Psychotherapeutic and neurobiological processes associated with ayahuasca's mental health and wellbeing outcomes: a proposed model and implications for therapeutic use

Daniel Perkins^{1,2,3}

Simon Ruffell^{2,3}

Kimberley Day²

Diego Pinzon

Jerome Sarris^{2,4,5}

¹ School of Social and Political Science, University of Melbourne, Melbourne, Australia, ² Psychae Institute, Melbourne, Australia, ³ Centre for Mental Health, Swinburne University, Melbourne, Australia, ⁴ NICM Health Research Institute, Western Sydney University, Sydney, Australia, ⁵ Florey Institute for Neuroscience and Mental Health, Melbourne, Australia.

Correspondence concerning this article should be
emailed to Daniel Perkins d.perkins@unimelb.edu.au

Abstract

Ayahuasca is a psychoactive Amazonian plant brew. It is usually made from the *Banisteriopsis caapi* vine, which contains three primary harmala alkaloids, along with the leaves of *Psychotria viridis* in which the potent psychedelic dimethyltryptamine (DMT) is found. DMT-harmaloid concoctions have gained popularity in recent years, due to growing anecdotal and scientific reports of therapeutic benefits associated with their consumption. Ayahuasca is now ingested in a variety of different settings across the globe, from traditional ethnobotanical to so called “neo-shamanic” ceremonies. Furthermore, related preparations involving alternative sources of DMT and harmala alkaloids are becoming increasingly common as knowledge of ayahuasca continues to spread internationally.

This paper reviews the existing literature and original qualitative data from the largest cross-sectional study of ayahuasca drinkers undertaken to date, the Global Ayahuasca Project, to propose a model of psychotherapeutic processes associated with the consumption of ayahuasca. We assert that it is these processes, facilitated by a range of neurobiological effects, that lead to beneficial mental health and wellbeing outcomes.

Our proposed model identifies five key psychotherapeutic processes inherent to the ayahuasca experience; somatic effects; introspection and emotional processing; increased Self-connection, value, and love; increased spiritual connection, and finally the gaining of insights and new perspectives. We note some important differences in these processes compared with other classic psychedelics as well as the implications of the model for the therapeutic use of ayahuasca.

Improved understanding of the psychotherapeutic processes involved with the ayahuasca experience will better equip practitioners to work with this potentially transformative concoction and enable the optimisation of therapeutic treatment models for potential clinical use.

Keywords: ayahuasca, DMT, harmala alkaloids, psychedelic therapy, psychotherapeutic processes, neurobiology, mental health, health behaviours

Introduction

A DMT-harmala alkaloid based traditional medicine known as ayahuasca has been used by indigenous cultures in the Amazon basin for healing, spiritual and other purposes for at least hundreds of years (Naranjo 1986, Shanon 2002). It is typically made from the *Banisteriopsis caapi* (ayahuasca) vine and the leaves of *Psychotria viridis* (chacruna) or *Diplopterys cabrerana* (chaliponga) (Ruffell, Netzband et al. 2020). The word ayahuasca is from the Quechua language meaning ‘vine of the souls’ (McKenna, Towers et al. 1984), and this concentrated liquid decoction can produce powerful changes in awareness and consciousness, which are considered central to its therapeutic effect (Wolff, Ruffell et al. 2019).

In addition to continuing traditional use, ayahuasca has been adopted as a religious sacrament by several Brazilian syncretic religions that have now expanded internationally to Europe, North America, and Australia (Shanon 2002, Tupper 2009, Trichter 2010, Lowell and Adams 2017). Recent decades have also seen large numbers of international tourists visiting South American countries seeking ayahuasca’s renowned therapeutic and spiritual or personal development effects (Kavenská and Simonová 2015, Peluso 2016). At the same time there has been a rapid growth in ceremonies using ayahuasca or related preparations (involving alternative plant sources of DMT and harmala alkaloids) in underground indigenous styled neo-shamanic ceremonies taking place in countries across the world (Tupper 2009, Trichter 2010, Gearin 2015). In this paper we use the term ayahuasca to refer to DMT-harmala alkaloid brews using traditional and non-traditional ingredients.

The paper involves a review of existing literature surrounding the efficacy and therapeutic application of ayahuasca, as well as qualitative data from the Global Ayahuasca Project (GAP). The GAP is the largest cross-sectional study of ayahuasca drinkers ever undertaken, involving 10,836 people from more than 50 countries and a variety of different traditions, including

syncretic religious, traditional ethnobotanical and the so called “neo-shamanic” Western settings. The study utilised an online self-report methodology to collect detailed quantitative and qualitative data - see Perkins et al. (2021) for the full study methodology. The GAP study received ethical approval from Melbourne University Human Research Ethics Committee (HREC number 1545143.3).

We use qualitative data from the GAP study to consider the key psychotherapeutic processes that are associated with beneficial mental health and wellbeing effects for participants drinking the brew, in addition to identifying neurobiological processes likely to facilitate such effects, and other relevant non-pharmacologically induced factors.

Evidence of Therapeutic Effects

Animal and Human Study Evidence

Although still evolving, there is growing scientific evidence indicating that DMT-harmala alkaloid preparations such as ayahuasca may have potential therapeutic utility in the treatment of several psychiatric disorders. Nonclinical and clinical studies, including a small number of double-blind randomised controlled trials have reported evidence of anti-depressive effects (Dos Santos, Osório et al. 2016, Osório, Sousa et al. 2016, Santos, Sanches et al. 2018, Almeida, Galvão et al. 2019, Sarris, Perkins et al. 2021), anti-addictive effects (Bouso and Riba 2014, Nunes, Dos Santos et al. 2016, Berlowitz, Walt et al. 2019, Perkins, Opaleye et al. 2021), and anxiolytic effects (Hilber and Chapillon 2005, Santos, Landeira-Fernandez et al. 2007, Dos Santos, Osório et al. 2016, dos Santos, Osório et al. 2021). Other research has reported therapeutic benefit in relation to Post-Traumatic Stress Disorder (PTSD) (Nielson and Megler 2014); suicidality (Zeifman, Palhano-Fontes et al. 2019, Zeifman, Singhal et al. 2021); grief (González, Carvalho et al. 2017, González, Cantillo et al. 2020) eating disorders (Lafrance, Loizaga-Velder et al. 2017, Renelli, Fletcher et al. 2020); borderline personality disorder

(Domínguez-Clavé, Soler et al. 2019); and Parkinson's disease (Serrano-Dueñas, Cardozo-Pelaez et al. 2001, Schwarz, Houghton et al. 2003).

A systematic review of 28 human ayahuasca studies reported that acute administration was well-tolerated and that neither acute nor long-term use was associated with increased psychopathology or cognitive deficits, but was associated with enhanced mood and cognition, increased spirituality, and reduced impulsivity (dos Santos, Hallak et al. 2016).

Psychological and Wellbeing Effects

Observational and qualitative studies investigating ayahuasca's therapeutic effects have identified improvements in some psychological skills or traits such as decentring (Franquesa, Sainz-Cort et al. 2018, Domínguez-Clavé, Soler et al. 2019); certain mindfulness capabilities (acceptance, non-judgemental and non-reactive processing, and improved observation) (Thomas, Lucas et al. 2013, Soler, Elices et al. 2016, Uthaug, Van Oorsouw et al. 2018); cognitive flexibility (Stemme, Deco et al. 2008, Murphy-Beiner and Soar 2020); and emotional regulation (Domínguez-Clavé, Soler et al. 2019).

Broader psychological and wellbeing benefits have been identified among healthy drinkers and those with mental health conditions (Bouso, González et al. 2012, Uthaug, Van Oorsouw et al. 2018, Perkins, Opaleye et al. 2021). These include increased confidence, optimism, independence and positive mood (Barbosa, Cazorla et al. 2009), as well as increased openness to therapeutic interventions (Winkelman 2014). Beneficial effects have also been reported in relation to interpersonal relationships, sense of self, creativity, somatic perception, sense of connection, substance use, and other health behaviours (Shanon 2000, Thomas, Lucas et al. 2013, Lafrance, Loizaga-Velder et al. 2017, Bathje, Fenton et al. 2021, Perkins, Opaleye et al. 2021).

Additional benefit may also be associated with the reported modulation of some personality traits after ayahuasca consumption including increased agreeableness, openness to experience, and extraversion, and reduced neuroticism and negative emotionality (Netzband, Ruffell et al. 2020, Mendes Rocha, Rossi et al. 2021, Weiss, Miller et al. 2021, Perkins, Pagni et al. Forthcoming).

Proposed Neurobiological Mechanisms

A range of neurobiological mechanisms have been proposed to contribute to the acute and longer-term therapeutic effects of DMT-harmaloid preparations. These appear to derive from combined effects of DMT (N, N- Dimethyltryptamine related) and the three primary harmala alkaloids (harmine, harmaline and tetrahydroharmine) (Ruffell, Netzband et al. 2020). Some of these pathways are shared with other classic psychedelics such as psilocybin and LSD (activation of serotonergic, dopaminergic and glutamatergic pathways via serotonin 5-HT_{2A} agonism), while others are specific to DMT (activation of the sigma-1 and trace amine-associated receptors) and the harmala alkaloids (Aricioglu-Kartal, Kayir et al. 2003, Riba, Valle et al. 2003, Brierley and Davidson 2012, Owaisat, Raffa et al. 2012).

Key neurological processes proposed to be associated with ayahuasca's therapeutic effects include decreased connectivity in the default mode network (DMN), increased neurogenesis and neuroplasticity, serotonergic and MAOI effects, reduced amygdala and insula reactivity, and decreased pro-inflammatory cytokines, as well as modulation of brain regions associated with interoception, affect, emotional processing and volition (Riba, Romero et al. 2006, dos Santos, Osório et al. 2016, Muttoni, Ardissino et al. 2019, Pasquini, Palhano-Fontes et al. 2020).

From a brain network perspective, it is suggested that ayahuasca temporarily modifies the ordinary flow of information within the brain by disrupting usual neural hierarchies (reducing

high order cognitive control and facilitating bottom-up information flow), thus facilitating inner exploration and new perspectives on reality via the relaxing and revision of existing beliefs (McKenna and Riba 2015, Carhart-Harris and Friston 2019). It is also proposed that psychedelics may induce a unique window of adult neuroplasticity, described as critical period plasticity, similar to that of the adolescent neurodevelopment phase (Lepow, Morishita et al. 2021).

This wide range of neurobiological effects is likely to facilitate multifaceted psychotherapeutic processes and provides an underpinning rationale for the proposed transdiagnostic application of ayahuasca in the treatment of mood and anxiety disorders, addiction and trauma (see Table 1).

Table 1: Association between ayahuasca induced neurobiological processes and dysfunctions across psychiatric disorders

Evidence of modulation by ayahuasca	Role in disorder			
	Depression	Anxiety	Addiction	Trauma
DMN activity (Palhano-Fontes, Andrade et al. 2015).	Hyperactivated & hyperconnected (Whitfield-Gabrieli and Ford 2012)	Hypo-connectivity with the affective network and decoupling with the ECN (Xu, Van Dam et al. 2019)	Altered connectivity and emotional processing. (Zhang and Volkow 2019)	Altered resting-state functional connectivity associated with PTSD symptoms (Lanius, Terpou et al. 2020)
Neuroplasticity (Ly, Greb et al. 2018)	Impaired (Price and Duman 2020)	Impaired (Krystal, Tolin et al. 2009)	Impaired (Sampedro-Piquero, de Guevara-Miranda et al. 2019)	Impaired (Kolassa and Elbert 2007)
Amygdala (Muttoni, Ardissino et al. 2019)	Abnormal functioning (Peluso, Glahn et al. 2009, Ramasubbu, Konduru et al. 2014)	Hyper-reactive (Shah, Klumpp et al. 2009, Alvarez, Kirlic et al. 2015)	Role in relapse (See, Fuchs et al. 2003)	Hyperactivity (Bruce, Buchholz et al. 2012)
Right insula (Sanches, de Lima Osório et al. 2016)	Hypo-active (Wiebking, de Greck et al. 2015)	Hyper-reactive (Shah, Klumpp et al. 2009, Alvarez, Kirlic et al. 2015)	Dysfunction (Paulus, Stewart et al. 2013)	Role in PTSD resilience (Jeong, Chung et al. 2019)
Interoception (Riba, Romero et al. 2006, Wang, Wu et al. 2019)	Impaired (Wiebking, de Greck et al. 2015, Eggart, Lange et al. 2019)	Heartbeat hypersensitivity (Domschke, Stevens et al. 2010)	Impaired detection and processing (Paulus, Stewart et al. 2013)	Impaired (Schaan, Schulz et al. 2019, Reinhardt, Zerubavel et al. 2020)

Psychotherapeutic processes

While research relating to the neurobiological processes underpinning therapeutic benefits reported with psychedelics compounds is relatively recent, the key role of associated psychotherapeutic processes has been widely recognised since the commencement of psychedelic research in the middle of last century (Leary, Litwin et al. 1963, Bonny and Pahnke 1972). A recent systematic review reported several types of psychotherapeutic processes across studies utilising psilocybin, LSD, ayahuasca, and MDMA in the treatment of various psychiatric disorders. These included the gaining of insights (into one's self, their disorder/s and its origin, interpersonal dynamics), altered self-perception (increased self-efficacy, reduced self-criticism), increased feelings of connectedness (internally, externally, and with the world/nature), transcendental experiences (mystical, religious or spiritual), and an expanded emotional spectrum (from bliss and love to anger and terror) (Breeksema, Niemeijer et al. 2020).

The psychotherapeutic process associated with ayahuasca consumption

By drawing from the existing literature and combining this information with real-world qualitative data from the GAP study we have developed a more comprehensive understanding of the psychotherapeutic processes associated with ayahuasca consumption, to better inform potential clinical applications. Our model of the psychotherapeutic elements of the ayahuasca experience is outlined below. The five key elements in this framework, discussed further below, are:

1. Somatic effects

- 2. Introspection and emotional processing**
- 3. Increased self-connection, value, and love**
- 4. Increase spiritual connection and awareness**
- 5. Gaining of insights and new perspectives**

In practice, these elements are highly interconnected, and occur in the context of facilitatory neurobiological effects to achieve beneficial mental health and wellbeing outcomes. We also note that there are non-pharmacologically induced factors that have been identified as contributing to mental health outcomes (Canda 1988, Barbosa, Cazorla et al. 2009, Kaasik, Souza et al. 2021, Perkins, Schubert et al. 2021). These can include interpersonal and community connections frequently associated with ayahuasca consumption (e.g. deep interpersonal connection, openness and sharing at the place of consumption; ayahuasca drinking community membership; and longer term connections with people who shared the experience), as well as aspects of the setting of consumption (e.g. support for preparation, during the acute experience, post-consumption; complementary therapeutic activities; and the nature of the ceremony/ritual itself). Other factors such as an individuals' state of mind, or "set", when consuming ayahuasca, and constituent levels in the brew itself, are also likely to influence their acute experience.

It is noteworthy that although the elements of our proposed psychotherapeutic model have some relevance to other classical psychedelics such as LSD and psilocybin (when used in therapeutic settings), we argue that there are important differences in the case of ayahuasca. These include a central somatic element, connection with a core-Self and profound self-love/acceptance, and insights and new perspectives which although present with other psychedelics appear far more specific and likely to catalyse significant life change.

As per Figure 1, the first four of these elements are interconnected and together support the gaining of new insights and perspectives, with all these processes then contributing to a range of outcomes that may support enhanced well-being and mental health. We believe a therapeutic framework that can connect with and support these psychotherapeutic processes will maximise the likelihood of therapeutic benefit.

Figure 1. Ayahuasca psychotherapeutic processes and outcomes underpinning improvements in mental health and wellbeing

A. Somatic effects

The acute ayahuasca experience is characterised by strongly enhanced somatic and kinaesthetic awareness and interoception (Shanon 2002, Espinoza 2014, Kaufman 2015), with such effects present to a far greater degree than with other psychedelic substances. Somatic effects, both positive and negative, are often strongly associated with other psychotherapeutic processes, and are suggested by Shanon (2014, p.62) to be ‘the most basic psychotherapeutic and healing aspect of the ayahuasca experience’ (Shanon 2002, Espinoza 2014, Shanon 2014, Kaufman 2015).

Somatic effects typically commence with the first perception of the brew being experienced physically by users as an ‘energetic force, sometimes relating to the plant energy, moving into and taking over the body or nervous system’ (Shanon 2002). Drinkers frequently experience specific healings from ayahuasca somatically and report precise awareness of how traumas and emotional issues are ‘stored’ in and ‘released’ from their bodies.

‘I felt a huge quantity of negative energy coming out of my body... and I thought I was dying. She [ayahuasca] spoke to me, she showed me traumatic situations from my childhood and told me that all this negative energy I had in my body was all the residues from those childhood events. After that, I felt like the burden I was carrying my whole life was gone, like someone just took it away’ (GAP Study)

‘I also experienced [ayahuasca] remove a range of emotional, physical and sexual traumas I have experienced. It went thru my veins and body and removed the pain. I released a lot of trauma and negative energy (GAP Study)

Throughout the acute experience, drinkers typically have a sense of an altered bodily state, sometimes perceiving something ‘foreign’ having a grasp of their bodies and where physical effects can be of cognitive significance and be integrated with spiritual experiences (Shanon

2002, Breeksema, Niemeijer et al. 2020). Proprioceptive senses are strongly enhanced and frequently include unusually fine degrees of sensitivity, control, or awareness of body parts, often connected with a sense of self-healing, or improved physical health (Shanon 2002, Shanon 2014).

‘I was shown my lungs at a microscopic level and how they work exchanging Oxygen and carbon dioxide and reminded of a broken promise not to smoke again... a voice (either mine or something else's) said “you've got one more chance” - I have never smoked tobacco in any way since that ceremony 2 years ago’

More broadly, the acute experience can involve intense bodily sensations, both positive and negative, such as feeling pure love or embodied traumas and emotional issues, semi-voluntary physical movements typically with a feeling of emotional release, as well as nausea and vomiting. Ayahuasca drinkers often experience what is known as “the purge” with the brew being referred to as “la purga” by some traditional practitioners (Domínguez-Clavé, Soler et al. 2016). This is largely due to the alteration in enzymes in the stomach caused by the harmala alkaloids as well as the effect on the serotonin receptors in the gut by DMT (Gershon 2004).

Such vomiting is traditionally considered a positive effect and is often reported by ayahuasca drinkers to provide immense emotional and psychological relief, connection with usually inaccessible emotions, and feelings of joy and personal transformation, in some cases life-long (Shanon 2002, Shanon 2014, Gearin 2015, Lafrance, Loizaga-Velder et al. 2017, Rush, Marcus et al. 2021).

Neurological studies of ayahuasca consumption have identified significant activation of the neural systems involved with interoception and emotional processing, particularly frontal and paralimbic areas and the anterior insula (right hemisphere), all of which have been associated with somatic awareness and heightened conscious perception of emotional and affective states

(Riba, Romero et al. 2006, Wang, Wu et al. 2019). The importance of ayahuasca's somatic aspect is also highlighted by a growing body of literature pointing to the neurological integration of interoceptive and emotional activity (Seth and Friston 2016, Strigo and Craig 2016, Tsakiris and Critchley 2016).

In addition to heightened somatic awareness in the acute experience, there is also evidence of reduced bodily dissociation from longitudinal and qualitative studies, a notion also conveyed by ayahuasca drinkers (Espinoza 2014, Kaufman 2015).

“I feel that my body is so much more present in my life now than before taking ayahuasca. It's as if I've been stuck in my thinking my whole life, and now that's different.” (GAP Study)

Similarly, in a qualitative study of 41 ayahuasca drinkers, Bathje et al. (2021) report participants commonly feeling different in their bodies after ayahuasca, with changes such as experiencing less bodily chronic stress, feeling more in tune with bodily sensations, relief from tics or muscle twitches, and feeling more energy, lightness, or a release or psychical/energetic blockages.

Such enhanced somatic awareness that may be achieved with ayahuasca can be therapeutically valuable in allowing connection with and processing of deep emotional material, potentially leading to better differentiation of emotions associated with bodily changes and improved emotional perception and regulation (Van der Kolk 2014, Schaan, Schulz et al. 2019).

‘I was holding on to trauma and fear. Ayahuasca showed me how to let go of it and gave me a new perspective to see myself through. This experience reminded me that I had forgotten how it feels to be relaxed in my body and Ayahuasca showed me the way back to this resting state.’ (GAP Study)

'Ayahuasca drew my awareness from my head back down into my body. I had cut myself off from feeling much in my body after bad experiences in my early teens and it helped to reconnect me.' (GAP Study)

Such effects are consistent with the new wave of somatic-based psychological therapies (Davis 2021) and are of relevance for various psychiatric disorders, including addiction (Paulus, Stewart et al. 2013), depression (Wiebking, de Greck et al. 2015), PTSD (Reinhardt, Zerubavel et al. 2020), and childhood trauma (Schaan, Schulz et al. 2019), where impaired interoceptive processing and anterior insula function, have been identified.

B. Introspection and emotional processing

The acute ayahuasca experience typically results in profound self-analysis in the form of visions and dreamlike sequences, an evocation of intense emotions, and the recollection and reprocessing of significant autobiographical material, including early life events, unresolved traumas, important relationships, experiences, or people (Shanon 2002, Echenhofer 2011, Perkins and Sarris 2021).

The level of mental clarity and emotional awareness is enhanced, enabling better recognition of dysfunctional thoughts and emotions, and maladaptive behavioural, emotional, and cognitive patterns, which can then be reframed, restructured and integrated in an accelerated psychotherapeutic process (Frecka, Bokor et al. 2016, Franquesa, Sainz-Cort et al. 2018, Renelli, Fletcher et al. 2018, Argento, Capler et al. 2019, Ruffell, Netzband et al. 2021, Scheidegger 2021).

'Ayahuasca has made me see why I think, feel, etc. as I do. It's helped me see and break negative patterns in my life, overcome my fears, and give me a deep sense of peace. It was like 20 years of therapy in my first weekend.' (GAP Study)

'I carried a tremendous amount of suppressed grief from a childhood of abuse, followed by an abusive first marriage. Drinking Ayahuasca has helped me to experience a "life review", pulling up suppressed painful memories, looking at them, processing them, and receiving, what I believe was crucial insight.' (GAP Study)

Consistent with such effects, a study of ayahuasca drinkers in Brazil identified quickened thought processes, exceptional understanding, 'Aha!' experiences, and feelings of clarity to be reported by around 90% of participants (Bresnick and Levin 2006). These processes can involve important reflections on the aetiology of mental health conditions, poor health behaviours, addictions, and destructive relationship patterns (Loizaga-Velder and Verres 2014, Franquesa, Sainz-Cort et al. 2018, Maia, Daldegan-Bueno et al. 2020). At times this can be emotionally confronting as participants feel their usual defences peeled away and are confronted with denied or unpleasant aspects of themselves and their innermost fears (Loizaga-Velder and Verres 2014, Franquesa, Sainz-Cort et al. 2018, Maia, Daldegan-Bueno et al. 2020). As Shanon (2002) describes, "One is cruelly confronted with one's self, and one finds oneself having no other option but to address issues that are often neither easy nor pleasant to handle". However, such difficult experiences are also commonly acknowledged by drinkers as useful learning or therapeutic experiences (Shanon 2002, Bresnick and Levin 2006, Kjellgren, Eriksson et al. 2009, Loizaga-Velder and Verres 2014, Franquesa, Sainz-Cort et al. 2018, Maia, Daldegan-Bueno et al. 2020).

'My first experience was profound love and recognizing the lack of love from my childhood aka abuse etc. My second experience went more deeply into the abuse from my childhood and was very hard, painful and scary, but necessary, and there was a sense of relief after.' (GAP Study)

Neurologically this process appears to be facilitated through the activation of neural systems associated with emotional processing and memory, providing access to deeply stored emotional material, while at the same time stimulating higher cortical areas, enabling processing and reconceptualizing of meaningful events and cognitive-emotional integration (Riba, Romero et al. 2006, Nielson and Megler 2014). The proposed disruption of neural hierarchies, discussed earlier, is also likely to support this emotional reprocessing via the relaxing and revision of existing beliefs.

C. Increased Self-connection, value, and love

As has been noted with other psychedelics, the ayahuasca experience is commonly reported to result in a shift in self-perception. However, with ayahuasca this goes beyond simply a reframing of previous self-perceptions, to include a renewed connection to what can be described as an authentic, wise, and compassionate core ‘Self’ as well as a renewed sense of self-love and value (Fericigla 2018, Renelli, Fletcher et al. 2018).

This ‘Self’ concept is consistent with that described by Schwartz as a ‘spacious essence in each person’ that, when accessed spontaneously, manifests leadership qualities including acceptance, calmness, clarity, compassion, perspective, and kindness, and has parallels in several Eastern spiritual traditions, and some humanistic psychology approaches (Schwartz 2013, Sweezy, Ziskind et al. 2013, Anderson, Sweezy et al. 2017).

The connection with this Self during ayahuasca experiences appears central in enabling emotional openness, introspection and associated challenging experiences to progress toward acceptance and emotional release. Of particular importance appears to be the harnessing of compassion and understanding and the removal of deeply held judgments about individuals themselves, their behaviours, and other people or events.

‘Showed the darkest parts in me and the worst of my behaviour and gave me the opportunity to forgive myself which helped me forgive those who have wronged me.’ (GAP Study)

After drinking ayahuasca, participants have been found to experience a greater sense of self-awareness, self-acceptance, and presence in themselves, as well as enhanced self-love, leading to greater empathy and improved interpersonal relationships (Kjellgren, Eriksson et al. 2009, Soler, Elices et al. 2016, Renelli, Fletcher et al. 2018). Such renewed Self-connection is evident in increased generalised self-efficacy, personal authenticity (Perkins, Pagni et al. Forthcoming), and increases in the psychological wellbeing domains of self-mastery and acceptance (GAP study). These reported improvements in psychological wellbeing have been found to be strongly predictive of better current mental health (Perkins, Schubert et al. 2021).

The increased Self-connection experienced with ayahuasca may also be central to reported increases in ‘decentring’, the meta-cognitive ability to take a detached view of thoughts and emotions (Fresco, Moore et al. 2007, Soler, Elices et al. 2016). This ability has been postulated as a trans-diagnostic index in psychopathology (Soler, Elices et al. 2016).

Several studies have also reported profound shifts in drinkers’ self-acceptance and self-love to be critical in catalysing mental health and addiction outcomes {Renelli, 2020 #340;Argento, 2019 #192; Thomas, 2013 #85}, which was also reported by GAP participants.

‘Ayahuasca helped me recognise my self-destructive ways using drugs and alcohol. The lessons of self-love and being true to oneself showed me that I did not want to poison my body, mind and spirit anymore with these substances.’ (GAP Study)

‘Greatly increased self-love. I now care a lot more about my well-being like you would for a loved one. Greatly increased emotional availability... Feel more in touch with my inner self. Motivated to make changes in life motivated by self-love.’ (GAP Study)

Data from the GAP study confirms the central place of this Self concept, with ‘higher’ or ‘true’ self this being the most commonly selected interpretation (>70%) of the source of information or insights gained during the acute experience (Perkins, Sarris et al. 2022).

D. Increased spiritual connection and awareness

The strength of the acute subjective spiritual experience has been identified as a strong predictor of therapeutic outcomes for individuals taking classical psychedelics, including ayahuasca (Russ, Carhart-Harris et al. 2019, Perkins, Opaleye et al. 2021, Perkins, Schubert et al. 2021). However, when compared with psilocybin or LSD, ayahuasca drinkers have been reported to have more positive and enduring mystical experiences with more lasting impacts on life satisfaction, social relationships, spiritual awareness, mood, and behaviour (Davis, So et al. 2019).

The ayahuasca experience is identified as among the top five most spiritually significant life experiences by around 70% of GAP study respondents, with over three quarters reporting insights or new perspectives regarding ‘a sense of sacredness, higher power or divine in the world’, and almost 90% indicating this has had a very positive effect on their life (Perkins, Sarris et al. 2022). Other commonly reported aspects of such enhanced spiritual connection, by more than half of drinkers, includes a sense of connection and kinship with the natural world, enduring connection with a plant spirit or intelligence, and a sense of interconnection between all things/events (Perkins, Sarris et al. 2022), which have also been reported in other research (Shanon 2002, Harris and Gurel 2012).

It appears that the deepened connection to nature reported is part of a broader increase in connectedness to Self, others, world/universe and a spiritual principle that has been associated with psychedelics such as psilocybin (Carhart-Harris, Erritzoe et al. 2017, Watts, Day et al. 2017). These peak experiences and spiritual insights have been proposed to be therapeutically

useful in supporting a new orientation to life in general (Kjellgren, Eriksson et al. 2009), as well as in catalysing spiritual elements of healing from addictions and other psychiatric conditions. (Liester and Prickett 2012, Loizaga-Velder and Pazzi 2014, Renelli, Fletcher et al. 2018)

A further common and unique aspect of the ayahuasca spiritual experience is the perception of receiving pure or divine love from plants, spirits, or other divine sources, which individuals can find profoundly transformative.

'I had previously been suicidal but the intense love I felt from the plants and the understanding of life that they gave me made it impossible for me to ever seriously consider this again.' (GAP Study)

'As a previous agnostic/atheist, I experienced infinite love from the divine/God, how my true self/consciousness is linked to everything and everyone and that my soul is eternal. My depression was cured. My crushing anxiety was cured.' (GAP Study)

New understandings and perspectives on death and dying are also regularly reported and can sometimes involve perceived near death experiences. Such experiences with psychedelics have been reported to confer long-term positive changes in well-being (Timmermann, Roseman et al. 2018) and may support change in unhealthy behaviours or psychological symptoms, and reduced anxiety of death among individuals with serious illnesses. (Loizaga-Velder 2013, Timmermann, Roseman et al. 2018, Maia, Daldegan-Bueno et al. 2020)

'I experienced the most intense level of fear I have ever experienced. I was out of my body and propelled into oblivion and faced death. After experiencing this level of fear, I have lost most of my anxiety in real life.' (GAP Study)

'I've visited death twice during ceremony, the first time being difficult because of resistance and confusion, The second being beautiful because of acceptance and surrender. Both

experiences, in their own way, taught me that death is not something to fear. I have the greatest and most humble respect for Divine Creation.’ (GAP Study)

Analysis of longitudinal data of ayahuasca naive drinkers has also identified increased levels of intrinsic spirituality and nature relatedness (Perkins, Pagni et al. Forthcoming). The use of a psychospiritual therapeutic support framework has been recommended based on data showing that spiritual/religious counselling provided with ayahuasca drinking (prior to/after the acute experience) is associated with a greater number of personal insights, reduced integration difficulties, greater perceived improvements in psychological wellbeing, and better current mental health status (Perkins, Schubert et al. 2021). This is understandable given the crucial place spiritual experiences often have in transforming mental health symptoms and facilitating wellbeing and life meaning for ayahuasca drinkers.

E. Insights and new perspectives

Closely connected with each of the areas above is the gaining of new insights and perspectives relating to an individual’s past, present and future, which can then have profound meaning and therapeutic value (Kjellgren, Eriksson et al. 2009, Frecska, Bokor et al. 2016). The gaining of these insights and perspectives (primarily during the acute experience) can be seen as offering the tangible potential for life change beyond simply introspection and emotional processing. Such insights during the ayahuasca experience have been found to be associated with improved psychological wellbeing, reduced alcohol and drug use, and reduced depression and anxiety symptoms among those with a prior diagnosis (Perkins, Opaleye et al. 2021, Perkins, Schubert et al. 2021, Sarris, Perkins et al. 2021).

The most common personal insights reported by drinkers in the GAP study include new understandings of their personality, new understandings about family and personal relationships, realisations about ethics, morals and their own conduct, revelations about their

life purpose and direction, new understandings of childhood events, patterns/dynamics in intimate relationships, and new understandings of their body function and care, all of which were reported by over 50% of participants (Perkins, Sarris et al. 2022). Other research has reported similar interpersonal, psychodynamic, and life purpose themes in drinkers' insights {Wolff, 2019 #199;Kavenská, 2015 #245;Loizaga-Velder, 2014 #572}, as well as insights relating to health and bodily functioning and care (Shanon 2002), and other new perspectives such as personal or creative interests (Shanon 2002, Kjellgren, Eriksson et al. 2009, Kavenská and Simonová 2015, Wolff, Ruffell et al. 2019).

There is evidence that these insights and new perspectives can contribute to meaningful life changes (Bouso, González et al. 2012, Franquesa, Sainz-Cort et al. 2018). Such changes commonly attributed to ayahuasca by GAP participants include the healing of longstanding personal rifts/conflicts, reductions in drug and alcohol use, and changing career or commencing study in a new area, each of which was reported by 30%-50% of study participants (Perkins, Sarris et al. 2022). Insights and life changes were also correlated, with for example, those reporting insights about their life purpose and direction being more likely to report subsequent vocational changes (Perkins, Sarris et al. 2022).

New insights and perspectives relating to alcohol and other drug use, diet, and other health behaviours is a key area that may provide ongoing therapeutic benefit (Loizaga-Velder 2013, Maia, Daldegan-Bueno et al. 2020). Around 50% of GAP respondents report taking care of their physical health and eating a healthier diet 'much more' than previously, with such responses more likely among drinkers also reporting insights about their body function and care (Perkins, Sarris et al. 2022).

Post ayahuasca, new perspectives on substance use described in terms such as ‘losing interest’, the ‘taste for alcohol’, or no longer liking how it felt in their bodies are commonly reported, for example:

‘I never considered myself to have an alcohol problem. About 3 weeks after the experience, I tried a sip of beer and it made me feel terrible. I realized that I never enjoyed the effect of alcohol in my body, and that I would never drink it again. I give ayahuasca credit for both opening me to the reality that alcohol was bad for my body, and that I had the strength to make the choice to stop drinking it.’

‘I feel more embodied and comfortable in my body. I find I cannot drink any more than a glass of wine or a beer and even then, I’ll lose interest halfway through. More than a glass and I feel queasy and toxic. I used to be heavily dependent on alcohol for stress relief (every night up to a bottle of wine on my own)’

Integrated effects

In practice, the proposed psychotherapeutic processes will usually be interconnected and mutually supportive, with for example introspection and emotional processing being facilitated by the connection to Self, somatic awareness and in some instances the spiritual connection. Such interconnected healing effects are also apparent in the healing descriptions of drinkers.

‘After engaging with the medicine, I have a deeper sense of myself, this physical body, as well as the spirit (ME, both the individual and universal selves). How I am connected, interconnected, and interrelated to all beings. I can see that my disease is a manifestation of historical trauma on my mother’s side, as well as my own childhood/sexual traumas... and that those energies/experiences were lodged deep within my body, leading to disease.’ (GAP Study)

'It was life changing. It has helped me to release my childhood traumas, come to a place of love and acceptance and released a number of emotional blockages in my body, after which I now have the ability to feel energy of myself and others.' (GAP Study)

'Drinking ayahuasca was life changing in that it made me go inside. It changed my focus to my inner world rather than just reacting to my environment. It helped me understand myself and others much more than I ever did before, which improved my relationships. It also changed my relationship with my body, my food choices, it made me lose interest in alcohol.' (GAP Study)

Implications for therapeutic application

Contemporary therapeutic approaches to the use of psychedelic compounds have differed somewhat depending on the substance and conditions being treated as well as the choice of an overarching or primary therapeutic framework (e.g. acceptance and commitment therapy - ACT, mindfulness-based cognitive therapy – MBCT, Internal Family Systems Therapy – IFS, or non-specific approaches). However, they all share a common structure based on the provision of psychotherapeutic support for participants: to prepare for the drug administration session, during the drug administration session, and to assist with integration in the days or weeks following drug administration (Mithoefer 2017, Schenberg 2018, Guss, Krause et al. 2020). Our model of psychotherapeutic processes associated with the ayahuasca experience provides unique and directly relevant insights to inform potential DMT-harmala alkaloid clinical treatment models at each of these phases.

Given the central place of somatic effects in ayahuasca's psychotherapeutic outcomes and the apparent enhanced somatic awareness window created (effects not generally seen with other psychedelics), the inclusion of additional somatic processing practices/tools and an overarching therapeutic framework incorporating a somatic dimension, is likely to be of

significant benefit to participants. The inclusion of this focus in preparation and integration will support a deepening of the acute experience (this has been reported for yoga/tai-chi (Perkins, Schubert et al. 2021)) and more effective post-administration processing of experiences and emotional content. While other psychedelic therapy approaches provide some guidance on incorporating somatic tools such as focussed bodywork or breathwork, these are not integrated as a core element of the approach and are dependent on the prior training of the therapist.

The common experience of connection to a core Self, which is a source of wise guidance, compassionate perspective, and leadership, is another novel aspect of the ayahuasca experience, and something that for many individuals with treatment resistant psychiatric disorders may have previously been substantially or entirely absent. The use of an overarching therapeutic framework that can foster a continued connection to and development of this inner resource via a non-pathologizing, participant led approach, is likely to have a range of benefits. These include supporting the effective processing of emotional material revealed during acute experiences, strengthening the individuals' personal capabilities and Self-leadership, and facilitating enduring therapeutic benefit. As the ayahuasca core Self connection is typically also a central aspect of the introspection and emotional processing, and insights and new perspectives processes, we believe this lens is ideally suited to working with such material therapeutically. In this regard it would also be beneficial for the treatment model to specifically note the wide range of life, personal and vocational changes that can be catalysed by the ayahuasca experience and highlight the type of support likely required for following through and implementing such changes.

The spiritual process identified in our model is shared by other frameworks and has been identified as important across the classic psychedelics (psilocybin, LSD, DMT)(Breeksema, Niemeijer et al. 2020). However, there is evidence of a greater level of depth to this experience

with ayahuasca. As such, we suggest that the selection of an overarching therapeutic framework that includes a psycho-spiritual element is likely to provide benefits for participants in clinical settings, who unlike traditional users of this brew, typically have no frame of reference in which to prepare for, understand, or integrate the powerful spiritual experiences commonly reported. Consistent with this idea, the use of spiritual or religious counselling across different naturalistic contexts of consumption has been associated with enhanced mental health outcomes (Perkins, Schubert et al. 2021). In relation to the use of a psycho-spiritual framework, we also note the high level of openness, vulnerability and suggestibility that can be induced by ayahuasca experiences, and hence the ethical need to ensure that such an approach is culturally sensitive, non-doctrinal, and personally empowering (allowing participants to derive their own meaning and not have this imposed by a therapist).

Finally, as mentioned above, we believe our model provides important information regarding the selection of an overarching therapeutic framework, and in this regard see the Internal Family Systems (IFS) therapy approach as currently the most complete and suitable candidate. It is an evidence-based approach that has a strong somatic element, is centred around the concept of a core Self involving many similarities to that experienced by individuals using ayahuasca, and with a goal of cultivating connection to this core-Self and enhanced personal self-leadership utilising a non-pathologizing, participant led approach. Further IFS incorporates a broad psycho-spiritual framework that is compatible with a wide range of personal spiritual or religious beliefs, and in which individuals are viewed as inherently spiritual beings (Schwartz 1995, Sweezy, Ziskind et al. 2013, Janes, Trevino et al. 2022). We acknowledge that other therapeutic approaches may also address the psychotherapeutic elements identified by our model and be suitable for consideration.

Potential Therapeutic Challenges

Despite the range of positive effects typically associated with the psychotherapeutic processes outlined, it is also important to note ways in which these may also contribute to therapeutic challenges. The introspection and emotional processing element with ayahuasca, for example, can involve a particularly vivid reconnection with or re-experiencing of prior traumatic experiences, including early life events. This is usually reported to be highly therapeutic, however for vulnerable individuals or in the absence of appropriate support, such effects may create mental health difficulties or re-traumatisation (Galvão-Coelho, Marx et al. 2021, Nielson, Megler et al. 2021).

'It's opened up old deep wounds, with some harsh uncomfortable truths, which I'm now slowly processing in weekly psychotherapy' GAP Study

Similarly, the strong somatic effects can deconstruct defence mechanisms such as dissociation and diminished interoception that are common among trauma survivors and shield them from experiencing overwhelming emotion (Van der Kolk 2014), as is described by Perkins and Sarris (2021, p.109):

"I experienced her (ayahuasca) in Peru.. Aya (ayahuasca) removed all the blocks that I had which were preventing me to feel the childhood traumas. It did a great job removing the blocks and because my environment was perfect at that time, I felt like in heaven. I felt one with the universe and I obtained a great physical health. After returning home, life was not so perfect anymore, and I started to feel all the traumas and now there was no block, nothing to stop me to FEEL the pain caused by traumas."

Spiritual experiences that include a feeling of imminent death along with extreme fear or panic have been associated with integration difficulties and longer term negative mental health outcomes (dos Santos, Osório et al. 2017, Perkins, Schubert et al. 2021, Perkins, Aicher et al.

Forthcoming). Further, the remarkable clarity of insights and new perspectives gained with ayahuasca may in rare cases lead to problematic interpretations such as rigid attitudes, grandiose thinking, ego inflation, narcissism, or ‘spiritual narcissism’ (Gastelumendi 2010, Fernández and Fábregas 2014, Loizaga-Velder and Pazzi 2014, Fericgla 2018). In other cases this may involve rushed major decisions such as changing career or ending a relationship, or exaggerated or unusually uninhibited behaviours expressing feelings, psychological wishes, fantasies, or conflicts (Shanon 2002).

More broadly the profound and multifaceted psychotherapeutic effects can prove a challenge for ayahuasca drinkers to assimilate and integrate and it is not uncommon for individuals to experience some level of emotional or psychological difficulty in the weeks or months following their experiences, with a higher number of such difficulties associated with poorer long term mental health outcomes (Perkins, Schubert et al. 2021, Bouso, Andi6n et al. forthcoming).

Discussion

The resurgence in psychedelic research that has occurred over the last decade is often referred to as the “psychedelic renaissance” (Sessa 2012). Preliminary studies are showing promising results for compounds including MDMA (Mithoefer, Mithoefer et al. 2018), psilocybin (Carhart-Harris, Giribaldi et al. 2021), and ayahuasca (Palhano-Fontes, Barreto et al. 2018). As such, there is substantial work underway seeking to understand the neurobiological mechanisms that may facilitate such change (Riba, Anderer et al. 2002, Riba, Romero et al. 2006, Sampedro, de la Fuente Revenga et al. 2017). At the same time and in recognition of the ability of these substances to induce profound psychological, emotional and spiritual experiences, various manualised treatment models are being developed by research groups around the globe providing guidance for those working with these substances in clinical

research settings (Johnson, Richards et al. 2008, Mithoefer 2017, Guss, Krause et al. 2020, Watts and Luoma 2020). The aim of these treatment models is to provide standardised support that will maximise benefits and minimise harms associated with such treatments. However, the development and evaluation of such models remains in its infancy. Further, there has been no manualised approach developed for the potential clinical use of ayahuasca and its accompanying psychotherapeutic processes are not yet well defined in the scientific literature (Franquesa, Sainz-Cort et al. 2018).

Here we utilise the existing literature and participant reports from the GAP study to develop a model of the psychotherapeutic processes associated with ayahuasca and highlight important differences when compared to other psychedelic compounds. Our model involves four interrelated core processes, 1) somatic effects, 2) introspection and emotional processing, 3) Self-connection, value, and love, and 4) spiritual effects, which together inform a fifth process 5) insights and new perspectives. We suggest that these processes, which are induced by the powerful psychoactive effect of the brew and facilitated by a range of neurobiological effects, are responsible for various beneficial mental health and wellbeing effects.

The processes we describe are consistent with those identified in several small prior qualitative studies. In a study of 14 individuals with substance use disorder and 15 therapists utilising ayahuasca in treatment, Loizaga and Pazzi (2014) note four inter-related psychotherapeutic processes: body oriented, transpersonal, insight oriented cognitive, emotional/social. Although these overlap with our model in some respects, notable differences include a narrower interpretation of bodily effects emphasising enhanced awareness primarily via purging, as well as anti-craving and detox effects; the absence of a concept of, and process of connection to, a core Self; and the insight oriented cognitive aspect being concerned primarily with individual psychodynamics and dysfunction, rather broader life direction and life purpose insights or other new perspectives including health behaviours (emphasised in our framework).

Another study of ayahuasca use with 16 individuals with an eating disorder reported psychotherapeutic processes that included the processing of painful feelings and memories, internalisation of self-love and acceptance, and spiritual elements of healing (Renelli, Fletcher et al. 2018). A physical/somatic component was not included, but this was mentioned in a related study with the same patient group in the form of strong physical acute effects, and for some, changed understanding or experience of their physical bodies (Lafrance, Loizaga-Velder et al. 2017). Finally, a study of regular participants in the Santo Daime ayahuasca church identified psychotherapeutic processes involving insights into individuals' physical, psychological, emotional and spiritual health resulting in positive modifications in values and behaviour (in particular acceptance and forgiveness, empathy and gratitude), as well as positive dietary and substance use changes, that later of which we consider an outcome (Villaescusa 2002).

Our framework serves to clarify and extend the existing knowledge of psychotherapeutic processes associated with the consumption of ayahuasca and provides critical information for the potential clinical use of this substance by enabling the optimisation of psychotherapeutic treatment models. Further definition of the powerful psychotherapeutic processes involved with psychedelic compounds also helps to elucidate the integrated psychotherapeutic and neurobiological source of remarkable outcomes being achieved in clinical trials to date. This information also provides a valuable perspective from which to reflect on the potential efficacy of a new class of non-hallucinogenic psychedelic-like compounds (Peters and Olson 2021). In the case of ayahuasca, which we note involves key neurobiological processes proposed for emulation in non-hallucinogenic 'psychedelics' (such as 5-HT_{2A} agonism and deactivation of the DMN), we believe our review and model suggest an indispensable role of acute altered state experience in catalysing therapeutic processes reported.

As discussed, it is important to also note that various non-pharmacological factors may also influence therapeutic benefit achieved. Moreover, not all drinkers of ayahuasca will experience the therapeutic processes described in our framework, and for those who do it is typically not a silver bullet, but a unique tool that may accelerate the healing process:

'Ayahuasca has been better for life than a decade of traditional therapy and medications / SSRIs. Saying that it's not a magic potion that fixes everything (in most cases). Rather it gives the inspiration to change your own life. It teaches someone to fish rather than giving them a fish.' (GAP Study)

There are also certain limitations that should be noted in relation to our review. Although a strength of the GAP dataset is its size and inclusion of ayahuasca drinkers across different contexts of consumption, it has minimal representation of Indigenous ayahuasca drinkers in Indigenous contexts (primarily non-Indigenous drinkers in Indigenous contexts are included). In addition, the voluntary nature of the survey methodology is likely to involve an overrepresentation of participants who are enthusiastic about ayahuasca and motivated to spend time completing the survey, versus those with neutral or negative experiences. It would be beneficial for future studies to operationalise and evaluate the individual and joint effects of the five key psychotherapeutic processes we propose, with this of particular value in well controlled clinical contexts.

Finally, while we believe the psychotherapeutic framework described will assist the design of appropriate therapeutic treatment models and consequently improve outcomes, we also note that such potential clinical use of ayahuasca also raises other issues relating to appropriate recognition and reciprocal relationships with indigenous communities from whom knowledge of ayahuasca originates.

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