

# Treating drug dependence with the aid of ibogaine: A retrospective study

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## Abstract

Ibogaine is an alkaloid purported to be an effective drug dependence treatment. However, its efficacy has been hard to evaluate, partly because it is illegal in some countries. In such places, treatments are conducted in underground settings where fatalities have occurred. In Brazil ibogaine is unregulated and a combined approach of psychotherapy and ibogaine is being practiced to treat addiction. To evaluate the safety and efficacy of ibogaine, we conducted a retrospective analysis of data from 75 previous alcohol, cannabis, cocaine and crack users (72% poly-drug users). We observed no serious adverse reactions or fatalities, and found 61% of participants abstinent. Participants treated with ibogaine only once reported abstinence for a median of 5.5 months and those treated multiple times for a median of 8.4 months. This increase was statistically significant ( $p < 0.001$ ), and both single or multiple treatments led to longer abstinence periods than before the first ibogaine session ( $p < 0.001$ ). These results suggest that the use of ibogaine supervised by a physician and accompanied by psychotherapy can facilitate prolonged periods of abstinence, without the occurrence of fatalities or complications. These results suggest that ibogaine can be a safe and effective treatment for dependence on stimulant and other non-opiate drugs.

## Keywords

Ibogaine, dependence, addiction, cocaine, crack

## Introduction

Problems related to drug use, abuse and dependence have been receiving increasing attention worldwide. The number of users of illicit drugs, such as cannabis, opioids, cocaine, and crack is estimated to be around 149–271 million (Degenhardt and Hall, 2012). On the other hand, lifetime use of licit drugs such as alcohol and tobacco is estimated at 55% and 30% of the world population, respectively (Storr et al., 2010). The consumption of such drugs has been associated with considerable morbidity and mortality (Degenhardt and Hall, 2012) as well as social problems (Nutt et al., 2007; 2010), making drug use, abuse and dependence one of the most important public health concerns in psychiatry.

Despite high rates of dependence, safe and effective pharmacological addiction treatments are still lacking. While pharmacological interventions do exist for opioid dependence treatment, they are targeted towards craving reduction (Nutt and Lingford-Hughes, 2008). One alternative approach for the treatment of opioid dependence is the use of ibogaine, a monoterpene alkaloid with strong psychoactive properties (Alper, 2001; Brown, 2013). Given its long-lasting and varied effects, a classification of ibogaine has proved challenging. Nevertheless, some have proposed classifying the compound as a hallucinogen, psychedelic or oneirogen (Alper and Lotsof, 2007).

Ibogaine is only one of a dozen alkaloids present in the root bark of the *Tabernanthe iboga* plant, traditionally used in Gabon, Cameroon and other parts of West central Africa in Shamanic rituals of the Bwiti religion (Alper, 2001). Around 1960, ibogaine gained more attention in the West when Howard Lotsof, an opioid-dependent patient, discovered that ibogaine might be a useful

therapeutic tool in the treatment of drug addiction, particularly in the alleviation of opioid craving (Alper, 2001; Brown, 2013).

After these initial uncontrolled case reports, non-clinical, clinical and laboratory-based research has sought to assess ibogaine's efficacy in the treatment of opioid addiction. At least two case studies have demonstrated the drug's effectiveness at reducing cravings during opioid withdrawal: one from 32 patients treated at a clinic (Mash et al., 2001), and another from 33 patients treated in non-medical settings (Alper et al., 1999).

Corroborating ibogaine's therapeutic effects in the treatment of opioid dependence are results from animal research, which have shown reductions in withdrawal signs in morphine-dependent animals (Dzolja et al., 1988; Glick et al., 1992; Leal et al., 2003;

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Parke et al., 2002; Sharpe and Jaffe, 1990), attenuation of morphine-induced place preference (Parker and Siegel, 2001), reduction in self-administration to morphine (Glick et al., 1991, 1994) and decreases in dopamine efflux in the nucleus accumbens or striatum after cocaine or morphine administration (Glick et al., 1994; Maisonneuve et al., 1991). Furthermore, animal research has also indicated a potential efficacy of ibogaine in reducing self-administration of alcohol (Rezvani et al., 1995), amphetamine (Maisonneuve et al., 1992) and cocaine (Cappendijk and Dzoljic, 1993; Glick et al., 1994).

In recent decades, ibogaine's therapeutic potential coalesced in what was termed "a medical subculture" (Alper et al., 2008) or a "vast, uncontrolled experiment" (Vastag, 2005) with more than 3000 documented cases reported until 2006 (Alper et al., 2008). This is attributed, at least in part, to ibogaine's hallucinogenic action, which can induce very potent and prolonged psychological and emotional effects.

However, in some places where the substance is illegal, ibogaine or iboga extracts are used without quality control and without the supervision of trained and qualified medical staff. Such conditions may be responsible for some of the fatalities that have been reported after ibogaine ingestion (Alper et al., 2012). Although it is not possible to determine a single factor to explain these adverse reactions (Alper et al., 2012), the presence of a Long-QT Syndrome is the most accepted explanation (Hoelen et al., 2009; Koenig et al., 2013, 2014; Maas and Strubelt, 2006; Paling et al., 2012; Pleskovic et al., 2012).

Prolongation of the electrocardiogram QT interval, the traditional measure of ventricular de- and repolarization, is associated with ventricular arrhythmia that can be caused by prolongation of ventricular repolarization or repolarization with disturbances (Van Noord et al., 2010). One of the most common causes of QT prolongation is the use of drugs, including anti-psychotic, anti-histaminic and gastrointestinal compounds. Importantly, QT prolongation has been reported in alcohol use (Aasebø et al., 2007) and withdrawal (Cuculi et al., 2006; Kino et al., 1981; Otero-Antón et al., 1997) as well as cocaine use (Hoffman, 2010). QT prolongation during alcohol withdrawal may persist for 7 days after alcohol consumption has ceased (Kino et al., 1981), while for cocaine it significantly diminishes after a week of cocaine abstinence (Levin et al., 2008).

These effects generally result from pharmacological inhibitory actions at delayed rectifier potassium channels encoded by the human ether a-go-go related gene (hERG) (Van Noord et al., 2010). Once ibogaine induces this pharmacological action (Koenig et al., 2013, 2014), it may potentiate QT prolongation from acute drug use or even from withdrawal, possibly causing a potentially fatal ventricular arrhythmia (Van Noord et al., 2010). Therefore, carefully monitoring QT prolongation has been proposed as an important safety measure (Roden, 2008). Yet this remains controversial, mainly due to the fact that not all QT prolongations are actually proarrhythmic, and that some proarrhythmias are found in the absence of QT prolongation (Hondeghe, 2008).

However, given that most of the fatalities associated with ibogaine occurred many hours or even days after ibogaine ingestion, acute toxic effects possibly related to QT prolongation may not explain some of these cases (Alper et al., 2012). As such, the occurrence of comorbidities, detected in 12 of the 14 reported cases, may have contributed to some of these deaths. Such comorbidities included liver disease, peptic ulcer disease, brain

neoplasm, hypertensive and atherosclerotic cardiovascular disease and obesity (Alper et al., 2012). Taken together, the complexity of these fatalities suggests that new studies about ibogaine's effect on the ECG are needed.

Despite the reported adverse reactions, the therapeutic use of ibogaine seems to be growing more prevalent, particularly among opioid-dependent individuals (Brown, 2013). Yet, evidence for the use of ibogaine in the treatment of other addictions, such as psychostimulant dependence, is still scarce, despite considerable research from animal models that suggests ibogaine has therapeutic potential for treating non-opioid drug dependence (Cappendijk and Dzoljic, 1993; Glick et al., 1994; Maisonneuve et al., 1992; Rezvani et al., 1995).

Given the current lack of pharmacological interventions for treating psychostimulant dependence, such as cocaine and crack-cocaine, the assessment of ibogaine's therapeutic potential in treating stimulant dependence is of particular importance, especially because most pharmacological treatments for stimulant dependence revolve around the use of benzodiazepines to alleviate symptoms of withdrawal (Nutt and Lingford-Hughes, 2008). In Brazil, although opioid consumption is extremely low (Eckschmidt et al., 2013; Fonseca et al., 2010), ibogaine has been used in the treatment of addiction to other classes of drugs since 2001. Given that there are important behavioral and neurobiological differences between addiction to opioids and to psychostimulants (Badiani et al., 2011), it is imperative to assess both the efficacy and safety of using ibogaine in the treatment of psychostimulant dependence. Here we provide a report based on retrospective results from an ibogaine treatment currently being practiced in Brazil, in order to assess the safety and efficacy of ibogaine in the treatment of addiction to non-opioid substances.

## Methods

We retrospectively evaluated data from a residential, private clinic in Curitiba, Paraná, Brazil, which treats patients with substance use disorders using cognitive behavioral therapy (CBT). The clinic owner, a psychologist, works in association with a physician who administers ibogaine hydrochloride (ibogaine HCl) in a private hospital in Santa Cruz do Rio Pardo, São Paulo, Brazil. Patients paid for the treatment, since both the clinic and the hospital are private institutions.

Patients were psychologically and physically evaluated at the clinic by a multi-professional team, including psychiatrists, psychologists, nurses, physiotherapists and music therapists. Drug dependence was reportedly established using the diagnostic criteria from the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV).

When the clinic first opened, patients were required to stay abstinent for at least 30 days prior to ibogaine administration, but this was later extended to 60 days after a new protocol was established. This change was reported as necessary to prevent any pharmacological interactions with ibogaine. This period was also considered important to ensure that patients were motivated to follow treatment procedures and to stop using drugs. The abstinence period could be achieved either at home or at the center as a 24-hour residential patient at the clinic.

Upon arrival at the clinic, if patients exhibited any violent behavior, they were confined to a special isolated room for a few

days. All patients were advised to stay at the clinic or at home after the ibogaine session, away from other people, duties or any kind of social activity for at least 7 days. Participants were only accepted into the ibogaine treatment if they agreed to comply with the psychological follow-up.

According to the general protocol provided, the inclusion criteria for the ibogaine treatment were general conditions of good health, as measured by routine clinical exams (electrolyte levels, aspartate aminotransferase, alanine aminotransferase, bilirubins, gamma glutamyl transferase, creatinine, blood sugar and hemogram), an absence of psychiatric comorbidities, strong psychological motivation to remain abstinent and willingness to participate in the psychotherapy before and after ibogaine administration, with familial support. Exclusion criteria were pregnancy, surgery in the last 6 months, uncontrolled high blood pressure, uncontrolled diabetes, cardiac arrhythmias, renal insufficiency, hepatic insufficiency, Alzheimer's disease and Parkinson's disease.

Ibogaine HCl was imported from a Canadian provider (Phytostan Enterprises, Inc.), individually for each patient, in powder form (5 g). Upon arrival, ibogaine was weighed and placed in capsules by a local pharmacy at the request of the physician responsible for importing ibogaine.

Patients were typically given a dose of 17 mg/kg, but this was subject to change depending upon the patients' weight at the time of treatment. Ibogaine administration was preceded by a 20 mg dose of domperidone, a dopamine D2/D3 receptor antagonist prescribed to reduce potential nausea from the ibogaine (Lotsof and Watchel, 2003) between 30 to 45 minutes prior to ibogaine administration. Doses were divided and administered in multiple capsules and if a patient exhibited a weak response to the initial dose, an additional 100 to 200 mg was administered to the patient. A total dose of 20 mg/kg was never exceeded.

Ibogaine was administered in the morning, around 9 a.m., with patients having been previously advised to eat just only a light breakfast that morning in order to prevent nausea. The acute effects lasted approximately 10 hours. Patients stayed in bed in a private hospital room, in silence. The physician responsible for the procedure remained in the hospital throughout the entire treatment and visited the patient's private room every 25 or 30 minutes.

During the effects of ibogaine, the doctor avoided influencing the patients' experiences, but provided any psychological or emotional support if needed. This typically involved reassuring clients that all effects and reactions were part of the experience. Patients were encouraged to be quiet, calm and confident. Blood pressure, cardiac frequency and oxygen saturation were measured at each of the visits to the patient room. Patients stayed in the hospital overnight, and were dismissed only after 24 to 48 hours. After leaving the hospital, they returned to the clinic for further psychological therapy.

Based on psychological evaluation of the patient in the months following ibogaine administration, it was sometimes decided by the psychologist and the physician that another ibogaine session might be beneficial to the therapeutic outcome. This was typically decided if patients experienced intense cravings, lapses (here defined as a brief return to drug use, with the patient rapidly asking again for help) relapses (here defined as a complete return to drug use), difficulty in changing old-habit patterns related to drug use, continued involvement with previous friends who were also drug users, or difficulty in reintegrating

with the family. The decision to take another dose or not was always decided upon through close consultation between the patient, family and therapeutic team.

Patient data were provided to the researchers separately by the clinic staff and by the physician responsible for both the ibogaine administration and patients' assistance during ibogaine sessions. In addition, lapse, relapse and abstinence data were obtained directly from the patients or their close relatives through telephone conversations. These data were obtained from 5–20 minute interview, without using specific questionnaires or rating scales. Abstinence was defined as not using any drugs, with the exception of the occurrence of brief lapses.

Data were then entered in a Microsoft Excel database, which was subsequently analyzed using SPSS 17.0 statistical software. Parametric data were analyzed by a Student's *t*-test and non-parametric data were analyzed using a Mann-Whitney *U* test or a Friedman's test followed by a Wilcoxon signed-rank test with Bonferroni correction. Associations between categorical variables were evaluated by Pearson Chi-square tests. Level of significance was set at  $p < 0.05$ , after Bonferroni correction when appropriate. Data are expressed in mean  $\pm$  standard deviation. Median and range are also reported for the examined variables.

All procedures for the study were approved by the Research Ethical Committee from Universidade Federal de São Paulo prior to the start of the research. However, all the treatment procedures had been previously conducted independently of the participation of the University and of the authors of the present investigation (except BRC who is responsible for the ibogaine administration). Patients consented to participating in the study at the start of each telephone conversation, where they would be asked about lapses, relapses, drug use and abuse history and their current pattern of use or abstinence.

## Results

### *Patient information*

Data were gathered from 75 drug-dependent patients (67 male, 8 female) who underwent a total of 134 ibogaine HCl sessions. Fifty-five patients (73%) were contacted by telephone, six (8%) were contacted and met in-person, and 14 (19%) were not available at the time of contact, but their data were provided by the patients' parents (11 cases), wives (2 cases), or ex-wife (1 case). Among those 14 individuals that could not be reached, 10 were residential patients at other clinics for drug dependence treatment at the time of contact, one was working abroad, two were in jail, and one was hospitalized due to an accident unrelated to ibogaine use.

There were no statistically significant differences ( $U = 186.5$ ;  $p = 0.16$ ) between the ages of male ( $34.16 \pm 8.33$  years old) and female ( $29.50 \pm 5.31$  years old) participants. Men were significantly heavier ( $79.32 \pm 12.25$  kg) than women ( $67.74 \pm 4.02$  kg) ( $U = 94.0$ ;  $p < 0.01$ ). There were no significant differences ( $U = 174.0$ ;  $p = 0.89$ ) in the number of previous treatments completed by male ( $5.40 \pm 0.91$ ) and female ( $3.83 \pm 3.31$ ) participants prior to joining the ibogaine program. Only six patients (8%) reported no drug treatments previous to joining the ibogaine program. One man had been in jail previous to joining the ibogaine treatment.

### Patient drug use history

Of the patients, 48 (64%) reported lifetime use of alcohol, 61 (81%) of cannabis, 62 (83%) of snorted cocaine, six (8%) reported previous use of injected cocaine and 51 (68%) reported having had previously used crack-cocaine. Some 54 patients (72%) were users of multiple substances: alcohol, cannabis, cocaine, and crack. Tobacco use was reported by 11 patients (15%). Opioid use was reported by only one female patient, who came from Italy with the specific purpose of undergoing ibogaine treatment. Other drugs mentioned included methamphetamine (one patient), "acid", "ecstasy", and prescription substances such as benzydamine (Benflogin) and metylphenidate (Ritalin).

There were no statistically significant associations between gender and use of alcohol ( $\text{Chi}^2 = 0.284, p = 0.594, n = 50$ ), cannabis ( $\text{Chi}^2 = 0.129, p = 0.719, n = 62$ ), cocaine ( $\text{Chi}^2 = 0.127, p = 0.722, n = 63$ ) or crack ( $\text{Chi}^2 = 0.053, p = 0.818, n = 68$ ).

Participants reported initiation of alcohol use at a younger age than other drugs ( $13.79 \pm 2.97$ , range 7–21), followed by cannabis ( $15.25 \pm 3.09$ , range 11–30), cocaine ( $19.21 \pm 4.57$ , range 12–32) and then crack ( $25.20 \pm 7.25$ , range 14–50). There were no significant differences between men and women regarding the age of onset of use for alcohol ( $t = 0.106, p = 0.916, n = 47$ ), cannabis ( $t = -1.891, p = 0.064, n = 59$ ) or cocaine ( $t = 0.303, p = 0.763, n = 58$ ). However, men started using crack ( $25.88 \pm 7.31$ , range 15–50,  $n = 41$ ) significantly later than women ( $19.60 \pm 3.51$ , range 14–23,  $n = 5$ ) ( $U = 41.0, p = 0.030, n = 46$ ).

### Ibogaine sessions

Although the physician has been working with ibogaine since 2001, the first treatment session with ibogaine in this sample took place on 9 January 2005 and the last on 22 March 2013. Twenty ibogaine HCl sessions (20%) occurred between 2008 and 2009, 53 (40%) between 2010 and 2011 and 52 (40%) between 2012 and March 2013.

All 75 patients underwent at least one ibogaine session. Among those, 33 (44%) took it twice, 14 (19%) took it three times, five patients (7%) participated in four sessions, two (3%) were administered ibogaine five times, and one patient (1%) took it nine times. Five women (63%) participated in only one ibogaine session, and three (38%) were administered ibogaine twice. There was no significant association between gender and the number of ibogaine sessions ( $\text{Chi}^2 = 2.166, p = 0.826$ ).

The mean time interval between the first and second ibogaine sessions among all participants was  $245.34 \pm 226.297$  days (range 31–979),  $303.14 \pm 277.93$  days (range 48–1012) between the second and third,  $111.60 \pm 100.30$  days (range 24–267) between the third and fourth,  $95.50 \pm 72.83$  days (range 44–147) between the fourth and fifth. Only one patient continued taking ibogaine after the fifth session (he took a total of nine treatments). Between the fifth and sixth session there was an interval of 87 days, followed by an interval of 93 days before the seventh session, of 88 days before the eighth session and more 96 days before the ninth session.

### Ibogaine dosage

The dose in the first ibogaine session was significantly higher among men ( $14.81 \text{ mg/kg} \pm 1.61, n = 67$ ) than among women

( $12.03 \text{ mg/kg} \pm 0.85, n = 8$ ) ( $U = 19.0, p < 0.001$ ). Only three women participated in a second ibogaine session, rendering data unsuitable to statistical comparison with the second dose of men. The second dose of the male patients was  $13.75 \text{ mg/kg} \pm 2.10$  ( $n = 31$ ), whereas for women it was  $11.85 \text{ mg/kg} \pm 0.21$ . In the third session, the dose for men was  $13.34 \text{ mg/kg} \pm 2.28$  ( $n = 14$ ), and in the fourth it was  $12.22 \text{ mg/kg} \pm 3.04$  ( $n = 5$ ). Only two male patients participated in a fifth ibogaine session; the doses were  $7.5 \text{ mg/kg}$  and  $14.89 \text{ mg/kg}$ . The one patient who took ibogaine over five times took a fixed dosage of  $7.5 \text{ mg/kg}$  in the sixth through ninth administrations.

### Relapses and abstinence status

All women reported that they were abstinent at the time of contact, and only two reported having had a relapse after the initial ibogaine session. Both of these women then took ibogaine a second time and have reportedly not relapsed since. Forty-eight men (72%) stated that they were abstinent, but 10 of those were currently undergoing other treatment interventions. Except for those 10, 38 (57%) men achieved abstinence with no other treatments.

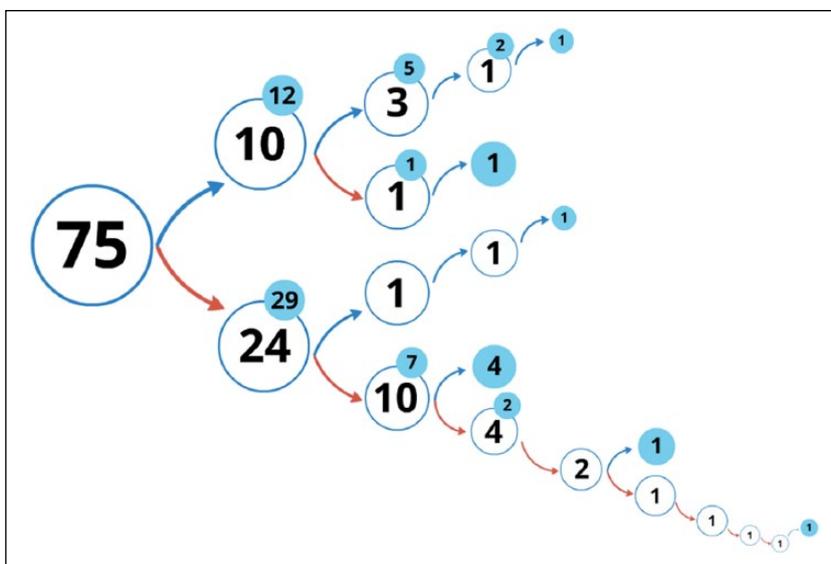
After the first ibogaine session, 22 of the male patients (29%) recovered without relapses, whereas 53 (71%) relapsed. After the second session, 15 patients (45%) maintained sobriety, and 18 reported relapse (55%). After the third session, eight (57%) remained abstinent, and six (43%) relapsed. After the fourth session, one patient did not relapse (20%), and four relapsed (80%). After the fifth session, one patient maintained abstinence (50%), and one patient relapsed, and continued to take ibogaine four more times. These data are visually depicted in Figure 1. There was a significant association between gender and relapse after the first ibogaine session, with men relapsing more frequently than women ( $\text{Chi}^2 = 9.009; p = 0.007$ ).

### Duration of abstinence

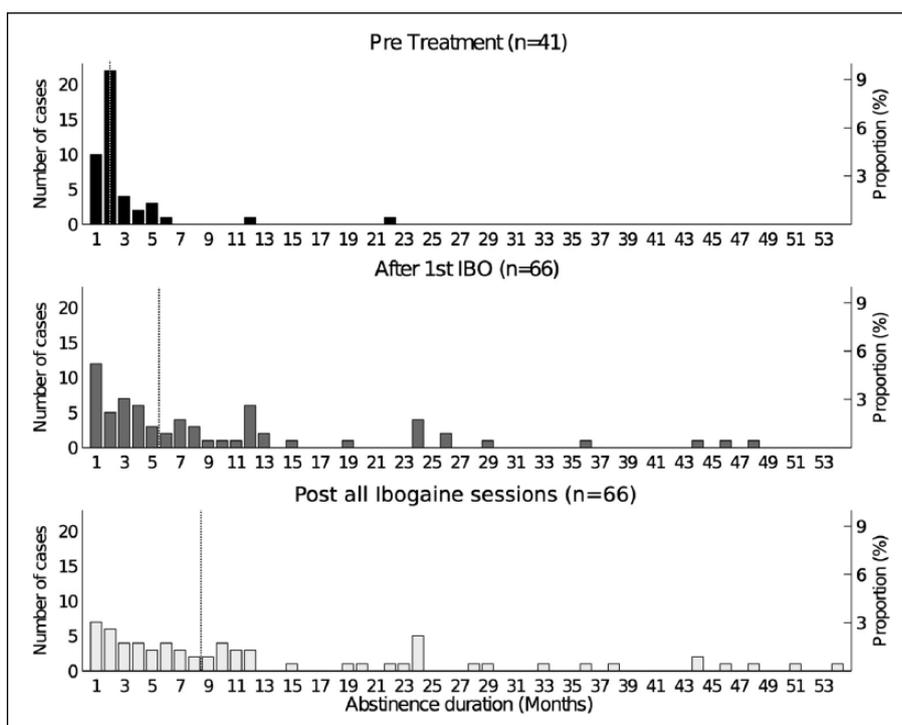
With the data obtained, it was possible to calculate the period of abstinence after the first ibogaine session and after all ibogaine sessions for 66 patients. Data regarding days of abstinence just before the first ibogaine session were also provided by 41 patients. There were no significant differences in the number of days of abstinence before taking ibogaine between men ( $190 \pm 265.82$ ) and women ( $75.26 \pm 60.36$ ) ( $U = 53.50; p = 0.11$ ).

There was a significant increase in the period of abstinence achieved when comparing the days before the first ibogaine session ( $88.30 \pm 15.92$ , median = 60.00), after the first ibogaine session ( $298.76 \pm 42.26$ , median = 165.00), and after all sessions combined ( $419.15 \pm 52.86$ , median = 252.00) (Friedman  $\text{Chi}^2 = 23.471; p < 0.001$ ), as shown in Figure 2.

Seventeen men reported abstinence since their ibogaine session, but with the occurrence of one and only relapse during this abstinence period. Thirteen of them were administered ibogaine only once. For this subsample, the number of days of abstinence between the most recent ibogaine session and the relapse ( $138.06 \pm 105.07$ , range 16–365 median = 120.00) was significantly shorter than the time of abstinence achieved after this relapse until contact with researchers ( $547.41 \pm 369.21$ , range 48–1292 median = 520.00) ( $Z = -3.385; p < 0.001$ ).



**Figure 1.** Summary of relapse occurrence in the 75 contacted patients after each ibogaine session. The numbers inside the larger blue circles represent the number of patients who participated in each treatment stage. Each step in the tree corresponds to one ibogaine administration. Numbers in the smaller light blue filled circles indicate the number of patients who had stopped at that point of treatment, and therefore were not administered ibogaine again. All upward blue arrows indicate patients who did not relapse after a given ibogaine administration. Downward red arrows point to the number of patients who did relapse after a given session. Each column represents the outcome of a given ibogaine administration (first, second, third and so on).



**Figure 2.** Abstinence duration data. Top = Days of abstinence spent at an inpatient clinic immediately previous to ibogaine administration. Middle = Days of abstinence after first ibogaine session. Bottom = Days of abstinence after all ibogaine sessions. Vertical lines in the histograms depict the corresponding median.

## Adverse reactions

No serious adverse effects, such as cardiac arrhythmias or fatalities, occurred in any patient. However, some mild adverse effects that have previously been reported in the ibogaine literature did occur frequently, but only during the acute effects of ibogaine. These include nausea, ataxia, vomiting, tremors, headaches and mental confusion. Importantly, not a single patient complained about ibogaine's physical or psychological effects, even in cases in which the experienced effects were considered very strong or unpleasant, or in cases where relapses occurred within a short period of time after treatment.

On the other hand, four patients (5%) complained about the psychotherapeutic process or other activities during the internment period at the clinic, or during the post-ibogaine psychotherapeutic sessions.

## Discussion

The most important result from the present data is that no fatalities occurred as a result of ibogaine administration in the controlled dosing (between 7.5 and 20 mg/kg) and medical setting described here. Furthermore, not a single case of serious negative reactions, such as cardiac arrhythmias or persistent ataxia, was reported. These data are relevant in a scenario where at least 19 deaths have been associated with iboga or ibogaine consumption until 2008 (Alper et al., 2012), two fatalities reported in 2013 (Jalal et al., 2013; Mazoyer et al., 2013) and at least three more cases of complications (Paling et al., 2012) reported to date. It is important to note that the dose used in the current work is far from the LD50 observed in studies with mice (263 mg/kg) (Kubiliene et al., 2008). This important safety precaution could be achieved in the current protocol only because ibogaine was not obtained from underground providers, since ibogaine is not controlled or prohibited in Brazil (Anvisa, 2014). The lack of persistent ataxia in the present study is a particularly important indicator of the absence of cerebellar toxicity, an effect observed after high doses (100 mg/kg) were administered to rats (Molinari et al., 1996; O'Hearn and Molliver, 1997; Xu et al., 2000).

The absence of fatalities in the present results suggests a relative safety of the use of ibogaine hydrochloride in a controlled hospital setting. It is also important to note that in at least five of the 21 (24%) previously documented fatalities, the substance ingested was not ibogaine HCl (Alper et al., 2012). Moreover, many of the documented fatalities occurred in underground treatments, where a physician was often not present (Alper et al., 2012; Jalal et al., 2013; Mazoyer et al., 2013; Paling et al., 2012). Another factor that may have contributed to the absence of medical complications in the present account might be the almost complete lack of opioid use history among the patients involved in the study. Indeed, pharmacological interactions between opioids and ibogaine have been implicated in some of the previous reported cases of fatalities (Alper et al., 2012; Brown, 2013). Finally, the treatment protocol includes a long mandatory abstinence period prior to the administration of ibogaine. This likely contributed significantly to the safety of the therapeutic approach by preventing any potential pharmacological interactions between the treatment and other drugs of abuse.

Given that Long-QT Syndrome, potentially induced by ibogaine, may be responsible for some fatalities, electrocardiograms

before and during ibogaine administration may be a reliable practice to reduce this kind of adverse effect. In the present work, however, results of electrocardiograms previous to ibogaine administration were provided to the researchers for only 36 patients (48%), because some of these treatments occurred many years ago.

To our knowledge, this is the first report to assess the outcome of the use of ibogaine for the treatment of patients who abused alcohol, cannabis, cocaine, and crack but not opioids (with only one European patient having a previous history of opioid use). This is likely the result of the generally low incidence of opioid abuse in Brazil (Baltieri et al., 2004; Fonseca et al., 2010). It is important to emphasize, however, that in this sample, alcohol and cigarette use may have been under reported by the patients, since these data were not obtained using a structured questionnaire. Thus, when asked about previous drug use, they may not have reported alcohol and cigarettes because these substances often do not fit into the cultural conception of a "drug." It should also be noted that it was not possible to specifically confirm the adopted criteria of dependence or distinguish between different types of drug dependence.

Considering the occurrence of relapses after ibogaine administrations, the present results are very encouraging. Although there were only eight women in the sample, all were found abstinent at the time of contact. Among men, 51% were also abstinent at the time of contact, and an additional 10 participants were also abstinent, but were participating in other drug dependence treatment interventions.

Since we were not able to analyze abstinence periods as a function of number of ibogaine treatments completed given the decreasing number of patients participating in subsequent ibogaine sessions, we analyzed only the length of abstinence achieved after the first session as compared with the average abstinence period achieved after all subsequent sessions combined. Despite this caveat, participants reported surprisingly long periods of abstinence, reaching a median of 5.5 months after the first ibogaine session and 8.4 months after all subsequent ibogaine sessions. This increase was statistically significant, corroborating previous reports that participating in more than one ibogaine session may be beneficial in achieving long-term abstinence (Brown, 2013). The abstinence periods reported after completing both a single and multiple ibogaine sessions was also significantly longer than the required period of abstinence achieved before ibogaine administration (median = 60). However, one might argue that this presents a potential confound in evaluating the treatment outcome of ibogaine, because the present sample only included individuals capable maintaining the one or two-month abstinence period required before the first ibogaine session. Yet contrary to this reasoning, most clients were only able to achieve and maintain sobriety as full-time residents in the clinic, where some were provided benzodiazepines to assist in the treatment process. Moreover, 69 patients (92%) had already tried other treatments for their drug-related problems without success. In patients' oral reports, most of those who recovered reported that the ibogaine session(s) were indeed essential to their recovery, although they acknowledged they may not have succeeded without the accompanying psychological treatment. The fact that 44% decided to participate in more than one ibogaine session further attests to the fact that they saw benefits in using ibogaine as part of their treatment. Furthermore, the proportion of patients reporting full abstinence (100% for women, 51% for men) was considerably greater than the less than 26% reported from psychotherapy alone (Ouimette et al., 1997). Even when

compared with other pharmacological interventions, the therapeutic outcome of ibogaine is robust: the abstinence period achieved after ibogaine treatment tended to be much longer than that observed in recent clinical trials for the treatment of psychostimulant dependence with the drug topiramate (Johnson et al., 2013; Mariani et al., 2012). However, we must be cautious when comparing data from this retrospective study with clinical trials due to methodological differences and biases.

Given that the present study employed retrospective methodology based on answers from unstructured interviews and data collected over a long period of time, it is not possible to infer a causal relationship between ibogaine and the observed outcomes. Indeed, only a randomized double-blind clinical trial could accurately assess this. Another important limitation to the present results is that data on both relapse occurrence and abstinence periods achieved were obtained directly from the patients' (or close relatives') reports.

Considering the limitations of self-reported data, it was recently suggested that, besides abstinence and relapse, it is also very important to take into account secondary measures to better evaluate drug dependence treatment outcomes (Tiffany et al., 2011). According to these authors, the most important variables to evaluate, in addition to reductions in drug use, are change in self-efficacy, psychosocial functioning, network support/social support, craving, and quality of life. Thus, it will be important to also consider these additional variables in future studies of ibogaine in the treatment of drug dependence.

Future studies should also seek to establish the advantages and disadvantages of using ibogaine instead of other related psychedelic compounds, such as LSD, which has therapeutic potential in the treatment of alcoholism (Krebs and Johansen, 2012). While ibogaine may be more effective at treating a wider range of chemical dependencies (e.g. opioids, alcohol, cocaine, crack) than other psychedelic substances, it may present higher risks for medical complications. For example, LSD has very low toxicity and none of the effects on heart rhythm (Hintzen and Passie, 2010) that ibogaine does.

Despite the limitations of the present report, outlined above, the present data are the first formal clinical report to our knowledge that suggests that ibogaine has a strong therapeutic potential in the treatment of dependence to stimulants and other non-opiate drugs and that the medical complications previously reported can be avoided by administering the compound in the presence of a physician in a safe and legal medical setting.

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### Conflict of interest

BRC has a financial interest in this work given that the ibogaine treatment is part of his private practice.

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