Journal of Psychoactive Drugs

ISSN: 0279-1072 (Print) 2159-9777 (Online) Journal homepage: https://www.tandfonline.com/loi/ujpd20

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To cite this article: Benjamin J. Malcolm, Martin Polanco & Joseph P. Barsuglia (2018) Changes in Withdrawal and Craving Scores in Participants Undergoing Opioid Detoxification Utilizing Ibogaine, Journal of Psychoactive Drugs, 50:3, 256-265, DOI: 10.1080/02791072.2018.1447175

To link to this article: https://doi.org/10.1080/02791072.2018.1447175

JOURNAL OF PSYCHOACTIVE DRUGS
2018, VOL. 50, NO. 3, 256–265
https://doi.org/10.1080/02791072.2018.1447175

Changes in Withdrawal and Craving Scores in Participants Undergoing Opioid Detoxification Utilizing Ibogaine

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ABSTRACT

Opioid use disorder (OUD) is currently an epidemic in the United States (US) and ibogaine is reported to have the ability to interrupt opioid addiction by simultaneously mitigating withdrawal and craving symptoms. This study examined opioid withdrawal and drug craving scores in 50 participants with OUD undergoing a week-long detoxification treatment protocol with ibogaine. The Addiction Severity Index (ASI) was used for baseline characterization of participants' OUD. Clinical Opioid Withdrawal Scale (COWS), Subjective Opioid Withdrawal Scale (SOWS), and Brief Substance Craving Scale (BSCS) scores were collected at 48 and 24 hours prior to ibogaine administration, as well as 24 and 48 hours after ibogaine administration. At 48 hours following ibogaine administration, withdrawal and craving scores were significantly lowered in comparison to baseline: 78% of patients did not exhibit objective clinical signs of opioid withdrawal, 79% reported minimal cravings for opioids, and 68% reported subjective withdrawal symptoms in the mild range. Ibogaine appears to facilitate opioid detoxification by reducing opioid withdrawal and craving in participants with OUD. These results warrant further research using rigorous controlled trials.

ARTICLE HISTORY
Received 11 August 2017
Accepted 20 January 2018

KEYWORDS
Addiction; iboga; ibogaine; opiate; opioid; substance

Introduction

Opioid use disorder (OUD) involving prescription and non-prescription opioids is currently epidemic in the United States (US) (Han et al. 2015). An average of 91 Americans die each day from opioid overdose and an estimated 2.5 million are addicted to opioids (CDC 2016; Quality 2015). Prescription opioids have been postulated to be a gateway to heroin use, as 79.5% of new heroin users had prior exposure to prescription opioids (Muhuri et al. 2013). Due to physical dependence produced by chronic opioid administration, opioid agonists and partial agonists such as methadone and buprenorphine are recommended as management options for opioid withdrawal (Dunlap and Cifu 2016).

While buprenorphine can increase retention rates in treatment programs compared to placebo, only high-dose buprenorphine (>16 mg/day) has been shown to decrease illicit opioid use, and buprenorphine has abuse and addiction potential itself (Jones et al. 2015; Mattick et al. 2014). Methadone has been shown to be more effective than buprenorphine in retaining patients in treatment programs (Mattick et al. 2014). However, it is no more effective in suppressing illicit opioid use and is limited by nonlinear pharmacokinetics, drug interactions, QTc prolongation, and risk of death (Mattick et al. 2014). Additionally, these treatment options leave patients dependent on opioids, which may not be in alignment with their treatment goals; they carry ongoing risks associated with opioid therapy, and may be limited in availability due to prescribing or dispensing requirements or restrictions. Opioid withdrawal may be managed with non-opioid supportive therapies or by tapering opioids, although success rates are low, with 91% of patients relapsing with this strategy due to continued craving despite successful detoxification (Smyth et al. 2010). Given epidemic morbidity and mortality as well as limitations of current treatments, it is clear that additional strategies for the management of withdrawal in OUD are needed.

Ibogaine, a psychoactive and psychedelic alkaloid found in the root bark of *Tabernanthe iboga* or bark of *Voacanga africana*, has a complex pharmacokinetic and pharmacodynamic profile that is not completely understood (Jenks 2002). Ibogaine exhibits significant affinity for targets in many neurotransmitter systems. Affinities and K_i values less than 10 μM were found at κ opioid receptors, N-methyl-d-aspartate (NMDA) glutamatergic receptors, dopamine and serotonin reuptake pumps, σ-1 and σ-2 receptors, as well as nicotinic

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Table 1. Studies evaluating opiate withdrawal in patients undergoing ibogaine detoxification.

Study	Subjects and Setting	Ibogaine Dose	Withdrawal Outcomes
Mash et al. 2001	32 opioid-dependent Treated in St. Kitts, West Indies	800 mg (~10 mg/kg)	↓ OOWS and OP-SCL scores 12, 24, and 36 hours post-ibogaine treatment ($p < 0.05$)
Brown and Alper 2017	30 opioid-dependent Treated in Baja, Mexico	1,540 ± 920 mg	SOWS scores ↓ from 31.0 ± 11.6 pre-ibogaine to 14.0 ± 9.8 at 76.5 ± 30 hours post-ibogaine ($p < 0.001$)
Noller, Frampton, and Yazar-Klonsinki 2017	14 opioid-dependent Treated in New Zealand	31.4 ± 7.6 mg/kg	SOWS scores ↓ from 25.21 ± 12.57 pre-ibogaine to 14.21 ± 14.08 at 12–24 hours post-ibogaine ($p = 0.015$)

OOWS = objective opioid withdrawal scale; OP-SCL = Opiate-Symptom Checklist; SOWS = subjective opioid withdrawal scale.

receptors (Litjens and Brunt 2016). Ibogaine is converted to noribogaine by the cytochrome P450 isoenzyme CYP2D6. There is significant heterogeneity within humans regarding metabolic capacity of CYP2D6. There are also drugs that inhibit the enzyme's metabolic capacity, creating potentially significant drug-drug interactions. One study found a 26-fold increase in peak plasma concentrations of ibogaine and a 66-fold increase in the area under the curve (AUC) or total drug exposure in patients that took ibogaine after being pretreated with a CYP2D6 inhibitor (paroxetine 20 mg) compared with a placebo (Glue et al. 2015b). This study exemplifies the role of CYP2D6 in the pharmacokinetics of ibogaine and its likely impact on efficacy and safety parameters of ibogaine use (Glue et al. 2015b; Litjens and Brunt 2016). In persons exhibiting the most common CYP2D6 phenotype (extensive metabolizers), the half-life of ibogaine was found to be 7.45 hours (Mash et al. 2001).

Noribogaine (12-OH-ibogaine) is an active metabolite with many overlapping receptor affinities with its parent compound, although it has notably higher affinity for κ and μ opioid receptors (Litjens and Brunt 2016). While noribogaine binds to the μ opioid receptor with high affinity and was originally reported to have full agonist activity, it lacked agonist effects such as pupillary constriction or respiratory depression in doses up to 60 mg in healthy volunteers and is currently thought to be a partial agonist or antagonist (Antonio et al. 2013; Glue et al. 2015a; Pablo and Mash 1998). Noribogaine is lipophilic and has a large volume of distribution in the body. Additionally, it has a much longer elimination half-life than ibogaine and was found to be 28–49 hours in a dose escalation study in healthy volunteers (Glue et al. 2015a). Due to persisting effects from slow elimination and modulation of the opioid system, it has been hypothesized that noribogaine may be playing a pivotal role in blocking opiate withdrawal symptoms or cravings and may provide a "self-tapering" effect to those undergoing opioid detoxification.

Ibogaine was first hypothesized to have utility in the management of OUD in 1962 and was patented as an interrupter of narcotic addiction in 1985 (Alper 2001; Brown 2013; Winkelman 2014). Since that time, a handful of case series and small studies have been conducted supporting the ability of ibogaine to interrupt opioid addiction by simultaneously mitigating withdrawal symptoms and cravings for opioids. A few case series reported absence of opioid withdrawal symptoms within 12–48 hours following ibogaine administration, although these studies did not employ the use of a rating scale (Alper et al. 1999, 2000; Luciano 1998; Sheppard 1994). The three studies that employed the use of a measurement scale in the extant literature evaluating opioid withdrawal symptoms in patients undergoing detoxification utilizing ibogaine are summarized in Table 1 (Brown and Alper 2017; Mash et al. 2001; Noller, Frampton, and Yazar-Klosinski 2017). To our knowledge, only Mash et al. have reported withdrawal outcomes using a validated observer or clinician rated scale, whereas other studies have used only subjective ratings.

Despite its novel pharmacologic profile, as well as promising preclinical and pilot data in humans, research regarding ibogaine's therapeutic potential is scarce. This may be due to ibogaine being classified as an illicit substance in the US and many other parts of the world, effectively hampering the ability to investigate the therapeutic potential of ibogaine for OUD. In Mexico, ibogaine remains an unregulated drug and continues to be used for management of addiction, including OUDs. US residents may travel across the border to access treatment with ibogaine and clinical programs exist to facilitate this type of "medical tourism." In the current study, we aimed to evaluate opioid withdrawal and drug craving scores using validated clinical instruments in participants with OUD undergoing a week-long detoxification treatment protocol with ibogaine HCl (ibogaine).

Methods

Program description

The program enrolls patients between the ages of 21 to 60 years old who are experiencing problematic substance use. The clinical continuum of care includes a three-part treatment program that includes coaching and medical screening prior to ibogaine administration, a week-long ibogaine detoxification treatment, and optional residential aftercare program or weekly recovery coaching. The first and third phases of treatment are typically carried out in the US, while the week-long detoxification protocol occurs in Mexico due to aforementioned legal restrictions of ibogaine administration in the US. The week-long ibogaine detoxification program takes place in an inpatient medical center during the first four days, and in a residential setting the final three days.

Individuals are excluded from treatment if they have severe psychiatric conditions, including current or past psychotic spectrum disorders, bipolar I disorder, current eating disorders, or symptoms of impaired reality testing or disorganized thinking. Medical exclusions for treatment include prolonged QTc interval, history of heart disease, pulmonary embolism, deep vein thrombosis, severe respiratory conditions such as emphysema or COPD, obesity, gastrointestinal disorders such as Crohn's disease or IBS, chronic infectious diseases, cerebellar dysfunction, delirium, organic brain disease or history of severe traumatic brain injury, epilepsy, current pregnancy, abnormal electrolytes, or impaired hepatic or renal function. Patients are also excluded from treatment if they have used alcohol, amphetamines, cocaine, or psychiatric medications in the week prior to treatment, or have used long-acting opioids such as buprenorphine or methadone in the four weeks prior to treatment. Patients on benzodiazepines are not discontinued. The program incorporates the Global Ibogaine Therapy Alliance (GITA) consensus clinical treatment guidelines as part of screening criteria and risk management, which include a host of medical and medication considerations for ibogaine treatment (Dickinson et al. 2015). It should be noted that the GITA clinical guidelines are an informational document and that GITA does not accredit or regulate ibogaine treatment centers, nor is it the aim of the document to establish a universal standard of care for ibogaine.

Prior to treatment at the ibogaine clinic in Mexico, applicants are converted to short-acting opioids, and maintenance therapies such as methadone and buprenorphine are required to be discontinued four weeks prior to ibogaine treatment. Upon arrival at the clinic, patients undergo a physical examination onsite with a staff physician. This exam includes a history and physical, 12-lead electrocardiogram, drug testing, complete physical, and a complete blood count with differential and metabolic panel. Patients are maintained on immediate-release (IR) morphine following their initial medical evaluation to prevent florid withdrawal up until approximately four hours before ibogaine administration. The approximate half-life of IR morphine in adults is 2–4 hours, meaning that patients should not be experiencing significant withdrawal symptoms at the time ibogaine is administered, yet would be experiencing peak withdrawal symptoms 24–48 hours later, when post-ibogaine measurements were taken if ibogaine were ineffective at reducing withdrawal.

The ibogaine treatment consists of oral administration of a total dose of 18–20 mg/kg of ibogaine hydrochloride. A test dose of 100 mg is administered initially, followed by the remainder of the calculated dose within two hours of the test dose. The ibogaine is Voacanga-derived and imported from Phytostan Enterprises, Inc., and is certified under Good Manufacturing Practice (GMP) guidelines. The treatment occurs in a medically supervised inpatient setting, which features vital sign, telemetry, intravenous saline and electrolytes, and monitoring of withdrawal symptom and mental status both during and after ibogaine. The treatment center has board-certified physicians who specialize in emergency medicine, and nurses and paramedics on site at all times while patients are in residence. If patients experience post-acute withdrawal symptoms at 72 hours post-ibogaine administration, they are given smaller doses of ibogaine (1–5 mg/kg) for the remaining treatment duration, with or without clonidine or gabapentin as needed.

Participants and study design

A retrospective chart review of participants admitted to a single residential ibogaine treatment center in Mexico during 2015 was conducted. The Addiction Severity Index (ASI), fifth edition (McLellan et al. 1992) was used at baseline to gauge the severity of participants' problems with opioid consumption. Participants were included if they participated in ibogaine treatment primarily for management of OUD and carried a diagnosis of OUD made by clinic physicians using DSM-5 criteria (APA 2013). Participants were excluded if they participated in ibogaine treatment for an indication other than problematic opioid consumption or were polysubstance users who indicated an alternative substance to be their primary problem class of drug.

Participants lacking complete Clinical Opioid Withdrawal Scale (COWS) scores were excluded.

COWS (Wesson and Ling 2003), SOWS (Handelsman et al. 1987), and Brief Substance Craving Scale (BSCS) (Somoza et al. 1995) scores were collected by a clinic physician at 48 and 24 hours prior to ibogaine administration, as well as 24 and 48 hours after ibogaine administration. Measurement times were approximately the same from day to day and mirrored the physician's naturalistic daily rounding practice as part of the clinical care provided. The COWS is a validated 11-item, clinician-administered scale with scores ranging from 0–48 and is scored as no withdrawal (<5), mild withdrawal (5–12), moderate withdrawal (13–24), moderately severe (25–36), and severe (>36) (Tompkins et al. 2009). The SOWS is a 16-item, self-administered scale with scores ranging from 0–64 and is scored as mild withdrawal (0–10), moderate withdrawal (11–20), and severe withdrawal (>20) (Handelsman et al. 1987). The BSCS is a three-item instrument that assesses intensity, frequency, and length of drug cravings (Somoza et al. 1995). In some participants, ASI, SOWS, or BSCS scores were missing, although COWS data were available for all participants. Results are labeled with the number of participants for which data were available. This study was determined to be exempt by Western University of Health Sciences Institutional Review Board due to using de-identified data as part of a retrospective chart review study.

Study outcomes and statistical analysis

Demographic and clinical variables collected at baseline included age, gender, and ASI. The ASI consists of a semi-structured interview that gathers information that is categorized into seven domains common to substance use disorders that impact patient lives. Domains include medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status, which are each given a composite score that is then interpreted as a low-, medium-, or high-level problem domain based upon predetermined instrument cutoffs. Baseline composite ASI data were analyzed descriptively.

The primary outcome variable was change in COWS scores pre- and post-ibogaine administration and was analyzed using a repeated measures analysis of variance (ANOVA). Secondary outcome variables included changes in SOWS and BSCS scores that were also analyzed using ANOVA. Alpha values were set to 0.05 for statistical significance and pairwise comparisons were used to ensure that any statistical differences discovered were between pre- and post-phases of ibogaine detoxification. Additional secondary outcomes included differences between COWS, SOWS, and BSCS scores 48 hours before ibogaine administration (baseline) and 48 hours after ibogaine administration. Percentages of participants experiencing different severities of withdrawal symptoms and cravings were analyzed categorically by predetermined symptom scale cutoff scores.

Results

Fifty participants were included in the studies' analysis of COWS data while 40 participants were included in the demographic analysis, as 10 participants were missing a baseline ASI (Tables 2 and 3).

The mean age in the sample was 31.28 ± 8.38 years (range 19–51 years) and 39% were female. Regarding the drug perceived to be the primary problem, most participants (60%, n = 24) reported heroin, while 15 (37.5%) reported prescription opioids, with one reporting an alternative (unknown) opioid. Of those who reported heroin use as their primary problem, 66.7% (n = 16) stated that the intravenous route was usually used, whereas among patients who reported prescription opioids as their primary problem, only one participant reported usually using the intravenous route. Most participants (82.5%) were polysubstance users and a wide range of secondary drug problems were reported, including alcohol, prescription opioids, sedative hypnotics and anxiolytics, cocaine, amphetamines, cannabis, and gamma-hydroxy butyrate (GHB). There were seven participants (17.5%) who did not report a secondary drug problem. Seventy-five percent (n = 30) reported receiving treatment for their drug problem in the past, while 85% (n = 34) endorsed prior use of methadone or buprenorphine. Fifteen percent reported at least one overdose requiring medical attention in the past, and participants reported spending an average of $1666.85 on drugs in the 30 days prior to the baseline ASI (S.D. $1833.99, median $1000, range $0–10,000). Additional demographic and drug use descriptive information can be found in Table 2.

ASI composite scores (Table 3) revealed an average composite score in the drug domain of 0.206 ± 0.06, indicating on average medium-level problematic opioid use, although 47.5% scored high enough to indicate a severe drug problem. Other composite domains in which a significant portion of the sample scored high enough to indicate a severe problem included family and social relationships, medical, and psychiatric domains. Alcohol was the least problematic domain for the sample overall.

Table 2. Patient and drug use demographics (n = 40).

Demographic	Category	%
Highest Level of Education Completed	Less than high school	5
	High school	17.5
	1–3 years of college	62.5
	Bachelor's degree	10
	Master's degree	5
Ethnicity	White	77.5
	Asian	5
	Other	17.5
Current marital status	Married	37.5
	Divorced	7.5
	Single/Never married	55
Employment in past 3 years	Full-time	50
	Part-time (stable)	10
	Part-time (irregular)	17.5
	Student	5
	Retired	2.5
	Unemployed	10
	Homemaker	5
Most problematic drug used	Heroin	60
	Prescription Opioid	37.5
	Other Opioid	2.5
Secondary most problematic drug used	None	17.5
	Alcohol	17.5
	Prescription Opioids	17.5
	Sedative/hypnotic	17.5
	Cocaine/Crack	12.5
	Amphetamines	7.5
	Cannabis	7.5
	GHB	2.5
Number of times receiving treatment for drugs and alcohol	0	25
	1–3	45
	4–9	22.5
	≥10	7.5
Number of overdoses requiring medical attention	0	85
	1	2.5
	2	7.5
	3	2.5
	4	2.5
Number of years using heroin	A few times only	47.5
	6 mo – 1 year	17.5
	1–5 years	12.5
	6–10 years	10
	>10 years	12.5
Number of years using prescription opioids	A few times only	42.5
	6 mo – 1 year	7.5
	1–5 years	37.5
	6–10 years	10
	>10 years	2.5

Table 3. Addiction severity index: Baseline composite scores (n = 40).

	Medical	Employment and Support*	Alcohol	Drug	Legal	Family and Social Relationships	Psychiatric
Composite ASI Domain Scores ± SD	0.306 ± 0.315	0.306 ± 0.29	0.08 ± 0.123	0.206 ± 0.06	0.072 ± 0.139	0.232 ± 0.227	0.208 ± 0.175
% Low severity	42.5	60	97.5	12.5	77.5	32.5	30
% Medium severity	25	30	2.5	40	7.5	25	47.5
% High severity	32.5	7.5	0	47.5	15	42.5	22.5

*n = 39 (1 missing value).

COWS scores averaged 8.2 ± 5.21 and 7.64 ± 5.27 at 48 and 24 hours prior to ibogaine administration, respectively, indicating that participants were observed to be experiencing mild opioid withdrawal symptoms while being maintained on immediate-release (IR) morphine (mild range score = 5–12). Mean group scores decreased to 5.26 ± 4.31 at 24 hours and to 3.30 ± 3.13 (non-clinical range) at 48 hours after ibogaine administration, indicating a reduction in withdrawal symptoms despite total cessation of opioids (Figure 1(a)). The repeated measures ANOVA for COWS scores showed significant decreases over time with pairwise comparisons indicating significant differences between pre- and post-ibogaine phases of the detoxification protocol (Wilk's Lambda = 0.463, F (3, 47) = 18.71, $p < 0.01$, $\eta 2 = 0.537$). At 48 hours after

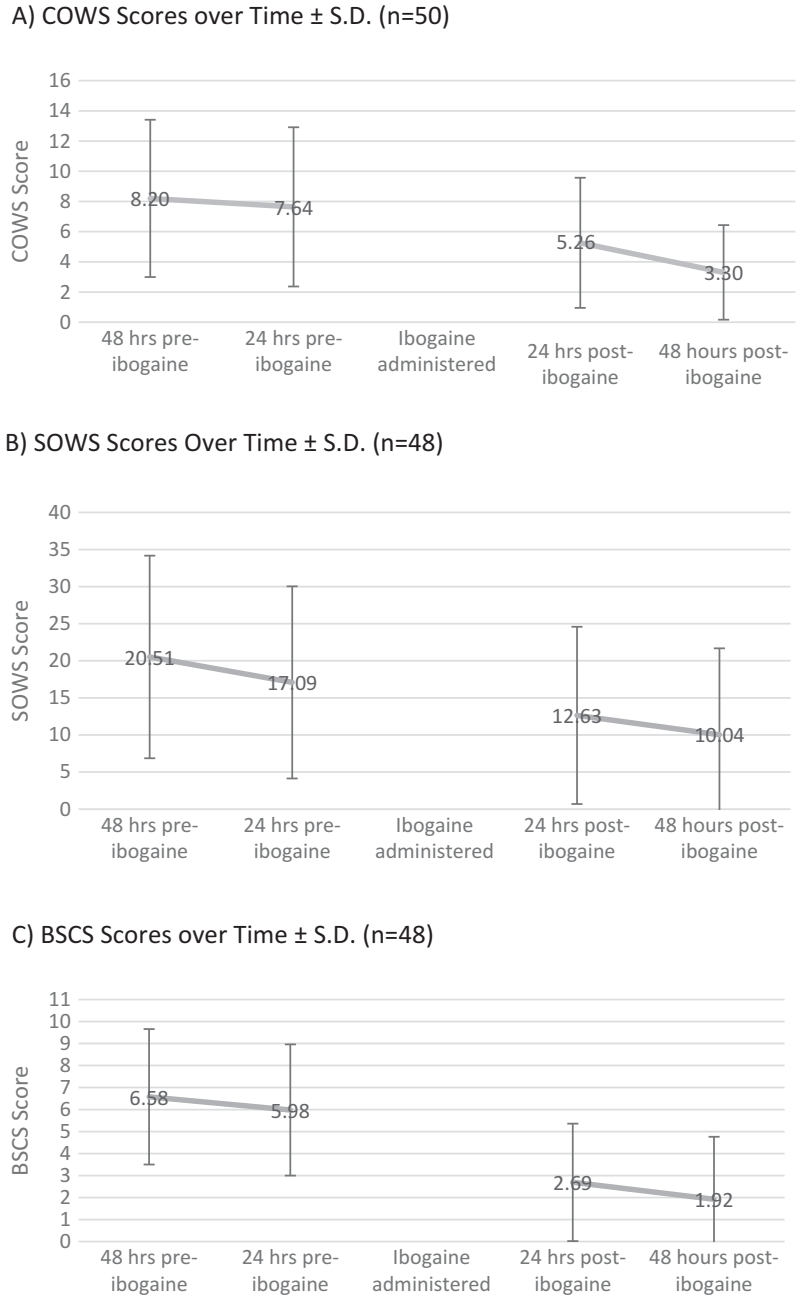

Figure 1. Opioid withdrawal and craving scores in subjects receiving ibogaine for opioid detoxification.

ibogaine administration, 78% (n = 39) of patients did not exhibit clinical signs of opioid withdrawal, 20% (n = 10) had mild signs, while 2% (1) had moderate signs.

SOWS scores averaged 20.51 ± 13.66 and 17.09 ± 12.95 at 48 and 24 hours prior to ibogaine administration, indicating that participants were subjectively experiencing severe and moderate opioid withdrawal symptoms while being maintained on IR morphine, respectively. This result may be explained due to high opioid tolerances or difficulty estimating morphine requirements in heroin users, resulting in the subjective worse withdrawal symptoms 48 hours prior to treatment compared with 24 hours prior. Scores decreased to 12.63 ± 11.95 10.04 ± 11.65 at 24 and 48 hours after ibogaine administration, indicating a reduction in subjective withdrawal symptoms (Figure 1(b)). The repeated measures ANOVA for SOWS scores showed significant decreases over time, with pairwise comparisons indicating significant differences between pre- and post-ibogaine phases of the detoxification protocol (Wilk's Lambda = 0.572, F (3, 45) = 11.24, $p < 0.01$, $\eta 2 = 0.428$). At 48 hours after ibogaine administration, 68% (n = 34) of participants

rated their opioid withdrawal symptoms as mild and 10% (n = 5) rated them as moderate; however, 22% (n = 11) reported feeling severe opioid withdrawal symptoms.

BSCS scores averaged 6.58 ± 3.08 and 5.98 ± 2.98 at 48 and 24 hours prior to ibogaine administration, respectively, indicating that participants were experiencing medium-level craving for opioids (BSCS range 0–12) while being maintained on IR morphine. Scores decreased to 2.69 ± 2.68 and 1.92 ± 2.83 at 24 and 48 hours after ibogaine administration, indicating a reduction in cravings (Figure 1(c)). The repeated measures ANOVA for BSCS scores showed significant decreases over time, with pairwise comparisons indicating significant differences between pre- and post-ibogaine phases of the detoxification protocol (Wilk's Lambda = 0.314, F (3, 45) = 32.80, p < 0.01, η2 = 0.69). At 48 hours after ibogaine administration, 79.2% (n = 38) of participants displayed minimal craving for opioids (score range 0–3), 14.6% (n = 7) rated their cravings as moderate (score range 4–6), while 6.3% (n = 3) rated their cravings as severe (score range 7–12).

Discussion

In the largest sample of observed opioid-dependent patients undergoing an ibogaine detoxification protocol to date, we found significant reductions in objective and subjective opioid withdrawal scale scores as well as significant reductions in patient-reported cravings for opioids. To our knowledge, there have been few published studies investigating ibogaine's effects on opioid withdrawal in humans (Alper et al. 1999; Brown and Alper 2017; Luciano 1998; Mash et al. 2001; Noller, Frampton, and Yazar-Klosinski 2017; Sheppard 1994). Our results are consistent with results reported previously and help to build an evidence base for further study of ibogaine in the management of withdrawal from opioids.

Ibogaine appears to be unique in that it can simultaneously attenuate withdrawal symptoms as well as opioid cravings in a relatively brief treatment timeframe. The ability of ibogaine to address psychological aspects of OUD, such as drug craving, is a potentially important advantage compared to existing therapeutic approaches, since relapse after successful detoxification presents a high risk of overdose-related death due to participants overestimating their tolerance and using doses similar to what they were previously accustomed to. By addressing this aspect of OUD, ibogaine may help position participants for greater success in their path of recovery, which is corroborated by reports of decreased drug use in longitudinal studies (Brown and Alper 2017; Davis et al. 2017; Noller, Frampton, and Yazar-Klosinski 2017). Ibogaine is not a "magic bullet" for OUD, and successful recovery in most individuals will likely require extensive support and aftercare. Furthermore, given ibogaine's psychedelic nature, support should be present in preparation for and during the experience in addition to afterwards, in order to maximize benefit and minimize risks of psychedelic therapy in accordance with successful treatment protocols used in evolving psychedelic research (Thomas, Malcolm, and Lastra 2017).

In recent years, psychedelics have gained momentum as experimental therapies for the treatment of various psychiatric disorders, including substance use disorders (Bogenschutz et al. 2015; Garcia-Romeu, Griffiths, and Johnson 2014; Krebs and Johansen 2012; Thomas et al. 2013; Thomas, Malcolm, and Lastra 2017). Compared to other "classical" psychedelic compounds like psilocybin or lysergic acid diethylamide (LSD), ibogaine is unique both from a subjective experience and safety perspective. Subjectively, ibogaine is described as oneiric, with more pronounced dream-like imagery, especially when the participant's eyes are closed. Participants may relive their past in a movie-like fashion, often accompanied by auditory phenomena as well as unpleasant emotional content or physical sensations (Schenberg et al. 2017). In contrast, compounds like psilocybin or LSD have a higher propensity for euphoria and feature more pronounced visual phenomena. Ibogaine also demonstrates a unique ability to mitigate opioid withdrawal compared with classical psychedelics; however, it appears to carry a higher risk of severe adverse outcomes, including fatalities, many with a suspected or confirmed cardiac etiology reported in the literature (Asua 2013; Hildyard et al. 2016; Litjens and Brunt 2016; O'Connell et al. 2015). Unfortunately, safety information, such as vital signs and telemetry reports, were not available for review in this study. Other adverse psychological reactions, including mania, have been described, and although rare, are also possible with classical psychedelics (Marta et al. 2015). Ibogaine detoxification should not be attempted in a medically unsupervised environment and access to emergency medical services should be available. At least one death has occurred within a study, although administration of ibogaine below the standard of care was suspected in this case (Noller, Frampton, and Yazar-Klosinski 2017). While ibogaine carries risks that are potentially severe and should not be casually overlooked, there are more people dying in the US every day from opioid overdoses than have ever been reported in the literature to have occurred with

ibogaine, which may help balance the risk-benefit calculus in favor of further research with ibogaine (CDC 2016; Litjens and Brunt 2016).

In considering reports of adverse effects during ibogaine treatment, the populations presenting for ibogaine detoxification treatment often exhibit greater severity and chronicity of addiction, intravenous drug use, medical co-morbidities and fragility after failing mainstream treatments, thus placing them at greater risk for medical complications during detoxification treatment. The epidemic degree of morbidity and mortality inflicted by licit and illicit opioid medications on US citizens may make it tempting to consider opioid detoxification with ibogaine if participants are refractory to first-line treatment options or are not interested in continued opioid dependence with buprenorphine or methadone. On the other hand, the clandestine nature of ibogaine clinics and lack of high-quality data from rigorous clinical trials supporting safety and efficacy may deter those considering use.

Our study used an open-label and retrospective design that lacked a control group, which introduces the possibility of a placebo effect and various forms of bias. The probability of a placebo effect accounting for observed results is thought to be low by the study authors, as effect sizes for all outcome measures were large and participants would be expected to be undergoing peak withdrawal symptoms 24–72 hours after opioid cessation, which is precisely when the post-ibogaine measurements were taken and scores were decreasing. Ibogaine has a complex mechanism of action that is not fully understood, although it includes long-acting and active metabolites; thus, continued opioid withdrawal blocking effects by drug metabolites despite normalization of mental status post-ibogaine cannot be ruled out (Litjens and Brunt 2016; Popik, Layer, and Skolnick 1995). Participants did tend to report a more severe level of withdrawal symptoms than clinicians both before and after treatment with ibogaine, which could indicate the presence of an observer bias in clinicians or possible drug-seeking behavior on behalf of participants.

Ibogaine appears to be able to effectively detoxify participants from opioids while simultaneously reducing cravings. Future studies should aim to elucidate predictive factors of treatment response, as well as employ greater methodologic rigor. Genetic or metabolic factors, such as the presence of variant CYP2D6 alleles, play a significant role in individual pharmacokinetics of ibogaine and elucidation of metabolic capacity prior to treatment could have a positive impact on efficacy and safety parameters. Due to the epidemic public health problem of opioid use disorders in the US, emergency measures should be taken to reduce barriers to legitimate medical research into ibogaine's addiction-interrupting properties and rigorous controlled trials testing safety and efficacy should be undertaken.

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