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Psychedelic Therapy: A Primer for Primary Care Clinicians—Ibogaine

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Background: Ibogaine is a plant-derived alkaloid that has been used for thousands of years in rites of passage and spiritual ceremonies in West-Central Africa. In the West, it has primarily been used and studied for its anti-addictive properties and more recently for other neuropsychiatric indications, including post-traumatic stress disorder, depression, anxiety, and traumatic brain injury.

Areas of Uncertainty: Ibogaine requires careful patient screening and monitoring because of significant safety issues. There is potential for cardiotoxicity (prolonged QT interval); without rigorous screening, fatal arrhythmias may occur. However, preliminary research suggests that co-administration of ibogaine with magnesium may mitigate cardiotoxicity. Additionally, ibogaine may have dangerous interactions with opiates, so patients who receive ibogaine treatment for opioid use disorder must withdraw from long-acting opioids. Other potential concerning effects of ibogaine include rare incidences of mania or psychosis. Anticipated transient effects during ibogaine treatment can include ataxia, tremors, and gastrointestinal symptoms.

Therapeutic Advances: Robust effects after a single treatment with ibogaine have been reported. In open-label and randomized controlled trials (RCTs), ibogaine reduces heroin and opioid cravings by upwards of 50%, up to 24 weeks after the treatment. An observational study of 30 Special Operations Forces veterans with mild traumatic brain injury reported that 86% were in remission from post-traumatic stress disorder, 83% from depression, and 83% from anxiety, one month after a single-dose ibogaine treatment.

Limitations: Although there are several observational and open-label studies, there is only a single double-blind, placebo-controlled RCT on ibogaine. More RCTs with large sample sizes must be conducted to support ibogaine's safety and efficacy.

Conclusions: Given the promising preliminary findings, ibogaine could potentially fill a much-needed gap in treatments for challenging conditions, including opioid dependence. Ibogaine's remarkable effects in traditionally treatment-resistant, combat-exposed individuals hints at its potential in broader populations with physical and psychological trauma.

Keywords: ibogaine, psychedelics, psychiatry, opioid use disorder, cocaine use disorder, addiction, PTSD, veterans

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CLINICAL CASE

A 56-year-old Navy Seal Veteran Explosives Ordnance Disposal specialist with multiple mild traumatic brain injuries (TBI) from combat and blasts, and multiple physical injuries including fractured thoracic vertebrae with an intact spinal cord presented for treatment. He was honorably discharged after 25 years of service and 9 combat tours in Iraq and Afghanistan. He was diagnosed with posttraumatic stress disorder (PTSD), depression, and polysubstance abuse including alcohol, Vicodin, and Adderall. He suffers from physical pain, headaches, and poor sleep. He is separated from his wife of 24 years and has 2 sons, ages 19 and 23 years, from whom he is estranged. Family relationships have deteriorated because of his anger. He has participated in residential treatment for PTSD and substance use disorder 3 times. He was unable to tolerate cognitive processing therapy or exposure therapy for PTSD. He has made 5 suicide attempts. He has not been able to stop abusing substances, self-medicating unmanaged symptoms. He is taking Prazosin (20 mg every night and 5 mg every morning) to help with nightmares and hyperarousal. He has tried several antidepressants without good effect, including 80 mg of Prozac, 250 mg of Zoloft, 30 mg of Lexapro, and 40 mg of Viibryd. He was able to tolerate each medication only up to 3 months before discontinuation because of lack of efficacy and intolerable side effects at their terminal doses. He admits also that he has not been compliant with medications. He is unable to work, is socially isolated with only sporadic contact with former Navy SEAL teammates despite their attempts to support him, and is at risk of homelessness. He continues to struggle with significant suicidal ideation.

BACKGROUND

History

Ibogaine is an oneirogen—from the Greek words óneiros ("dream") and gen ("to create")—alkaloid typically derived from the root bark of the *Tabernanthe iboga* or the *Voacanga africana* plants.[2,4] The root bark of the iboga tree, which is native to the west coast of central Africa, has a long history of use in spiritual, medicinal, and rite of passage ceremonies in the Bwiti spiritual tradition of Gabon and Cameroon.[5] The first documented use of iboga in the West was by French explorers in the late 1800s. In the mid-20th century, it was used in France as an antidepressant and stimulant called Lambarène before becoming illegal there.[5] During this time, ibogaine was also gaining attention for its potential to treat addictions.[2,6,7]

Chemistry and mechanism of action

Ibogaine's chemical structure consists of a complex tricyclic indole molecule with an isoquinuclidine moiety. The molecule contains a nitrogen atom that is able to form hydrogen bonds and act as a proton acceptor, contributing to its ability to interact with various neurotransmitter receptors in the brain.[8]

Ibogaine is metabolized through O-demethylation by cytochrome CYP2D6 enzymes in the gut wall and liver.[9–11] This O-demethylation produces ibogaine's primary metabolite, noribogaine. Although ibogaine's plasma half-life is 4–7 hours, noribogaine's is as long as 28–49 hours.[3,12] Noribogaine is subsequently converted to noribogaine glucuronides.[12] In rats, 30%–40% of ibogaine is detected unchanged in urine and feces 24 hours after administration.[13] The large amount of unmetabolized ibogaine indicates that it is slowly released. This may be attributed to its storage in fatty tissue, which results from ibogaine's lipophilicity.[14,15]

Unlike LSD, *N*,*N*-dimethyltryptamine (DMT), and psilocybin, ibogaine is not a classical psychedelic, so the 5-HT_{2A} receptor does not play a significant role in its mechanism of action. Ibogaine has high affinity for κ-opioid, μ-opioid, *N*-methyl-D-aspartate (NMDA), and sigma-2 receptors, and it also inhibits voltage-gated ion channels.[6,7,16–20] Sigma receptors are a hypothesized active site for other neuropsychiatric agents, including fluvoxamine[21,22] and DMT (see the "DMT and Ayahuasca" chapter of this special edition). Ibogaine's NMDA antagonism and κ-opioid agonism may mediate its efficacy for treating substance use disorder and withdrawal.[6,23,24] NMDA binds glutamate, which plays a crucial role in the expression of addiction-related behaviors.[25,26] Additionally, in animal models, κ-opioid receptors play a role in stress-induced reinstatement of drug-seeking behaviors.[27] Ibogaine is also thought to have an effect on the expression of various neurotrophic factors (NFs) including brain-derived neurotrophic factor and glial-derived neurotrophic factor, which may further contribute to the enduring anti-addictive and antidepressant properties of ibogaine.[17,28] Additionally, ibogaine has been found to have anti-inflammatory and antioxidant effects.[29]

PTSD in veterans

Ibogaine shows promise for treating PTSD in veterans. The intensity of combat deployments, exposure to

repeated blasts, exposure to repeated traumatic events, and high risk of injury all contribute to a complex of diagnoses with overlapping symptoms that can be refractory to treatment.[30] Treatment resistance, stigma related to seeking help within this population,[31] and dropout rates as high as 39% with conventional exposure-based treatments[32] can contribute to the development of substance use disorders, which arise from a desire to self-medicate, and suicidal ideation, further complicating the symptom presentation and treatment efficacy. Veteran suicide rates are approximately 1.5 times the rate of non-veterans, with up to 30% of suicides related to substance use.[33]

AREAS OF UNCERTAINTY

Ibogaine carries a much higher risk of fatality than classical psychedelics; a total of 33 ibogaine-related deaths have been publicly reported.[6,7,34,35] The majority of the health and safety risks of ibogaine can be attributed to its cardiotoxicity (for an extensive review, see Ref. 3). Ibogaine may prolong the QT interval of the heart and subsequently induce life-threatening Torsades de Pointes arrhythmia.[20,34,36–38] The underlying mechanism may be ibogaine's inhibition of human ether-à-go-go Related Gene (hERG) potassium channels, which play a crucial role in mediating the repolarization of the cardiac action potential.[39,40] Lengthening the action potential in ventricular cells subsequently extends the QT interval.[41,42] In general, blockage of hERG channels is a primary contributor to drug-induced QT interval prolongation.[3]

Prolonged baseline QT interval, which can be induced by common medications such as antibiotics and antidepressants,[43] and hERG mutations associated with long-QT syndrome[44] are therefore risk factors for consuming ibogaine. Other preexisting cardiovascular conditions may heighten the risk of fatality. In a review of 19 fatalities associated with ibogaine use, 6 of the cases had preexisting heart conditions, such as coronary artery sclerosis, hypertension, myocardial infarct, cardiac hypertrophy, and dilated cardiomyopathy.[45] However, another review identified eight cases, including one fatality, in which cardiac abnormalities such as ventricular tachyarrhythmias and prolonged QT intervals occurred during ibogaine treatment, despite no preexisting cardiovascular conditions or family history.[6]

However, a recent observational study demonstrated that coadministration of magnesium with ibogaine may reduce the risk of cardiotoxicity.[46] Here, 30 Special Operations Forces veterans (SFVs) with mild traumatic brain injury sought out ibogaine therapy at a clinic in Mexico for various functional limitations and psychiatric symptoms. There were no instances of clinically meaningful QT prolongation, bradycardia (slow heart rate), tachycardia (fast heart rate), or hemodynamic instability. Additionally, no serious treatment-emergent adverse effects were reported. Magnesium depletion causes mitochondria in the heart to swell because of sodium influx and potassium efflux, which leads to the death of myocardial fibres.[47] Therefore, magnesium supplementation in the past has been shown to reduce the QT interval.[48]

Fatalities have also happened when ibogaine users were concurrently addicted to multiple drugs, such as cocaine, alcohol, and methamphetamine, while also abusing heroin, for which they were seeking treatment.[45] Ibogaine can potentiate the analgesic effects of opioids, which increases the risk of overdose.[49] Additionally, some opioids such as methadone inhibit CYP2D6, the enzyme that metabolizes ibogaine.[50] (Thus, independently of substance use disorders, poor inhibition of CYP2D6 may also be a risk factor for ibogaine treatment.) Therefore, appropriate precautions must be taken to mitigate the risk of fatality during ibogaine treatment for opiate use disorder. Certain opioids that are used to commonly facilitate withdrawal from heroin are long-acting; for instance, methadone can have a half-life as long as 46 hours.[51] It is crucial to ensure that these long-acting opioids are no longer present in the plasma before a patient begins ibogaine treatment, so clinicians recommend switching to short-acting opioids up to two weeks in advance.[49,52] Clinicians advise against tapering other medications, such as benzodiazepines.[49] (It is important to note that there are currently no FDA-approved guidelines for the screening, administration, and monitoring of ibogaine treatment.)

Although there was one fatality in an FDA-approved clinical trial in the mid-1990s, most open-label trials, RCTs, and other studies conducted on humans since then have not reported any serious adverse events, let alone fatalities.[1,8,9,11,12,53–55] One observational study published in 2017 reported one fatality among 15 participants, which was ruled to be the result of a breach in the treatment provider's duty of care.[29] When ibogaine providers diligently follow health and safety protocols, the likelihood of fatality seems to be low.

Even with proper medical care, however, ibogaine does cause transient ataxia and tremors. In one study on ibogaine for treating opioid use disorder, ataxia was observed in all 14 participants; however, the ataxia fully subsided within 24 hours for all participants.[56] Conditions that are associated with motor impairments, such as Parkinson's disease or multiple

sclerosis, may be contraindications for ibogaine treatment, although this has yet to be investigated in a study. Other potential adverse effects include psychosis; one review reported 3 cases of mania after ibogaine use, but it is important to note that they all occurred in unregulated settings, where providers may not have been following established protocols.[57]

There has been mixed evidence of neurotoxicity in animal and human research on ibogaine.[6] Initial research suggested that ibogaine, by stimulating the inferior olivary nucleus in the medulla oblongata,[58] causes Purkinje cells in the rat cerebellum to degenerate,[59] perhaps explaining long-term motor deficits in these rats. However, the dose used in this study (100–300 mg/kg) was much higher than the typical therapeutic dose of ibogaine (6–30 mg/kg).[20] A lower dose of 40 mg/kg did not cause Purkinje cells to degenerate.[60] In humans, there are no records of cerebellar or Purkinje cell damage after ibogaine use, even among fatalities.[61]

In efforts to improve the toxicity of ibogaine, use has been made of alternatives like noribogaine, a metabolite of ibogaine and the synthetic compounds 18-MC and Tabernanthalog. None of these alternatives are psychoactive. Noribogaine is unlikely to be less cardiotoxic than ibogaine, given that fatalities tend to occur 24–76 hours after the consumption of ibogaine and the half-life of noribogaine is on a similar timescale.[3,12] Preliminary evidence shows that 18-MC does not slow down heart rate, induce tremors, or damage the cerebellum, even at high doses, in rats.[62] However, more research is needed. In rodent studies, Tabernanthalog has exhibited anti-addictive and antidepressant effects and neuroplastic changes, and it seems to have lower potential for cardiotoxicity than ibogaine because it is 100-fold less potent at inhibiting hERG channels.[63,64]

THERAPEUTIC ADVANCES

Most of the clinical research on ibogaine to date has focused on its anti-addictive properties, which have proven useful for treating opioid use disorder (OUD) and cocaine use disorder. (Abuse of ibogaine itself is not a concern.[3]) Animal studies suggest that ibogaine significantly reduces the severity of withdrawal symptoms from opioids and decreases opioid and cocaine self-administration.[17,18]

In humans, there has been one double-blind RCT (Table 1) and at least six observational studies that reported changes in OUD or cocaine use disorder symptoms from ibogaine treatment, and a number of retrospective surveys and case reports (see Ref. 65 for a systematic review). The first observational study examined 27 opioid- and/or cocaine-dependent participants in an ibogaine treatment clinic in St. Kitts and found that ibogaine significantly reduced opioid cravings. Thirty six hours after treatment, desire and intention to use opioids decreased by 53.1% and 51.8%, respectively, as measured by the Heroin Craving Questionnaire (HCQ-29).[53] However, there was no significant effect of ibogaine on desire or intention to use cocaine, as determined by the Cocaine Craving Questionnaire (CCQ-29). An observational case series of 191 participants in the same clinic determined that ibogaine significantly diminished multiple dimensions of heroin craving, as measured by the HCQ-29 scale. In particular, one month after treatment, desire or intention to use opioids decreased by 50.2%.[54] Unlike in the previous, smaller study, ibogaine brought about a significant, 39.6% reduction CCQ-29 ratings of desire or intent to use cocaine. The only RCT to date, in which 10 participants received the ibogaine treatment and 10 others were assigned placebo, demonstrated a significant 64.9% reduction in cocaine cravings 24 weeks after the treatment, according to ratings on

Table 1. Contemporary (21st-century) clinical trials on ibogaine.

Study	Type	Dosing	Sample	Findings
1	Double-blind, placebo-controlled RCT	1800 mg of ibogaine (dried extract)	20 people with cocaine dependence	Significant reduction in cocaine cravings between placebo and ibogaine group at 72 hours (MD in MCCS scores: −5.6) and at 24 weeks (MD in MCCS scores: −4.1)

Note that this does not include observational studies. Refs. 9 and 53 seem to be observational studies, even though they do not explicitly label themselves that way.
MD, mean difference; MCCS, Minnesota cocaine craving scale.

the Minnesota Cocaine Craving Scale (MCCS).[1] In other observational studies, ibogaine not only reduced cravings but also caused people to abstain from opiates. One such study on 14 opiate addicts found that all but 2 participants (85.7%) tested negative for opioids at a 6-month follow-up.[29] In another study on 30 participants who received ibogaine treatment at a different site, 50% were abstinent from heroin at a one-month follow-up.[52]

The observational studies suggest that ibogaine is potentially far superior to the available treatments for OUD. In a systematic review of buprenorphine maintenance therapy, which is one of the preferred treatments for OUD in the United States, only 18% of participants across studies were abstinent after one month, and relapse rates exceeded 50% in all studies.[66] Another systematic review of tapered methadone treatment revealed that only 25% of participants on average abstain from opiates at a mean follow-up time of 1.5 months.[67]

Ibogaine is also highly effective for managing opioid withdrawal symptoms. One observational study on 50 OUD patients reported that 78% of participants did not exhibit objective signs of opioid withdrawal 48 hours after ibogaine treatment.[68] In other observational studies, significant reductions in self-reported withdrawal symptoms ranged from 54.8% to ~66%, up to nine days after the ibogaine treatment.[9,29,52,68]

One RCT in 27 participants investigated noribogaine, ibogaine's primary metabolite, which, as stated above, is not psychoactive.[8] The primary aim of the RCT was to establish the safety and tolerability of noribogaine treatment. Noribogaine did not result in significant improvements in opioid withdrawal symptoms and cravings.

Ibogaine may also be effective for treating PTSD and other associated conditions, such as depression and alcohol use disorder.[69–71] Robust findings have been reported in observational studies of SFVs with combat-related PTSD symptoms and symptoms of traumatic brain injury, including subjective cognitive complaints. A retrospective survey of 65 SFVs who received combined ibogaine and 5-MeO-DMT therapy (each drug was administered once, in two sessions separated by two days) at a psychedelic clinic in Mexico found that the treatment significantly decreased symptoms of PTSD ($d = 3.6$), depression ($d = 3.7$), and cognitive impairment ($d = 2.8$).[71] Ibogaine is also associated with significant decreases in suicidal ideation ($d = 1.9$). This result is especially important given that suicidality is significantly higher in veterans than in the general population.[33, p. 202] However, because the survey by Köck et al[65] is purely retrospective, participants may have overestimated their symptoms before receiving the treatment. A subsequent observational study of 86 SFVs at the same clinic, which conducted both pretreatment and posttreatment measurements, showed that the same combined ibogaine + 5-MeO-DMT treatment significantly reduced self-reported PTSD ($d = 0.414$) and depression symptoms ($d = 0.275$).[69] In the same study, a subgroup of 45 participants initially met criteria for risky alcohol use. One month after the combined treatment, 24% were abstinent, and 33% became nonrisky drinkers; after 6 months, 16% were abstinent, and 31% were nonrisky drinkers.[70] Finally, the most recent observational study of 30 SFVs, which was discussed above, coadministered ibogaine with magnesium to reduce cardiotoxicity.[46] Immediately after treatment, total scores on the World Health Organization Disability Assessment Schedule 2.0 (WHODAS-2.0) decreased significantly by 10.3 points ($d = 0.74$, $P < 0.001$). That is, participants improved from mild-to-moderate disability to borderline no-to-mild disability. One month after treatment, participants experienced a further mean decline of 14.8 points in WHODAS-2.0 scores, such that most participants had no disability. Significant decreases in ratings of PTSD, depression, and anxiety were also reported, both immediately and 1 month after treatment, with $d > 2$ in all cases. Remarkably, at 1 month, 86% of participants were in remission from PTSD (total Clinician-Administered PTSD Scale-5 [CAPS-5] score <12), 83% in remission from depression (total Montgomery-Åsberg Depression Rating Scale [MADRS] score <8), and 83% in remission from anxiety (total Hamilton-Anxiety Rating Scale [HAM-A] score <8).

CONCLUSIONS

Originating from West Central Africa as a sacrament for spiritual rituals and rites of passage, ibogaine has gained appreciation in the West as a powerful antidote for opiate addiction and, more recently, TBI and PTSD. Observational studies have shown that ibogaine is promising for treating these conditions. However, double-blind, placebo-controlled RCTs with large sample sizes have yet to be conducted. Compared even to other psychedelics, research on ibogaine is still in its infancy. Although ibogaine initially raised concerns because of fatalities arising from cardiotoxicity and interactions with opiates, recent clinical research suggests that fatalities can be avoided with careful screening and monitoring of participants. That being said, formal clinical practices should be developed to further improve patient safety.[65] These should include guidance for proper and thorough patient screening,

management of drug interactions, appropriate monitoring throughout treatment, dosing, caution regarding potential co-administrations and co-therapies, and ibogaine supply and purity oversight.[2,34]

We conclude by noting that the recreational use of iboga has fueled rampant trafficking of the iboga root,[72] and Western medicalization of iboga may lead to further endangerment of the plant and appropriation of African cultural practices. The Gabonese people have made efforts to address these concerns through the adoption of the Nagoya Protocol, an international treaty implemented in 2014.[73] The intention of this protocol is to promote sustainable growth of iboga and harvesting practices in which funding flows back to the communities that produce this valuable resource.[73,74] At this time, however, participation in this treaty is voluntary. Current laws around psychedelic research and use have the potential to impact traditional uses of psychedelic medicines in unintended ways. Work led by indigenous communities is currently underway to develop ethical practices to respect and include indigenous traditions and communities, acknowledge traditional practices, and ensure ethical and responsible resource access and management.[75]

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