the effects of concomitant cannabis use during AYA sessions should be the subject of clinical research efforts in the future.

The reviewed studies also suggest that long-term AYA use by adults and adolescents is not associated with psychiatric disorders or neuropsychological deficits (Barbosa et al., 2009; Bouso et al., 2012, 2015; Da Silveira et al., 2005; Doering-Silveira et al., 2005a; Fábregas et al., 2010; Grob et al., 1996; Halpern et al., 2008). In fact, the reviewed studies suggested that continuous AYA use was associated with remission of psychiatric disorders such as drug abuse/dependence and mood and anxiety disorders (Barbosa et al., 2009; Bouso et al., 2012; Da Silveira et al., 2005; Fábregas et al., 2010; Grob et al., 1996). Moreover, adolescents raised within the syncretic church UDV were significantly less likely to engage in last year and last month self-administration of alcohol compared to the non-AYA exposed

control subjects (Doering-Silveira et al., 2005b), and regular AYA use by adults was associated with changes in personality traits and in life attitudes and views, characterized by reduced impulsivity and shyness and increased independence, confidence, gregariousness, optimism, religiousness, transpersonal feelings and spirituality (Barbosa et al., 2009; Bouso et al., 2012, 2015; Grob et al., 1996). However, these results should be interpreted with caution, since it is difficult to differentiate whether the improvements described are a consequence of AYA ingestion or of participating in a religious group, which can improve quality of life and well-being (Panzini et al., 2007).

These results are line with a previous study that assessed the psychological health and cognitive functioning of a group of 61 Navajo Native Americans members of the Native American Church, who regularly ingested the mescaline-rich cactus peyote (Halpern et al., 2005). Long-term peyote ingestion was not significantly associated with deficits on the Rand Mental Health Inventory (RMHI) and on 10 neuropsychological tests of memory and attentional/executive functions. Furthermore, the above results suggesting reduced anxiety and impulsivity associated with AYA ingestion are in agreement with a case report that described the use of AYA to reduce violent behavior (Frecska, 2008).

Among the reviewed studies, there is an absence of research in humans to evaluate the effects of AYA in pregnant women and in children, although this population can also take part in the AYA rituals (Dos Santos, 2010, 2013; Labate, 2011). Although they are usually exposed to smaller doses and to less frequent participation, children of all ages participate in the rituals (Dos Santos, 2010, 2013; Labate, 2011). It is known that the period from birth to early adolescence is characterized by major restructuring of brain anatomical and functional characters by neuronal pruning, that will define which connections will be maintained and reinforced and which will be eliminated (Schafer et al., 2012). Neuronal adverse events that occur in this period, such as trauma and exposure to toxic substances, may have an impact on future cognitive functioning (Gogtay et al., 2004). Although neurodevelopmental studies reported that animals exposed to intrauterine AYA showed some anatomical alterations such as dilated brain lateral ventricles, these effects were observed only when the dose used was 10 times greater than the usual ritualistic dose (Oliveira et al., 2010). Moreover, as pointed above, it is important not to uncritically generalize animal data to humans (Dos Santos, 2010, 2013). Since some AYA users are exposed to the brew from intrauterine life and during the formation of the neural tube, it would be important to carry out research with the child population of AYA users for risk assessment.

Finally, more research is needed regarding the possible pharmacological interactions resulting from the combination of AYA alkaloids (especially the β -carbolines) with monoamine oxidase (MAO) inhibitors and monoaminergic and serotonergic substances like selective serotonin reuptake inhibitors, tryptophan or antidepressives in general, since these combinations could potentially produce the serotonin syndrome (Callaway and Grob, 1998; Dos Santos et al., 2013a, 2013b).

Conclusion

Neuropsychological studies have demonstrated impaired performance of working memory in AYA users under the influence of

the substance and better performance in other executive functions such as planning and inhibitory control (after acute and long-term AYA intake) in experienced users compared to occasional users and non-users. Research with neuroimaging showed the activation of frontal and paralimbic brain regions. The controlled/ritualistic use of AYA has a good safety profile, and recent research has suggested that AYA can have therapeutic effects on the remission of some psychiatric disorders such as major depression and substance dependence.

However, these preliminary studies were not controlled and the long-term effects of AYA, as well as the mechanisms of action responsible for these effects, are still largely unknown and therefore need to be further clarified. Thus, the lack of studies highlights important gaps, such as the aforementioned lack of research with children and pregnant women who drink the tea. Another factor which indicates the need for more research is the lack of studies with populations that have health problems, considering that the tests carried out had exclusion criteria for psychiatric and other diseases. Furthermore, more studies assessing the effects of AYA in naïve users are needed considering that most studies conducted so far assessed experienced AYA consumers, which may limit the generalizability of the results since these individuals are well adapted to long-term AYA use.

Therefore, more research is necessary to better understand the effects of AYA and its therapeutic potentials, avoiding the reckless spread of information devoid of scientific basis, which may interfere with the conduct adopted in clinical practice (Dos Santos et al., 2013b, 2016).

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