CHAPTER

5

A case report SPECT study and theoretical rationale for the sequential administration of ibogaine and 5-MeO-DMT in the treatment of alcohol use disorder

Joseph P. Barsuglia[*,†,‡,§,1], **Martin Polanco**[*,†], **Robert Palmer**[¶], **Benjamin J. Malcolm**[‖], **Benjamin Kelmendi**[#], **Tanya Calvey**[**]

[*]*Crossroads Treatment Center, Tijuana, Mexico*

[†]*Mission Within, Oakland, CA, United States*

[‡]*New School Research, LLC, North Hollywood, CA, United States*

[§]*Terra Incognita Project, NGO, Ben Lomond, CA, United States*

[¶]*Yale School of Medicine, New Haven, CT, United States*

[‖]*College of Pharmacy, Western University of Health Sciences, Pomona, CA, United States*

[#]*Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States*

[**]*Faculty of Health Sciences, University of the Witwatersrand Medical School, Johannesburg, South Africa*

[1]*Corresponding author: Tel.: +1-805-404-2833, e-mail address: jbarsuglia@me.com*

Abstract

Ibogaine is a plant-derived alkaloid and dissociative psychedelic that demonstrates anti-addictive properties with several substances of abuse, including alcohol. 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) is a naturally occurring psychedelic known to occasion potent mystical-type experiences and also demonstrates anti-addictive properties. The potential therapeutic effects of both compounds in treating alcohol use disorder require further investigation and there are no published human neuroimaging findings of either treatment to date. We present the case of a 31-year-old male military veteran with moderate alcohol use disorder who sought treatment at an inpatient clinic in Mexico that utilized a sequential protocol with ibogaine hydrochloride (1550 mg, 17.9 mg/kg) on day 1, followed by vaporized 5-MeO-DMT (bufotoxin source 50 mg, estimated 5-MeO-DMT content, 5–7 mg) on day 3. The patient received SPECT

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neuroimaging that included a resting-state protocol before, and 3 days after completion of the program. During the patient's ibogaine treatment, he experienced dream-like visions that included content pertaining to his alcohol use and resolution of past developmental traumas. He described his treatment with 5-MeO-DMT as a peak transformational and spiritual breakthrough. On post-treatment SPECT neuroimaging, increases in brain perfusion were noted in bilateral caudate nuclei, left putamen, right insula, as well as temporal, occipital, and cerebellar regions compared to the patient's baseline scan. The patient reported improvement in mood, cessation of alcohol use, and reduced cravings at 5 days post-treatment, effects which were sustained at 1 month, with a partial return to mild alcohol use at 2 months. In this case, serial administration of ibogaine and 5-MeO-DMT resulted in increased perfusion in multiple brain regions broadly associated with alcohol use disorders and known pharmacology of both compounds, which coincided with a short-term therapeutic outcome. We present theoretical considerations regarding the potential of both psychedelic medicines in treating alcohol use disorders in the context of these isolated findings, and areas for future investigation.

Keywords

Combination psychedelic therapy, Ibogaine, Alcohol use disorder, Addiction, Psychedelic, SPECT, 5-MeO-DMT

1 INTRODUCTION

Multiple psychedelic compounds demonstrate initial evidence of anti-addictive properties in the treatment of alcohol abuse (Albaugh and Anderson, 1974; Bogenschutz et al., 2015; Krebs and Johansen, 2012; Nielson et al., 2018; Oliveira-Lima et al., 2015), which is a top preventable leading cause of death in the United States (National Institute on Alcohol Abuse and Alcoholism, 2017). The Food and Drug Administration approved medications to treat alcoholism, such as disulfiram, naltrexone, and acamprosate, have demonstrated limited efficacy, and more effective treatments are warranted against this deadly condition (Garbutt, 2009; Johnson, 2008). Ibogaine is a plant-derived psychedelic dissociative compound that is administered internationally in controlled settings (Brown, 2013; Brown and Alper, 2017; Noller et al., 2018) and demonstrates addiction-interrupting properties with alcohol (Carnicella et al., 2010; Rezvani et al., 1995; Schenberg et al., 2014). Additional investigation is required to assess the efficacy of ibogaine in treating alcohol use disorders and document effects on the human brain. Ayahuasca is a widely used hallucinogenic Amazonian plant mixture which contains *N*,*N*-dimethyltryptamine (*N*,*N*-DMT) and is associated with reduced alcohol use in ritual users (Fábregas et al., 2010) and animal models (Oliveira-Lima et al., 2015). Psilocybin is an alternate organic psychoactive tryptamine which demonstrates efficacy for treating alcohol dependence in humans (Bogenschutz et al., 2015; de Veen et al., 2017), and its anti-addictive effects are meditated through occasioning mystical-type experiences (Nielson et al., 2018). A lesser studied, though pharmacologically related tryptamine, 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) occasions mystical

experiences at a similar or greater intensity than psilocybin (Barsuglia et al., 2017; Davis et al., 2018a), possesses anti-addictive properties (Dakic et al., 2017; Davis et al., 2018a), and thus may have benefit in treating alcohol use disorders. The following investigation includes a rationale for administering both ibogaine and 5-MeO-DMT in the context of alcohol addiction treatment, and the resultant neurological sequelae in a case study of an individual treated for alcohol abuse with both compounds in a psychedelic treatment program in Mexico.

1.1 IBOGAINE BACKGROUND AND POTENTIAL AS A TREATMENT FOR ALCOHOL USE DISORDER

Ibogaine is a primary alkaloid present in the root bark of the *Tabernanthe iboga* plant, which has an ancient history of ceremonial use in Central Africa. In recent decades, a number of studies have demonstrated the efficacy of ibogaine in treating opioid dependence (Brown and Alper, 2017; Davis et al., 2017; Malcolm et al., 2018; Noller et al., 2018). The treatment response rates to a single administration of ibogaine in recent observational studies with opioid users are promising. Remission statistics range from 75% in a small ($n = 14$) 1-year observational follow-up study in New Zealand (Noller et al., 2018), to 30–50% in larger observational studies from clinics in Mexico (Brown and Alper, 2017; Davis et al., 2017). These observational outcomes far surpass general efficacy ranges of widely utilized opioid replacement drugs such as methadone and buprenorphine (average 8–35%) (McCarty et al., 2017; Weiss et al., 2011). Ibogaine demonstrates a spectrum of anti-addictive properties with a number of substances of abuse, including cocaine, amphetamines, nicotine, and alcohol (Brown, 2013; Schenberg et al., 2014). Pharmacological models suggest that ibogaine is a promising therapeutic agent for treating alcohol use disorders; however, to date, no formal studies have examined this specific application in humans.

Ibogaine demonstrates complex, broad, and novel pharmacological mechanisms of action to consider in the potential treatment of alcohol use disorders (Alper, 2001). The alkaloid has low micromolar affinity for μ and κ opioid receptors, σ_1 and σ_2 receptors, serotonin reuptake transporter (SERT) and dopamine transporter (DAT), and is an *N*-methyl-D-aspartate (NMDA) and α3β4 nicotinic acetylcholine receptor (nAChR) antagonist that increases glial-derived neurotrophic factor (GDNF) expression and substance P immunoreactivity (Alburges et al., 2000; Brown and Alper, 2017; Jacobs et al., 2007; Lavaud and Massiot, 2017; Mash et al., 1998). Ibogaine is hepatically metabolized by CYP2D6 to an active metabolite, noribogaine, which has a longer duration of action with a documented half-life of 28–49 h in CYP2D6 extensive metabolizers (Glue et al., 2015). Anti-addictive effects on drug craving and improvements in mood persist after the elimination of both ibogaine and noribogaine, suggesting a longer-term neuroadaptive response after ibogaine/noribogaine exposure (Brown and Alper, 2017; Pearl et al., 1997).

Ibogaine demonstrates pre-clinical evidence for treating alcohol abuse through multiple pathways. In rodents, ibogaine reduces alcohol intake in alcohol-preferring

rats in preference and relapse paradigms (He, 2005; Rezvani et al., 1995); the anti-addictive effect is theorized to occur in part through upregulation of GDNF in the ventral tegmental area (VTA) (He, 2005). The VTA is a major region implicated in reward neurocircuitry (He and Ron, 2006), and chronic alcohol use inhibits the excitability of VTA neurons (Bailey et al., 1998) and firing rates of dopamine cells in this region (Bailey et al., 2001). The rewarding addictive properties of alcohol are associated with stimulation of dopaminergic and serotonergic systems broadly (Marcinkiewcz et al., 2016). Ibogaine's effect on psychological dependence (craving) with multiple substances of abuse has been attributed to its long-acting effects on DAT and SERT (Rezvani et al., 1995). Individuals with alcohol dependence demonstrate lower baseline availability of SERT in the midbrain compared to controls (Ho et al., 2011), and ibogaine is a noncompetitive inhibitor of SERT (Bulling et al., 2012), shown to increase serotonin in the striatum allegedly through this mechanism (Wei et al., 1998). In rodent models, ibogaine administration increases serotonin and dopamine release in mesolimbic pathways, including the nucleus accumbens, striatum, and the prefrontal cortex (Broderick et al., 1994; Maisonneuve et al., 1992; Wei et al., 1998), which are all prominent regions of therapeutic interest in the treatment of alcohol use disorder (Gilpin and Koob, 2008). The μ opioid receptor has demonstrated a functional role in the rewarding and reinforcing effects of alcohol (Méndez and Morales-Mulia, 2008) as well as craving (Nutt, 2014), and ibogaine binds μ, κ, and δ opioid receptors (Litjens and Brunt, 2016). However, neither ibogaine nor noribogaine activates G-proteins associated with morphine administration, or produces signs and symptoms of opioid intoxication in opioid naïve persons (Antonio et al., 2013). Therefore, it seems that ibogaine is able to produce a neuroadaptive effect on endogenous opioid systems that reverses opioid tolerance and may be implicated broadly in its "addiction-interrupting" effects with other substances such as alcohol. Additionally, ibogaine is an NMDA antagonist, and drugs with this mechanism, such as ketamine, memantine, or NMDA regulators, such as acamprosate have shown promise in reducing symptoms of alcoholism and cravings (Ron and Wang, 2009). Ibogaine has no affinity for GABA receptors and is not thought to be effective in treating acute alcohol withdrawal syndrome.

In addition to its direct anti-addictive neurobiological properties, ibogaine occasions potent dissociative and waking dream-like (oneiric) states that engender transformative psychological insights (Heink et al., 2017; Schenberg et al., 2017). In individuals with substance use disorders, ibogaine stimulates heightened memory retrieval specifically related to drug abuse, the perception of one's own future with or without drug use, and visions which reveal powerful insights into the psychological factors contributing to the addiction, such as emotionally unresolved personal traumas (Schenberg et al., 2017). Several studies have shown that lifetime trauma incidence is a primary predictor of developing an addictive disorder (Garami et al., 2018; Konkolÿ Thege et al., 2017; Mandavia et al., 2016), and during ibogaine treatment, individuals with different forms of substance addictions consistently report therapeutic processing of autobiographical imagery, childhood experiences, and

evocation of repressed traumatic memories (Davis et al., 2017; Schenberg et al., 2017; Winkelman, 2014). One study found that the subjective intensity of altered states of consciousness during the ibogaine experience was associated with an individual's ability to make adaptive changes as well as how "changed" a person felt as a result of treatment (Heink et al., 2017). In a retrospective study, ibogaine treatment responders were more likely to report their ibogaine experience as spiritually meaningful, and that they gained insight into the cause of their addiction compared to non-responders (Davis et al., 2017). In addition, ibogaine administration is associated with improvement in mood and anxiety symptoms (Davis et al., 2017; Mash et al., 2001; Noller et al., 2018), which are precipitants and contributors to alcohol-related problems (Allan et al., 2015). Collectively, ibogaine demonstrates multiple potential pharmacological and psychological properties for treating alcohol use disorders.

1.2 5-MeO-DMT BACKGROUND AND POTENTIAL AS A TREATMENT FOR ALCOHOL USE DISORDER

5-MeO-DMT is a relatively less researched organic short-acting psychoactive indolealkylamine (Szabo et al., 2014; Yu, 2008). 5-MeO-DMT is found naturally in the bufotoxin of the Colorado River toad (Lyttle et al., 1996; Weil and Davis, 1994) and various plant species (Lycaeum, 2001; Ott, 2001; Shulgin and Shulgin, 2002; Smith, 1977), and is also synthetically produced (Hoshino and Shimodaira, 1936). When vaporized, 5-MeO-DMT causes potent visionary and auditory changes as well as alterations in time perception (Ott, 2001; Shulgin and Shulgin, 2002) and is rapidly metabolized, with a half-life of 12–19 min (Acosta-Urquidi, 2015; Shen et al., 2010). Experiential reports suggest that inhalation of vaporized 5-MeO-DMT engenders a potent range of experiences ranging from spiritual ecstasy and enlightenment, to feelings of near-death anxiety and panic (Erowid, 2018). To date, there are no controlled studies on the effects of 5-MeO-DMT in humans.

In a recent epidemiological study of over 500 individuals who utilized different forms of 5-MeO-DMT (i.e., synthetic, bufotoxin, plant sources, snuffs) in uncontrolled settings, many users reported therapeutic effects attributed to their use (Davis et al., 2018a). The majority of participants in the study who endorsed having psychiatric diagnoses indicated that their symptoms improved following 5-MeO-DMT use, including post-traumatic stress disorder (79%), depression (77%), and anxiety (69%). Most respondents reported consuming 5-MeO-DMT infrequently (<once/year), for the purpose of spiritual exploration, and not more than four times in their lifetime. In this study, 5-MeO-DMT reportedly demonstrated a safe profile as evidenced by reports of low intensity of challenging experiences (e.g., fear, anxiety) and low addiction liability (i.e., very low rates of craving, or legal, medical, psychiatric treatment associated with consumption).

In terms of its psychopharmacological properties, 5-MeO-DMT is a structural analog of serotonin and melatonin and has an affinity for the $5HT_{1A}$ and $5HT_{2A}$

pathways with a prominent affinity for $5HT_{1A}$ over $5HT_{2A}$, and also activates $5HT_{3A}$, $5HT_5$, $5HT_6$ and $5HT_7$ receptors (Halberstadt and Nichols, 2010; McBride, 2000), D1, D3, and alpha-2 receptors to a lesser degree (Ray, 2010), and is a ligand for σ_1 receptors (Szabo et al., 2014). 5-MeO-DMT is present endogenously in human blood, urine, and spinal fluid (Barker et al., 2012; Benington et al., 1965; Franzen and Gross, 1965; Guchhait, 1976) and is shown to be neuroprotective (Dakic, 2017), anti-inflammatory (Dakic et al., 2017; Szabo et al., 2014), influence morphogenesis of human brain cells (Dakic et al., 2017; Szabo et al., 2014), modulate immune responses (Dakic et al., 2017), and have anti-depressant properties (Riga et al., 2017). In a human EEG study, both vaporized synthetic 5-MeO-DMT (2–5 mg) and bufotoxin (30–40 mg) produced a temporary reversible reconfiguration of brain network dynamics, suppressed Alpha activity, induced a shift from Alpha to Theta, created hypercoherence in all bands, and increased gamma power. Subjects demonstrated a rapid total return to baseline electrophysiological functioning at approximately 40 min after administration. The observed EEG patterns collectively coincided with subjective reports of peace, calm, and clarity during the resolution phase (Acosta-Urquidi, 2015).

5-MeO-DMT demonstrates potential for treating alcohol use disorders. In a proteomics study, 5-MeO-DMT revealed anti-addictive properties (Dakic et al., 2017) due to its ability to downregulate metabotropic glutamate receptor 5 (Dakic et al., 2017), which is implicated in the rewarding effects of alcohol (Bird et al., 2008). 5-MeO-DMT is a $5HT_{1A}$ and $5HT_{2A}$ agonist, and classic psychedelics with similar serotonergic effects (e.g., LSD, psilocybin) consistently demonstrate therapeutic potential in treating alcohol use disorders (Abuzzahab and Anderson, 1971; Krebs and Johansen, 2012; Nielson et al., 2018). A closely related compound, *N*,*N*-DMT in the form of the Amazonian ayahuasca brew, reduced addictive behaviors in an animal model of alcohol dependence by inhibiting behavioral sensitization to alcohol (Oliveira-Lima et al., 2015) which was theorized to be due to the serotonergic properties of this tryptamine (Shen et al., 2010). In the aforementioned epidemiological investigation of 5-MeO-DMT users, individuals with alcoholism or hazardous drinking (66%, $n = 75$ out of 113) reported improvements in their conditions following 5-MeO-DMT use, suggesting initial evidence of potential as a therapeutic agent in alcohol use disorders.

5-MeO-DMT occasions mystical-type experiences which predict positive outcomes in human studies with other serotonergic hallucinogens in the treatment of addictive disorders (Bogenschutz and Johnson, 2016; de Veen et al., 2017; Loizaga-Velder and Verres, 2014). In review of the effects of classic hallucinogens such as LSD and psilocybin, mystical-type experiences are identified as the strongest mediator of therapeutic efficacy across treatment studies with multiple addictive substances (Bogenschutz and Johnson, 2016). In investigations using psilocybin-assisted treatment for alcohol dependence, the intensity of mystical experience is consistently identified as a key predictor of outcomes (Bogenschutz et al., 2015; Bogenschutz and Johnson, 2016; de Veen et al., 2017). 5-MeO-DMT is shown to reliably occasion mystical-type experiences (Davis et al., 2018a) of similar or greater intensity than psilocybin (Barsuglia et al., 2017). Thus, theoretically, 5-MeO-DMT

may possess similar or potentially greater efficacy in treating alcohol use disorders than psilocybin. These findings are in line with philosophical understandings of the central role and impact of spiritual/mystical experiences on behavior change in Alcoholics Anonymous (AA) (Krentzman et al., 2013; Sandoz, 2014; Tusa and Burgholzer, 2013) and the AA founder Bill Wilson's belief that LSD could help alcoholics find "a power greater than ourselves" (Hill, 2012).

1.3 RATIONALE FOR SEQUENTIAL TREATMENT PROTOCOL AND STUDY

Ibogaine and 5-MeO-DMT independently demonstrate preliminary pre-clinical and observational evidence as potential agents for treating alcohol use disorder, and utilizing both compounds in sequence may have additive effects. Ibogaine is a dissociative psychedelic with oneiric properties that has multiple aforementioned anti-addictive mechanisms, as well as the ability to generate therapeutic psychological insights, suggesting promise in treating alcohol use disorders. There are no published neuroimaging studies to date that have examined the effects of ibogaine in humans. While ibogaine catalyzes close-eyed dream-like visions and insight, it typically does not occasion mystical-type experiences (i.e., transcending time/space, complete ego dissolution) to the extent or type as classic psychedelics, as users typically retain awareness of their identity and surroundings (Davis et al., 2017; Rodger, 2018; Schenberg et al., 2017). Further, ibogaine possesses negligible affinity for $5HT_{2A}$ and $5HT_{1A}$ receptors (González et al., 2018), which are sites commonly attributed to the mysticomimetic and anti-addictive effects of classic hallucinogens (i.e., LSD and psilocybin) in treating alcohol use disorders (Kyzar et al., 2017) and are known mechanisms of action of 5-MeO-DMT (Krebs-Thomson et al., 2006). 5-MeO-DMT has predictable aforementioned short-acting pharmacokinetic properties and does not demonstrate lingering residual effects, unlike other longer-acting $5HT_{2A}$ and $5HT_{1A}$ psychedelics with anti-addictive and anti-depressant properties such as psilocybin and LSD. Therefore, 5-MeO-DMT was implemented in a sequenced psychedelic treatment program with ibogaine because of its ability to occasion therapeutic mystical-type experiences, in addition to possessing anti-addictive and anti-depressant properties in vivo (Dakic et al., 2017) and in epidemiological surveys (Davis et al., 2018a). 5-MeO-DMT similarly lacks documentation of its clinical effects in humans with addiction. Therefore, we documented the clinical effects and pre- and post-treatment changes on cerebral blood flow via single-photon emission computed tomography (SPECT) in an individual with alcohol use disorder who was seeking a combination protocol of ibogaine and 5-MeO-DMT for addiction treatment.

2 CASE REPORT

The patient was a 31-year-old male, right-handed, biracial (Native American, African American) military Air Force veteran who presented for treatment of alcohol use disorder. The patient's alcohol use in the 5 months prior to treatment consisted of

consuming 2 L of hard cider (4.5% alcohol content, 68 ounces = 5–6 drinks), 6–7 days of the week in the evening. Before this period, he had a 2.5-year history of alcohol abuse that included weekend binge drinking (typically a 750 mL bottle of vodka per incident) which led to impulsive behavior, and negative interpersonal consequences such as physical altercations and legal issues. He reported currently drinking in order to "feel stable" and cope with social isolation, homelessness, and poverty. He was diagnosed with post-traumatic stress disorder (PTSD) and alcohol use disorder according to diagnostic and statistical manual 5th edition (DSM-5) criteria through the United States Department of Veteran's Affairs (VA) and received disability funding for PTSD. He reported inability to cut down or stop drinking, and his alcohol use exacerbated his PTSD and interfered with his ability to build his startup business. He noted when attempting to stop drinking for several days, he would experience increased irritability and cravings, although denied the presence of acute withdrawal symptoms (i.e., nausea, vomiting, and sweating).

Current psychiatric symptoms included sub-diagnostic PTSD, and depressive symptoms, including daily and cyclical irritability, depressed mood, and impulsivity and anger exacerbated by interpersonal triggers. He reported feeling "wound up," "unstable," and "overwhelmed," with poor concentration, reduced appetite, initial insomnia, self-doubt, low self-esteem, and social isolation. At baseline, the patient was administered the Beck Depression Inventory-II (BDI-II, Beck et al., 1996), PTSD Checklist for DSM-5 (PCL-5, Weathers et al., 2013b), and the Life Events Checklist for DSM-5 (LEC-5, Weathers et al., 2013a). The patient's BDI-II score was 18, which was indicative of mild depression. PCL-5 score was 30, which fell slightly below the clinical threshold for PTSD screening ($\geq$33), and his symptom endorsement pertained primarily to negative alterations in cognition and mood (criterion D) as well as arousal, hypervigilance, and reactivity (criterion E). LEC-5 was notable for past experience of physical and sexual assault, combat exposure, and causing physical harm to others. He was diagnosed with unspecified mood disorder. These screening measures were not repeated.

His PTSD symptoms began in the military (at age 20) where he had issues with physical altercations with other active duty military personnel and several during which he felt fearful for his life (DSM-5, A1 criteria). During his service, he began to develop nightmares that included people chasing him with guns, or being unable to hurt someone he was attempting to attack in self-defense. He reported a history of developmental trauma, in which his father abandoned the family in early childhood and he was subsequently placed in foster care.

Before ibogaine treatment, he received group therapy in an outpatient program at the local VA hospital for 2 years, as well as weekly psychotherapy for 6 months for alcohol use and PTSD. He reported a personal history of sporadic experimentation with ayahuasca and psilocybin mushrooms during the past 3 years. He noted experiencing improved mood from these psychoactive plant mixtures, but reported that they were ineffective in helping him to quit drinking alcohol. He denied prior medication treatment for his alcohol use.

Remote neuropsychiatric history was significant for childhood attention deficit hyperactivity disorder (ADHD), for which he was prescribed mixed amphetamine

salts. He reported using this prescription as needed one to two times per week starting in high school up until 6 months before the current evaluation (approximately 15 years of use). He discontinued this medication because he felt he was no longer receiving benefit. Medical history was otherwise unremarkable. Family medical history was significant for alcohol abuse (mother and father), polydrug abuse (father), anxiety disorder (mother, father, brother, and sister), and depression (mother).

3 PROCEDURES

3.1 TREATMENT COURSE

The patient was treated in a 4-day program that included administration of ibogaine HCl and 5-MeO-DMT at a treatment facility in Mexico. He was required to refrain from drinking alcohol for 1 week prior to admission and reported he was able to do so, given his high motivation for ibogaine treatment and additional peer support the week prior to treatment. His urine alcohol toxicology results were negative upon arrival. Ibogaine administration took place in an inpatient medical center during the first 2 days of the program, after which he was transferred to a residential setting for the final 2 days. The program included medical screening and monitoring, psychotherapeutic preparation, and post-experience integration counseling. The program utilized the Global Ibogaine Therapy Alliance (GITA) consensus clinical treatment guidelines as part of screening criteria and risk management (Dickinson et al., 2016). Additional descriptions of the treatment program and medical guidelines are presented in Malcolm et al. (2018) and Davis et al. (2017, 2018b).

The patient was administered 1550 mg of ibogaine HCl (17.9 mg/kg, patient weight 86.5 kg) with the first three doses given in 30 min intervals (500, 500, 300 mg) with a fourth dose (250 mg) given 3 h after the prior dose, which was administered in part due to the patient's request. The ibogaine HCl was *Voacanga*-derived and imported from Phytostan Enterprises, Inc., and certified under Good Manufacturing Practice (GMP) guidelines. During treatment, the patient's vital signs, ECG (by telemetry), and mental status were monitored. He was administered 500 mL of intravenous normal saline for hydration, 1 ampule of magnesium sulfate, and ranitidine 50 mg for nausea prior to his first dose of ibogaine HCl. Five clinical staff members were present throughout the course of treatment which included one paramedic, one nurse, and two physicians (internal medicine, and a surgeon/emergency medicine specialist), and a program counselor.

During ibogaine treatment, the patient exhibited ataxia upon attempting to walk to the bathroom at 4.5 h post-initial administration and experienced episodes of vomiting lasting for approximately 20 min at 5 h and at 6 h. He had also experienced several episodes of acute panic at 5 h and was assisted by clinical staff at that time.

During his counseling session (integration) in the morning following treatment, he described contents of the psychedelic/visionary aspects of his experience. He reported experiencing close-eyed visions shortly after the third ibogaine dosage that began with images of floating through the universe and being surrounded by the stars. He began to ask himself questions that were previously transcribed with the

counselor pertaining to his alcohol use and past traumatic events. He noted when he would ask himself or "God" a question, he experienced being visually transported to a new realm. He described these realms similar to levels of a video game, and the symbols and images were not immediately associated with the contents of his questions. However, after being "transported to several levels," he began to see the symbols were showing him the answers to his questions in symbolic form. For example, on one "level," he was visually taken to a scene of "pesky beings that were leeching energy from [his] body," which he later interpreted as, "the spirit of the yeast in the alcohol that was holding onto [him]." He reported that when he became nauseated the, "pesky beings" were telling him not to vomit. When he began to physically vomit, the beings were shouting "No!" and appeared to be leaving his body through the purging. He also described seeing, "a universal cosmic matrix that had a central column of electric light and spiritual beings merging into the light." The "pesky beings" were telling him not to enter the light, but he was given "a pair of rocket boots" by "the creator of the matrix" and merged into the light, which felt healing and empowering to his "true self."

On day 3 of treatment, the patient was administered the short-acting tryptamine, 5-MeO-DMT in the form of inhaled vaporized bufotoxin from the Colorado River toad (50 mg of bufotoxin estimated to contain 5–7 mg of 5-MeO-DMT) (Metzner, 2013; Weil and Davis, 1994). Prior to the 5-MeO-DMT session, he received education and preparation pertaining to the nature of the substance, its origins, possible therapeutic benefits, potential risks, and techniques for navigating transcendental psychedelic states. He also fasted from foods and liquids for 12 h prior to his session (overnight plus morning). He was led in a breathing exercise and guided imagery prior to receiving the compound. For delivery, an Eclipse (brand) handheld essential oil vaporizer was utilized for administration. The toad bufotoxin was heated with a torch lighter in a glass vial to the point of vaporization of all contents. He was instructed to exhale the entire contents of his lungs. As soon as vapors began to emit from the bufotoxin, he was instructed to inhale slowly and consistently filling his lungs to capacity, take a brief final inhale, and hold the full inhalation for a minimum of 10 s. At the end of 10 s, the facilitator guided him to exhale and lay down. Meditative, non-lyrical music was utilized in the background. A medical doctor and a facilitator/guide were present during the entirety of his session.

The patient's 5-MeO-DMT session lasted 45 min with acute effects, and within 60 min from administration he demonstrated a full return to baseline orientation and mental status. During the patient's treatment, after exhalation of the vapors, he initially experienced physical purging through dry heaving that lasted for several minutes. He then laid relatively still in a supine position for the remainder of his experience. He exhibited euphoric mood and expansive affect with the following verbalizations 10 min after administration, "It's just love. Everything. All of it. That is all that exists. Love is it." Upon debriefing from his session several hours afterward, he believed this experience was the single-most peak transformational experience of his life. He reported he lost all sense of his body and surroundings, and was "transformed on a cellular level into infinite energy and pure love," and described, "all of [his] stress and difficulties throughout [his] life felt like they occurred for a meaningful purpose, and the traumas of [his] past were washed over by an infinitely

loving energy." He noted while he was purging, he felt like "suppressed and dark emotional energy was leaving [his] body." He reported in summary, "it was a deeply spiritual and healing experience."

3.2 SPECT PROCEDURES

SPECT examinations were performed in a resting state at baseline at 48 h prior to ibogaine administration and at follow-up 5 days post-ibogaine administration/3 days after 5-MeO-DMT. See Table 1 for a timeline of SPECT imaging and the treatment protocol. The SPECT was performed in the following manner: The patient was placed in a dimly lit, quiet room. The patient remained quiet for several minutes, with eyes open to allow his mental state to equilibrate to the environment. For both resting studies, 99m Tc hexamethylpropylene amine oxime (Ceretec) was dosed by age and weight and injected after the initial equilibration period. A tomographic brain study was performed approximately 30 min later using a high resolution Picker (Phillips) Prism XP 3000 triple-headed gamma camera with fan beam collimators. Data were acquired in 128×128 matrices, yielding 120 images per scan with each image separated by 3 degrees separation spanning 360 degrees. The data were pre-filtered using a low pass filter with a high cutoff. Attenuation correction was performed using a linear method. Coronal, sagittal, and transaxial tomographs were reconstructed with a slice thickness of approximately 9 mm. The transaxial tomographs were parallel to the orbital meatal line. The tomographs were displayed using a standardized linear color scale, rendered in the Odyssey step-20 scale, which scales all voxels to the brain maximum and assigns each a color gradient based upon its percentile of activity. Each color step represents a (not necessarily linear) five-percentile-point change in rCBF.

Table 1 Imaging, Treatment Course, and Follow-up Timeline

Day 0	Pre-treatment baseline SPECT imaging—Los Angeles @ 10:30
Day 1	Treatment day 1
	ECG/medical screening—Mexico
	Psychological preparation orientation
	Ibogaine HCl administration @ 20:00
Day 2	Treatment day 2
	Rest and psychological support
Day 3	Treatment day 3
	5-MeO-DMT administration @ 9:00
	Daylong therapeutic integration
Day 4	Departure and at home integration
Day 5	At home integration
Day 6	Post-treatment follow-up SPECT imaging—Los Angeles @ 10:00 (110 h post-ibogaine administration, 73 h post-5-MeO-DMT administration)
Day 30	Telemedicine follow-up
Day 90	Telemedicine follow-up

The studies were read by visual inspection in all three planes in three-dimensional surface brain maps (looking at the most active 45% of brain activity), and three-dimensional active brain maps (comparing average activity with the most active 15% of brain activity). All of the brain areas were visually rated on a non-linear scale of 0 (normal activity) to 4 (+) increased or 4 (−) decreased activity similar to Raji et al. (2015). The following semi-quantitative rating scheme was used to visually rate rCBF on the step-20 scale using the following formula: Activity rated above the 95th percentile was assigned a score of 4+; 91–95th was scored 3+; 86–90th was scored 2+; 81–85th was scored 1+; 61–80th was scored 0; 56–60th was scored −1; 51–55th was scored −2; 46–50th was scored −3; and 41–45th was scored −4 from Amen et al. (2008). Outside of the cerebellum, 60–80% of the maximum value in the brain was determined to be normal. Only abnormal areas are reported. Abnormalities are reported as *increased* above 80% or *decreased* based below 60%.

Three-dimensional reformats were generated for review based upon Picker Prism Odyssey Rendering Software. Image renderings include a surface view, looking at the top 45% of brain activity, which allows physicians to quickly visualize significant cortical hypoperfusion (Fig. 1), and an internal active view where the most active 15% and 8% of the brain are rendered, allowing physicians to quickly visualize areas of hyperperfusion (Fig. 2). SPECT examinations and clinical readings were performed in Irvine, California at Amen Clinics.

4 RESULTS

4.1 SPECT

4.1.1 Baseline

The patient's baseline pre-treatment resting-state SPECT revealed moderately decreased activity bilaterally of the inferior orbitofrontal cortices and temporal lobes as well as mildly decreased activity bilaterally of the occipital lobes and the medial cerebellum. Decreased internal cerebellar activity and very mild scalloping was noted. There was severely increased activity of the right putamen and moderately increased activity of the posterior cingulate. The findings were deemed suggestive of a past history of potential brain injury because of the pattern of decreased prefrontal and bilateral temporal lobe activity (see Figs. 1 and 2).

4.1.2 Post-treatment

The patient's post-treatment scan was performed 110 h post-ibogaine administration and 73 h post-5-MeO-DMT administration. In comparison to the baseline scan, there was an improvement in the decreased activity in the temporal lobes, which was only mildly decreased. The occipital lobes and internal cerebellar activity were improved. There was continued moderately decreased activity bilaterally of the inferior orbitofrontal cortex. In the active view, the bilateral caudate, left putamen, and right thalamo-limbic pathway were moderately increased, whereas there was a decrease in perfusion in the right putamen.

Results from changes in ratings of the patient's ROI values were subtracted, Time 2 minus Time 1, which yield rating change values and are presented in Table 2. The

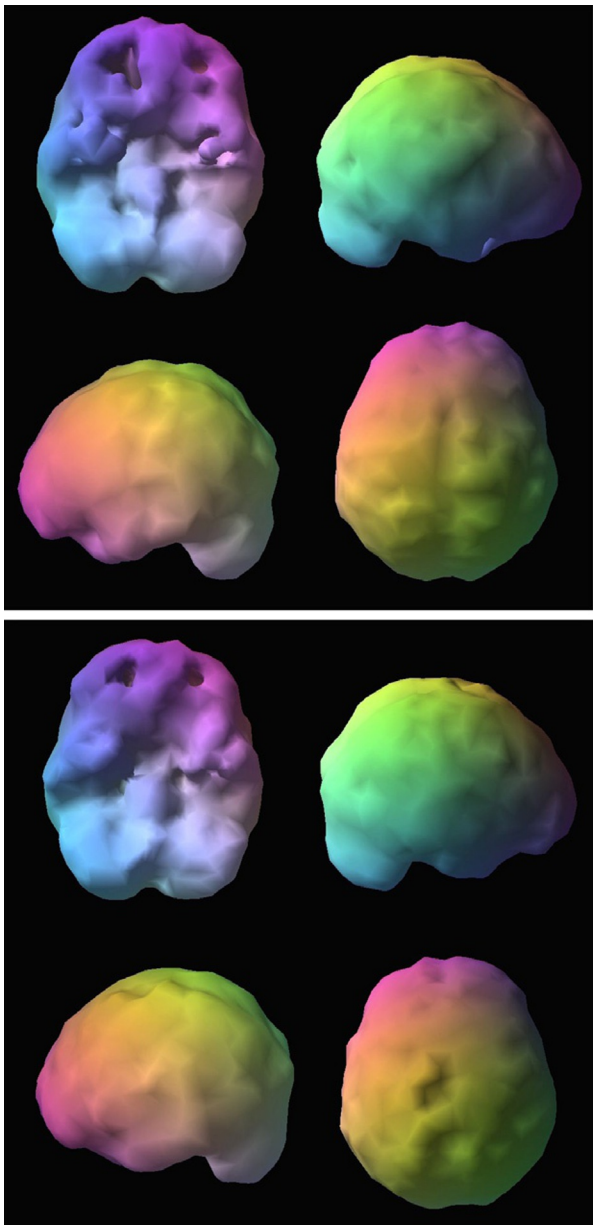


FIG. 1

SPECT surface scans at baseline (top) and 5 days post-treatment (bottom). *Note.* Surface scan threshold set at 55%, looking at top 45% of brain perfusion activity.

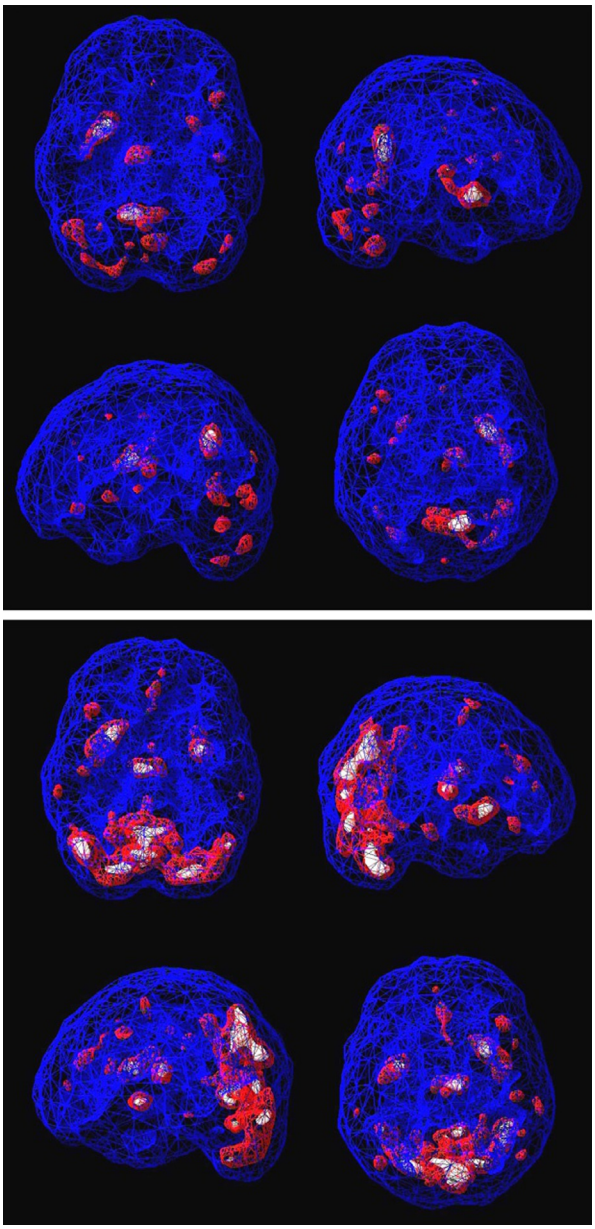
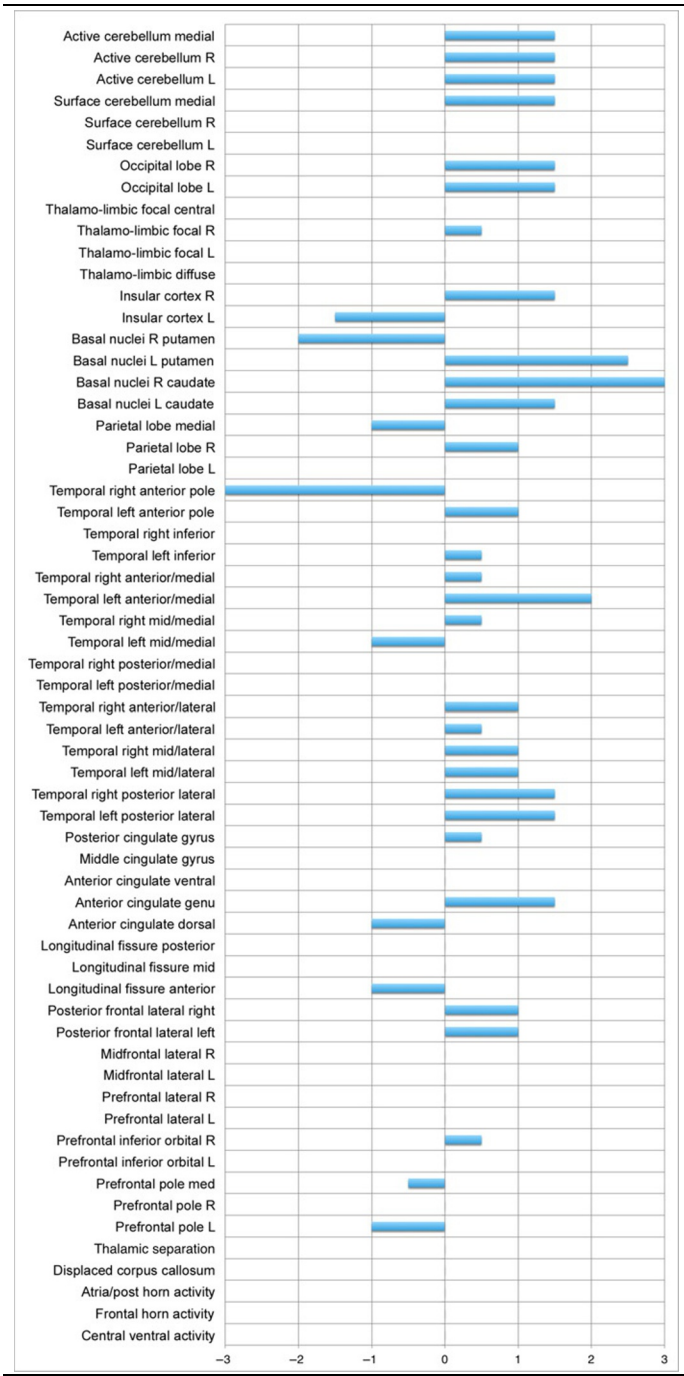


FIG. 2

SPECT active scans at baseline (top) and 5 days post-treatment (bottom). *Note.* Active scans where blue color = 55%, looking at top 45% of brain perfusion, red = top 15%, and white = top 8% of cerebral blood flow in that subject's brain compared to their whole brain perfusion. A healthy control shows full even, symmetrical perfusion with most active area in the cerebellum.

Table 2 Changes in Visual Ratings of Perfusion in Regions of Interest Between Baseline and Posttreatment



most notable increases ($\geq$1.5 rating change) were in the basal nuclei (caudate bilaterally, left putamen), temporal lobes (left anterior, right and left lateral posterior), cerebellum (surface medial, active left, right, and medial), occipital lobe (right, left), insular cortex (right), and anterior cingulate (genu). The most notable decreases (≤ -1.5 rating change) were in the right anterior temporal pole, right putamen, and left insular cortex.

4.2 SUBJECTIVE POST-TREATMENT REPORT

In a clinical interview with the patient at 110 h post-ibogaine administration (before his post-treatment follow-up SPECT), he reported feeling physically and mentally calmer, with improved mental focus/concentration, clarity, mood, and a "comforting absence of thought." He reported feeling no cravings for alcohol. He noted the ibogaine treatment felt like it helped him to work through unresolved feelings toward his estranged father, who unexpectedly happened to call him 48 h after his treatment for the first time in several years. He noted his 5-MeO-DMT experience was beneficial in "bringing in a feeling and perspective of unconditional love" to various traumatic events which occurred during his life, and with helping him to forgive and accept himself for his perceived shortcomings. Additionally, he reported a feeling of "universal oneness that [he] would never forget." At 1-month phone follow-up, the patient reported not having consumed alcohol since his treatment and experiencing minimal cravings. He reported moderate distress associated with instability in his business and lack of personal income. At 3-month follow-up, he reported at approximately 10 weeks post-treatment he had returned to drinking one to two alcoholic beverages (Boochcraft, $\sim$7% alcohol content) per week, which was relatively less compared to his prior baseline daily drinking habits (5–6 drinks per day). He noted an enduring sense of peace, mental clarity, and increased energy and emotional stability that was most notable in the first 3–4 weeks following treatment, and persisted to a somewhat lesser degree at 3 months. He noted feeling surprised by a lasting improved ability to manage and control his anger and respond less reactively in social situations. He also expressed interest in returning to do another ibogaine treatment in the future.

5 DISCUSSION

5.1 REVIEW OF CASE

We presented the case of a 31-year-old individual who sought treatment with ibogaine and 5-MeO-DMT for alcohol use disorder. He also had a prior history of PTSD and demonstrated sub-diagnostic PTSD and depressive symptoms at the time of treatment. His ibogaine experience included meaningful and therapeutic dream-like visions pertaining to his alcohol use and transpersonal/cosmic imagery. His 5-MeO-DMT treatment was associated with self-report of release of negative emotions and transformational insights, and peak transcendental and positive mood

states. Following treatment, he reported acute remission of alcohol use, reduced cravings for alcohol and improvements in cognition, mood, and interpersonal functioning which persisted for greater than 1 month, but diminished to a degree in the interval between 2 and 3 months. Baseline SPECT imaging revealed reduced orbitofrontal, temporal, occipital and cerebellar perfusion which are primary regions of pathological SPECT findings in alcohol abuse (Luo, 2015; Moselhy et al., 2001; Pach et al., 2007). Post-treatment, the patient demonstrated increased perfusion in bilateral caudate nuclei, left putamen as well as in temporal, occipital and cerebellar regions, which are visually prominent on surface scans (Fig. 1, see inferior underside view—anterior/inferior temporal regions) and on internal views (Fig. 2, see basal nuclei, occipital, and cerebellar regions). Overall, the patient demonstrated an aggregate increase in perfusion in multiple regions of interest associated with alcohol addiction in the literature. We present theoretical associations of the neurobiological effects of ibogaine and 5-MeO-DMT with findings in this case, identify potential synergistic effects of these compounds, make recommendations for future investigation, and describe the limitations of this study.

5.2 CASE FINDINGS AND THEORETICAL ASSOCIATIONS WITH IBOGAINE IN TREATING ALCOHOL USE DISORDERS

Based upon the reductions in alcohol use/cravings and changes in brain functioning in this case, and the known neuropharmacological properties of ibogaine, we present several speculative associations relevant for treating alcohol use disorders. As a caveat to interpretation in this case, the patient's follow-up neuroimaging occurred at 3 days after 5-MeO-DMT (approximately 283 half-lives) and 5 days after ibogaine (approximately 3 half-lives), so he would likely still have had noribogaine in his system. Therefore, all connections drawn are highly theoretical and it is not possible to attribute the observed changes to either compound. With these caveats, we tentatively present the patient's neuroimaging findings in tandem with known regions of interest in the literature pertaining to alcohol-related pathology and the known effects of ibogaine.

The patient demonstrated baseline cerebellar hypoperfusion, which is common in alcoholism (Gilman et al., 1990; Harris et al., 1999) and after treatment he exhibited improvement in cerebellar perfusion (see Fig. 2 and Table 2). Alcohol-related cerebellar pathology includes alterations in Purkinje and granule cells (Luo, 2015) and the inferior olivary nucleus (Napper and West, 1995) and these cells in the cerebellum are sensitive to the effects of ibogaine (Litjens and Brunt, 2016; O'Hearn and Molliver, 1997). The stimulation of cerebellar regions by ibogaine in this case could theoretically be due to its effects on prominent receptor sites in the cerebellum including NMDA/glutamate (as an antagonist) (Llansola et al., 2005; Skolnick, 2001), dopamine (via DAT) (Giompres and Delis, 2005; Kim et al., 2009), and σ_1 (Hayashi and Su, 2005) and μ opioid receptors (Polastron et al., 1990; Schadrack et al., 1999). Recent investigations into cerebellar functioning and addiction identify this region as an intermediary between motor behavior and reward processing as well

as motivational and cognitive control processing, which are cognitive functions associated with alcohol addiction (Moulton et al., 2014). Additionally, the cerebellum is implicated in processing drug-induced cue-related memories, and alcoholics demonstrate over-responsive recruitment of the cerebellum during task demands compared to normal subjects (Miquel et al., 2016).

Improving cerebellar perfusion, which occurred in this case, could be hypothesized to have anti-addictive effects via loops with corticostriatal-limbic tracts, notably through dopaminergic and glutamatergic direct projections from the cerebellum to the VTA (Miquel et al., 2016) which are responsible for the persistence of drug-related conditioned memories as well as drug escalation behavior (Everitt, 2014). Miquel et al. (2016) identified several primary reasons why the cerebellum plays a crucial role in addiction neurocircuitry: namely addictive drugs target the primary molecular mechanisms of synaptic plasticity in the cerebellum, lead to drug sensitization in cerebellar-mediated dopaminergic and glutamatergic tracts, the cerebellum is involved in persistent drug-related Pavlovian learning, and structural alterations of the cerebellum represent a possible endophenotype of addiction as individuals with alcoholism and many forms of drug addiction exhibit cerebellar abnormalities (Miquel et al., 2016). Therefore, if ibogaine fosters neuroadaptive cellular changes and unlearning of conditioned drug responses through cerebellar pathways, this molecule may provide insight into the functional role of the cerebellum in treating alcohol addiction. Lastly, μ opioid receptors are highly expressed in the cerebellum (Mrkusich et al., 2004; Polastron et al., 1990) and are functionally associated with alcohol reinforcement mechanisms, and alcohol dependence results in μ opioid receptor polymorphisms (Méndez and Morales-Mulia, 2008). Ibogaine demonstrates affinity for μ opioid receptors; however, its binding affinity is low (10–100 μM) and the precise mechanism of action is unknown (Antonio et al., 2013).

The cerebellum is a frequent region of interest in both therapeutic as well as toxicological investigations into the properties of ibogaine. The motor impairments induced by ibogaine are associated with excitatory activity in the inferior olivary nucleus within the medulla oblongata (O'Hearn and Molliver, 1997). In certain species, ibogaine has shown to be toxic at high dosages to Purkinje cells in the vermis (O'Hearn and Molliver, 1993) as well as simplex lobules of the cerebellum (Molinari et al., 1996) which is hypothesized to be due to glutamate excitotoxicity, yet this has not been found in humans. In contrast, others have claimed that ibogaine is neuroprotective via NDMA antagonism (Leal et al., 2000; Popik et al., 1995) and upregulation of GDNF (He and Ron, 2006), and ibogaine is patented for reducing and preventing excitotoxic damage to cells (Olney, 1989). Thus further investigation of these mixed findings needs to be examined in humans with therapeutic range doses.

In this patient, perfusion in the basal nuclei (caudate/putamen), occipital lobe, and temporal lobes were increased following treatment. The increased blood flow noted in the caudate and putamen in this case may hypothetically correspond with ibogaine's noted effects on μ and κ opioid receptors DAT, SERT, and substance P immunoreactivity (Alburges et al., 2000; Bulling et al., 2012; Wei et al., 1998),

which are densely expressed in these regions and commonly demonstrate hypoperfusion in chronic alcohol use (Suzuki et al., 2010). The development of alcohol craving is hypothesized to be linked to the mesolimbic pathway, including the caudate (Modell and Mountz, 1995). Ibogaine has documented dopaminergic effects on the human caudate (Mash et al., 1995) and the caudate and putamen in an animal model (Ali et al., 1999). The uniform increase in occipital perfusion in this case could be explored as partially related to ibogaine's effect on cholinergic muscarinic receptors, which are represented in high density in occipital V1 and V2 regions (Groleau et al., 2015; Gu, 2003) and are associated with processing of reward and drug cue-triggers (Yalachkov et al., 2015). Lastly, the patient demonstrated an improved pattern of temporal lobe perfusion, which is a primary foci of alcohol-related pathology (Pach et al., 2007) and is associated with alterations in learning/memory and language in alcoholics (Squeglia et al., 2014), and exhibited most dramatically in the neurodegenerative condition of Wernicke–Korsakoff syndrome (Nahum et al., 2015).

Post-treatment scans in this patient revealed increased perfusion in the anterior cingulate and the right insula, coupled with a decrease in left insular perfusion. Perfusion in the genu of the anterior cingulate increased following ibogaine treatment in this case, which is a structure that demonstrates persistent abnormalities in individuals with alcohol use disorder (Volkow et al., 1997) and mood disorders (Drevets et al., 2008). Alterations in glutamatergic processing in the anterior cingulate is associated with reward and alcohol cue processing (Cheng et al., 2018) and self-control (Laukkanen et al., 2015), and ibogaine could have a meaningful effect in regulating glutamate processing in this region as a noncompetitive NMDA antagonist (Leal et al., 2003; Popik et al., 1995). Additionally, functional connectivity in the cingulate is associated with future relapse in alcohol-dependent individuals, therefore improving signaling in this region could serve a preventative function (Zakiniaeiz et al., 2017). The insula is a region activated by environmental cues and drug cravings in multiple addictions (Droutman et al., 2015; Naqvi et al., 2014), and the right insula (as compared to left) plays a more dominant role in interoceptive awareness (Craig, 2009; Gu et al., 2013) and representation of aversive somatic markers which guide risk-taking and decision-making behavior, which are central processes in addiction (Paulus et al., 2003). Individuals with alcohol dependence demonstrate reduced insular volume (Senatorov et al., 2015) and reduced right insular connectivity is associated with disrupted self-awareness and metamemory functioning in alcoholics (Le Berre et al., 2017). The insula has a high density of μ opioid and dopamine receptors (Naqvi and Bechara, 2009) which are receptor sites of known binding affinity for ibogaine and thus may be foci of interest in future examinations of the effects of this compound.

The current case is an example of the frequent comorbidity and interrelatedness of alcohol use disorders and post-traumatic stress that is recurrently described in the literature (Coffey et al., 2010; Flanagan et al., 2016; Mccauley et al., 2012) and ibogaine may have effects in treating post-traumatic stress, thus serving a dual therapeutic function in this population. The patient reported a series of visionary experiences

during ibogaine treatment, some of which included beneficial insights surrounding his alcohol use and childhood trauma as well as metaphysical and transpersonal visions. The patient endorsed therapeutic processing of traumatic material during ibogaine, which he considered as causal factors to his drinking (e.g., "pesky beings," childhood trauma). The visionary elements of his ibogaine treatment were therapeutically meaningful for him, which is consistent with prior studies documenting the importance of the psychedelic content of ibogaine experiences across substance users (Davis et al., 2018b; Schenberg et al., 2017; Winkelman, 2014). One study suggests that ibogaine may facilitate the reintegration of traumatic memories and dissipate addiction-related behavioral patterns through induction of an oneiric and "plastic" brain state, in part, similar to that of REM sleep (Brackenridge, 2010).

Perhaps the most stark pre/post visual contrast on neuroimaging was the increase in the patient's cerebellar functioning after treatment, which may have relevance in the treatment of PTSD. Cerebellar functioning is proving to have a primary role in emotional processes relevant to PTSD including emotional regulation (Turner et al., 2007), processing fear memory traces, translation of emotional states into autonomic and motor responses (Sacchetti et al., 2009), and emotional learning and pain perception (Adamaszek et al., 2017). Ibogaine's effects on cerebellar functioning have been investigated in terms of motor impairments and toxicology (Helsley et al., 1997; Molinari et al., 1996), yet, the ability of ibogaine to stimulate cerebellar activity may be a focus of future therapeutic interest and lend insight to the nature of the therapeutic trauma processing that is commonly reported during ibogaine experiences (Davis et al., 2017; Schenberg et al., 2017).

The patient demonstrated temporary subjective improvements in mood and cognition, which have been documented in observational studies of opioid users who received ibogaine treatment (Davis et al., 2017; Mash et al., 2001). In this case, these changes were noted as helpful in improving his global functioning and ability to have a clinically meaningful period of abstinence from alcohol use. The patient's reported mood improvement following his treatment is consistent with a retrospective study of ibogaine users who reported post-treatment improvements in mood that lasted 1 month or longer (43% of sample), with 10% reporting increases that lasted for more than 5 months (Davis et al., 2017). This patient also identified a greater ability to manage and control his anger, suggesting improvement in emotional regulation. This specific finding is consistent with a retrospective study of opioid users treated with ibogaine who endorsed persistent post-treatment benefits specifically with reduced unhealthy anger, and increased capacity for coping with stress and the ability to tolerate difficult/painful feelings (Davis et al., 2018b). Given the high prevalence of depression (Khalid et al., 2000; Kuria et al., 2012) and anger issues in alcoholic patients (Cougle et al., 2017), the mood-related benefits of ibogaine would be advantageous in treating prevalent comorbidities in alcohol use disorders. In this case, the patient reported a subjective decline after several months in the overall beneficial effects of his treatment. In the literature, multiple versus single ibogaine treatments are associated with better outcomes in substance users (Schenberg et al., 2014). Thus additional administrations of ibogaine in controlled studies may yield more durable results.

The mood and cognitive related benefits of ibogaine may be associated with its effects on SERT, DAT, sigma, NMDA, nAChR, opioid receptors, and GDNF production (Bulling et al., 2012; Glick et al., 1997; He, 2005) which are established mechanisms, sites and properties of interest in the treatment of depression (Ceskova and Silhan, 2018; Daws, 2009; Lin and Tseng, 2015; Lutz and Kieffer, 2013; Sacco et al., 2004) and cognitive enhancement (Bolshakova et al., 2016; Collingridge et al., 2013; Karabacak et al., 2015; Singewald et al., 2015). Ibogaine demonstrates affinity for σ_1 receptors. Activation of σ_1 receptors is shown to ameliorate anxiety in animals (Ji et al., 2016) and is a focus of interest in the treatment of depression and anxiety (Kulkarni and Dhir, 2009). Of note, ibogaine was historically marketed as an anti-depressant in France from 1939 to 1970 (Goutarel et al., 1993) and has been investigated for potential cognitive enhancing effects (Forsyth et al., 2016). The patient's description of improved cognitive clarity and focus following his treatment course is a common report among patients following ibogaine administration (Schenberg et al., 2016, 2017). Ibogaine's affinity for σ_1 receptors could also serve a neuroprotective function (Bowen, 2001), as these receptors are a target of interest in treating cognitive impairment (Niitsu et al., 2012; Van Waarde et al., 2011), are densely expressed in the cerebellum (in particular in Purkinje cells) (Hayashi and Su, 2005), and regulate the release of dopamine (Sershen et al., 1996) which may have cognitive enhancing effects. Thus, in addition to its direct anti-addictive effects, ibogaine exhibits potential for treating co-morbid pathologies associated with alcohol use disorders which were features present in this case including PTSD, depression and cognitive dysfunction.

5.3 CASE FINDINGS AND THEORETICAL ASSOCIATIONS WITH 5-MeO-DMT IN TREATING ALCOHOL USE DISORDERS

As a caveat in interpreting the effects of 5-MeO-DMT in this case, the use of this short-acting tryptamine 2 days after ibogaine and 3 days prior to the follow-up scan is a confounding agent for making definitive interpretive conclusions. The metabolic effects of 5-MeO-DMT on human brain functioning have not been investigated to date. In the only prior published human study ($n = 23$) on the neurophysiological effects of 5-MeO-DMT, on QEEG, vaporization of 5-MeO-DMT produced a temporary reversible reconfiguration with a total return to baseline electrophysiological functioning at approximately 40 min after administration (Acosta-Urquidi, 2015). Despite the relatively rapid excretion and return to baseline observed on QEEG, there may be persisting neuroadaptational effects of 5-MeO-DMT (Dakic et al., 2017) that could impact cerebral blood flow 3 days post-administration, making any inferences speculative. Given these caveats, we present associations between the pharmacology of 5-MeO-DMT, the theoretical potential for treating alcohol disorders, and observed clinical and imaging patterns in this case as an exploratory perspective for future investigations.

5-MeO-DMT exhibits theoretical potential in addiction treatment via neurobiological effects on serotonin and σ_1 receptors, as well as in occasioning mystical experiences and alleviation of traumatic stress which were observed in this case.

5-MeO-DMT demonstrates prominent affinity for multiple serotonin receptors (predominantly $5HT_1$ and $5HT_7$ subtypes) (Ray, 2010) which are highly expressed in many regions relevant to the treatment of alcohol addiction. Chronic alcohol exposure results in reduced turnover of $5HT_{1A}$ metabolism in the striatum, which was an area of increased perfusion in this case following treatment (Belmer et al., 2016; Kelaï et al., 2008). The $5HT_{1A}$ receptor via glutamate and gamma-aminobutyric acid modulation has a modulatory effect on the cingulate cortex and the default mode network (Hahn et al., 2012), which is a primary network influenced by *N*,*N*-DMT and psilocybin, which are both related serotonergic tryptamine psychedelics with established anti-addictive properties (Barrett and Griffiths, 2017; Palhano-Fontes et al., 2015). 5-MeO-DMT demonstrates binding affinity for $5\text{-}HT_7$ receptors, which are expressed with high density in the hypothalamus, thalamus and hippocampus, as well as the dorsal raphe nucleus, amygdaloid body and septal nuclei (Gellynck et al., 2013; Thomas and Hagan, 2004). The $5\text{-}HT_7$ receptor is identified as a potential treatment target for alcohol abuse, as it may mediate alcohol consumption and seeking/craving behavior and is also expressed in the ventral tegmental area (associated with reward and addiction) and the striatum (i.e., caudate putamen) (Hauser et al., 2014).

In this case, 5-MeO-DMT occasioned a mystical experience and facilitated emotional processing of trauma, which is similar to outcomes of observational studies of 5-MeO-DMT users, and studies of the effects of other pharmacologically related psychoactive tryptamines. The patient in this case reported characteristics attributed to mystical experiences including positive/peak mood effects, ego loss, and a spiritual unitive-type experience (universal oneness), and being "washed over by an infinitely loving energy." As previously identified, 5-MeO-DMT occasions mystical experiences with similar or greater intensity and frequency than psilocybin (Barsuglia et al., 2017; Davis et al., 2018a), which predict efficacy in investigations of using psilocybin to treat alcohol use disorders (Bogenschutz et al., 2015). The patient in this case described his 5-MeO-DMT treatment as a peak transformational life experience that felt spiritual in nature and helped him to release long held emotional trauma associated with his alcohol addiction. This patient's report of addiction and trauma-related benefits are reflected in the previously cited epidemiological study of 5-MeO-DMT users which found improvements in 79% of individuals diagnosed with PTSD and 66% of individuals with alcoholism following use. In studies with ayahuasca, which contains *N*,*N*-DMT (and similarly activates σ_1 receptors) individuals are able to process traumatic memories, which is hypothesized to occur in part through the anti-amnesic effects of σ_1 receptor activation (Inserra, 2018) which are densely expressed in the amygdala (Inserra, 2018) and the hippocampus (Tsai et al., 2009). Changes in amygdala and hippocampal perfusion were not observed in this case; however, an increase in perfusion in the right thalamo-limbic region was observed which is an area of hypoperfusion in PTSD and associated with avoidance and fear processing in this condition (Kim et al., 2007).

In addition to trauma resolution, 5-MeO-DMT demonstrates anti-depressant properties which could help treat mood-related comorbidities in alcohol use

disorders (Dongier, 2005). In the aforementioned epidemiology study (Davis et al., 2018a), 77% ($n = 242$ out of 314) of individuals previously diagnosed with depression reported an improvement in their condition following administration of 5-MeO-DMT, which was also observed in this case study. 5-MeO-DMT demonstrates anti-depressant properties in vivo on human cerebral organoid cells which include upregulation of integrins, pronounced actions on synaptic plasticity and cell survival (Dakic et al., 2017) in addition to affinity for serotonin and σ_1 receptors which have known anti-depressant effects (Shen et al., 2010; Szabo et al., 2014). The related tryptamines psilocybin and ayahuasca (containing *N*,*N*-DMT) demonstrate potent and rapid anti-depressant effects in multiple human studies (Carhart-Harris et al., 2016, 2018; Palhano-Fontes et al., 2018). In a SPECT study of depressed patients treated with ayahuasca, the anti-depressant effects corresponded to increased perfusion in the right insula which was similar to perfusion findings in this isolated case (Sanches et al., 2016), is associated with regulation of sympathetic arousal and is a region of interest in the treatment of depression (Tegeler et al., 2014). Therefore, further investigation of the use of 5-MeO-DMT in the treatment of alcohol addiction and PTSD, as well as mood-related comorbidities would be advantageous.

5.4 LIMITATIONS

It is possible that the observed changes on neuroimaging are behaviorally associated with the period of cessation of alcohol use and subjective improvement in mood and cognition; however, given the sample size ($n = 1$) and sequential administration of two psychedelic compounds in the treatment course, it is not feasible to draw any causal or mechanistic conclusions. The sequential administration precludes any definitive interpretations about the neurological or clinical effects of either compound. Broader generalizations cannot be drawn from a single case study, and the patient's history cloud the etiological picture, despite their real-world high frequency of comorbidity in patient populations with alcohol use disorders (McHugo et al., 2017; Neupane et al., 2017). Additionally, the patient was screened at 5 days post-treatment and thus the duration and temporal resolution of these neurological effects are unknown. Lastly, the patient's post-treatment account of his substance use was based upon self-report and he was not monitored under medical care in this time frame; thus his subjective report could be questionable.

5.5 POTENTIAL SYNERGISTIC EFFECTS OF THE SEQUENTIAL PSYCHEDELIC THERAPY PROTOCOL

A number of psychedelic medicines are currently being examined in clinical trials and assessed for safety, mechanisms of action and potential applications in the treatment of addiction (Carhart-Harris and Goodwin, 2017; Sessa and Johnson, 2015). Virtually all scientific investigations of psychedelic compounds have explored the efficacy of single agent compounds as monotherapies in treating alcoholism such

as 3,4-methylenedioxymethamphetamine (MDMA) (Sessa, 2017), psilocybin (de Veen et al., 2017), and LSD (Abuzzahab and Anderson, 1971). Experimental paradigms require controlled investigation of single compounds, yet, there is a vast history of utilizing psychedelics and plant medicines in sequence or in combination in underground settings (Orsolini et al., 2018; Stolaroff, 2004) and global shamanic contexts (Jauregui et al., 2011) in order to potentiate therapeutic effects. Moreover, there is precedence for the therapeutic use of multi-class drug combinations and polypharmacy in psychiatry (Jakovljević, 2013; Shrivastava et al., 2013). In preliminary investigations of the therapeutic effects of psychedelic medicines, the outcomes of single compounds far surpass the efficacy of traditional psychiatric interventions, and thus combining or sequencing/staging psychedelic agents may be advantageous and synergistic in treating chronic, treatment-resistant and epidemic conditions such as alcohol use disorders.

There may be overlapping and synergistic effects in utilizing ibogaine and 5-MeO-DMT in sequential administration. In the experience of team members of this clinic with approximately 1000 patients, we noted pre-treatment with ibogaine potentiated the dosage effects of 5-MeO-DMT. 5-MeO-DMT demonstrates affinity for multiple serotonergic pathways and ibogaine has been shown to inhibit the serotonin transporter, which could produce synergistic and longer lasting effects in sequential administration. Classic psychedelics are known to recruit glutamatergic neurotransmission through the complex interplay between the serotonergic and glutamatergic systems which control neuronal excitability in networks involved in depression and addiction (Guiard and Di Giovanni, 2015; Sampedro et al., 2017). In fact, serotonin and glutamate positively interact with certain brain regions and both have a tendency to become self-reinforcing (Guiard and Di Giovanni, 2015). The increased levels of serotonin due to combined ibogaine and 5-MeO-DMT therapy may lead to an increase in local glutamate release (Guiard and Di Giovanni, 2015). Ibogaine's affinity for the NMDA receptor could function to prime the brain for this complex interaction, possibly by inducing an upregulation of the AMPA receptor (Lodge and Mercier, 2015). When administered in sequence, the glutamatergic, cholinergic and opioidergic affinities of ibogaine are combined with the serotonergic affinities of 5-MeO-DMT targeting the neuromodulatory systems central in alcohol-related neuropathology.

Ibogaine and 5-MeO-DMT demonstrate multiple potential neurotherapeutic properties relevant to the treatment of addiction, including affinity for σ_1 receptors, and the stimulation of GDNF and possibly BDNF. σ_1 and NMDA receptors function together to promote neuroprotection. σ_1 disrupts protein-protein interactions between NMDARs and their associated intracellular signaling machinery, specifically the neuronal nitric oxide synthase (nNOS) (Pabba and Sibille, 2015). This targeted disruption of protein-protein interactions between NMDARs and nNOS results in lower levels of nitric oxide generation, thus having a neuroprotective effect. Both 5-MeO-DMT and ibogaine have an affinity for the σ_1 receptor and could work together to minimize the potential neurotoxic effects of increased glutamate. Ibogaine

stimulates GDNF production (He, 2005) and 5-MeO-DMT as a $5HT_{1A}$ and σ_1 receptor agonist may stimulate production of brain-derived neurotropic factor (BDNF) (Jiang et al., 2016; Salazar-Colocho et al., 2008). GDNF production supports growth and survival of dopaminergic (DA) neurons (Choi-Lundberg et al., 1997) and hippocampal synaptogenesis (Ledda et al., 2007), and σ_1 receptor activation is associated with increases in BDNF which is crucial for neuronal plasticity (Autry and Monteggia, 2012) and regulates alcohol-drinking behaviors (Pandey, 2016). Psilocybin and ketamine (an NMDA receptor antagonist) are shown to upregulate BDNF production (Ly et al., 2018) and have anti-addictive effects in alcohol dependence (McAndrew et al., 2017; Nielson et al., 2018). 5-MeO-DMT and ibogaine may have similar potential given their respective pharmacological profiles. The aggregate neuroprotective properties of both ibogaine and 5-MeO-DMT could have adaptive effects on recovery from alcohol addiction and alcohol-related neuropathology. This could explain how previous treatments with ayahuasca had no effect on the patient's alcohol abuse, yet the combined therapy provided a lengthy abstinence period with improvements in mood.

In terms of potential risks, the bufotoxin which contains 5-MeO-DMT after combustion/vaporization may contain some trace amounts of bufotenine (Weil and Davis, 1994) which could add cardiac burden on top of the significant cardiac risks associated with ibogaine. Thus, additional analysis of the contents of vaporized bufotoxin needs to be conducted to establish or rule out the presence of this alternate tryptamine in vaporized contents. Combination psychedelic therapy requires that clinicians exercise extreme caution during the administration and interpretation of the necessary cardiac, psychiatric and general health screening protocol as well as during the treatment itself. In light of the initial reports of therapeutic effects of these compounds and the current global disease burden of alcohol-related health issues and morbidity, future observational investigation is necessary in countries where these compounds are most available and accessible for research.

6 CONCLUSION

Ibogaine and 5-MeO-DMT demonstrate initial behavioral and pharmacological evidence as potential treatments for alcohol use disorder. SPECT imaging revealed improvements in multiple relevant brain regions associated with substance addiction in a patient with alcohol use disorder. Through visionary/transcendental mystical-type experiences, the patient processed psychological content associated with his trauma and addiction history. These findings could serve to advance future investigations and controlled human neuroimaging studies. Future studies should examine the neurological effects of both compounds independently in larger samples, document the in vivo effects during treatment, and correlate outcomes with phenomenology of psychedelic states. In this case and the literature, both compounds also present therapeutic potential in the treatment of post-traumatic stress. Given the comorbidity and

global disease burden of PTSD and alcoholism, additional research is necessary and timely. Both 5-MeO-DMT and ibogaine are natural plant-based substances that possess multiple therapeutic properties, however, remain scheduled in the most strict drug classifications in the United States and Europe with substances such as heroin and bath salts, making research highly restrictive, limited and cost prohibitive.

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