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The ibogaine medical subculture

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Abstract

Aim of the study: Ibogaine is a naturally occurring psychoactive indole alkaloid that is used to treat substance-related disorders in a global medical subculture, and is of interest as an ethnopharmacological prototype for experimental investigation and possible rational pharmaceutical development. The subculture is also significant for risks due to the lack of clinical and pharmaceutical standards. This study describes the ibogaine medical subculture and presents quantitative data regarding treatment and the purpose for which individuals have taken ibogaine.
Materials and methods: All identified ibogaine "scenes" (defined as a provider in an associated setting) apart from the Bwiti religion in Africa were studied with intensive interviewing, review of the grey literature including the Internet, and the systematic collection of quantitative data.
Results: Analysis of ethnographic data yielded a typology of ibogaine scenes, "medical model", "lay provider/treatment guide", "activist/self-help", and "religious/spiritual". An estimated 3414 individuals had taken ibogaine as of February 2006, a fourfold increase relative to 5 years earlier, with 68% of the total having taken it for the treatment of a substance-related disorder, and 53% specifically for opioid withdrawal.
Conclusions: Opioid withdrawal is the most common reason for which individuals took ibogaine. The focus on opioid withdrawal in the ibogaine subculture distinguishes ibogaine from other agents commonly termed "psychedelics", and is consistent with experimental research and case series evidence indicating a significant pharmacologically mediated effect of ibogaine in opioid withdrawal.

Keywords: Ibogaine; *Iboga* alkaloid; Substance-related disorders; Opioid-related disorders; Substance withdrawal; Medical ethnography

1. Introduction

Ibogaine is the most studied of the *iboga* alkaloids (Bartlett et al., 1958), a group of naturally occurring and synthetic indole alkaloids, some of which reportedly reduce opioid withdrawal symptoms and drug self-administration in humans (Luciano, 1998; Alper et al., 1999; Mash et al., 2001) or preclinical models (Glick et al., 2001). Presently in the setting of homes, hotel rooms and private clinics in North America and Europe, individuals in increasing numbers are taking ibogaine in what has been termed "a vast uncontrolled experiment" (Vastag, 2005).

1.1. History

The ritual eating of iboga has been a psychopharmacological sacrament in the Bwiti religion for several centuries, and was likely practiced among Pygmies in much earlier times (Fernandez, 1982). In Gabon and elsewhere in West Central Africa, ibogaine is ingested in the form of scrapings of *Tabernanthe iboga* root bark. The ritual aim of eating iboga has been

Abbreviations: 18-MC, 18-methoxycoronaridine; AC, adenylyl cyclase; EKG, electrocardiogram; FDA, United States Food and Drug Administration; GDNF, glial cell line-derived neurotrophic factor; GPCRs, G protein-coupled receptors; Ibogaine HCl, ibogaine hydrochloride; LSD, lysergic acid diethylamide; mAChRs, muscarinic acetylcholine receptors; MDMA, 3,4-methylenedioxymethamphetamine; MI, myocardial infarction; NAc, nucleus accumbens; nAChR, nicotinic acetylcholine receptor; NIDA, United States National Institute on Drug Abuse; NMDA, *N*-methyl-D-aspartate.

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conceptualized as "binding"; the binding across time through ancestral contact, or binding participants socially on the basis of a common shared experience of a distinctive consciousness and system of belief (Fernandez, 1982; Fernandez and Fernandez, 2001). In the colonial era Bwiti became a context of collective psychological resistance to the anomie and demoralization related to the strain on indigenous community and family institutions. Bwiti offered a dignified realm of spiritual endeavor, "the work of the ancestors" and social cohesion. Following Gabonese independence in 1960, Bwiti has remained constellated with national identity and contemporarily retains significant social and political importance (Swiderski, 1988; Samorini, 1995).

Iboga has not commonly been used to treat addiction in the traditional African Bwiti context. Iboga has been sought as a treatment for some somatic conditions, in particular for infertility (Fernandez, 1982). In the colonial era the indigenous community experienced a crisis due to a sharp decline in fertility caused by venereal disease stemming from prostitution and the separation of men from their families by the large-scale physical relocation of indigenous workers. The possibility of an objective basis for the use of iboga in this setting is suggested by evidence associating *iboga* alkaloids with antimicrobial activity or effects on cell-mediated immunity. *Iboga* alkaloids are reportedly active against *Candida albicans* in the intact animal (Yordanov et al., 2005). In vitro studies indicate reversal of multidrug resistance in human cancer cells (Kam et al., 2004) and activity against *Mycobacterium tuberculosis* (Rastogi et al., 1998), human immunodeficiency type 1 virus (Silva et al., 2004), and the tropical parasite *Leishmania amazonensis* (Delorenzi et al., 2002).

The first observation of ibogaine as treatment for substance-related disorders in 1962 involved a network of lay drug experimenters who ingested a variety of hallucinogens and systematically recorded their experiences (Lotsof and Alexander, 2001). Withdrawal symptoms were unexpectedly absent in heroin-dependent individuals who had taken ibogaine. Common to various sociological definitions of the term "subculture" is a system of beliefs, norms and values apart from a superordinate culture (Clarke, 1974; Dowd and Dowd, 2003). The ibogaine subculture has elicited wariness from the "superordinate culture" of conventional clinical medicine (Kleber, 2001), and has been invoked regarding the null hypothesis that ibogaine's reported effect in opioid withdrawal is not pharmacologically mediated, but is instead accounted for by suggestion and ritual (Sharpe and Jaffe, 1990). The ibogaine subculture is also significant as the setting of case report evidence that influenced the decision of the National Institute on Drug Abuse (NIDA) to pursue its ibogaine project (Alper, 2001), and the Food and Drug Administration (FDA) to approve a clinical trial (Mash et al., 1998).

Ibogaine is unscheduled in most of the world, with the exception of the US, Belgium, Denmark, France, Sweden, Switzerland, and Australia where it is illegal. Ibogaine has not been popular as a recreational drug regardless of its legal status (Kleber, 2001), and apparently only two arrests involving ibogaine are known to have occurred in the US (Ranzal, 1967; Lane, 2005). *Iboga* alkaloids reportedly are not self-administered, and do not produce withdrawal signs following chronic administration in animals (Aceto et al., 1992). As of late 2006, ibogaine hydrochloride (HCl) was available for $400–$500 USD per gram (ethnogarden.com, 2006), and the dosage typically used for opioid withdrawal is in the range of 1–2 g. Purity on the order of 97–98% has been reported on certificates of analysis for supplies of ibogaine HCl used in the subculture. Ibogaine is also available as *Tabernanthe iboga* extract or dried root bark.

1.2. Clinical use

Ibogaine, either as *Tabernanthe iboga* root bark or ibogaine HCl is the only *iboga* alkaloid that has reportedly been administered to humans, with apparently only one exception, a study in which 12 normal volunteers were evaluated with some brief neuropsychological tests after receiving the naturally occurring *iboga* alkaloid ibogaline (Schmid, 1967). Ibogaine HCl has been typically administered as a single oral dose in the range of 10–25 mg/kg of body weight. Patients physically dependent on opioids have described significant attenuation of withdrawal symptoms within several hours of ingesting ibogaine, with subsequently sustained resolution of the opioid withdrawal syndrome (Alper et al., 1999; Mash et al., 2001). The advantages attributed to ibogaine are higher tolerability relative to other standard treatments for acute opioid withdrawal, and an interval of diminished drug craving that may last days to months following a treatment. Individuals also take ibogaine in search of psychological or religious insight, typically at dosages lower than those used in the treatment of opioid withdrawal.

There are no randomized controlled clinical trials of ibogaine, and the available clinical data is limited mainly to two open label case series. One series from the US and the Netherlands included self-reported outcomes of a consecutive series of 52 treatments involving 41 different individuals, some of who were treated on multiple occasions mainly for the indication of dependence on opioids or stimulants (Alper, 2001). Thirty-six percent of the treatments were associated with self-reported intervals of 6 months or longer of abstinence from the primary drugs of dependence for which treatment had been sought. A subset of 33 individuals were treated for the indication of opioid withdrawal with a single dose of ibogaine averaging 19.3 mg/kg (Alper et al., 1999). Twenty-five of these patients had full resolution of opioid withdrawal without drug seeking behavior that was sustained throughout a 72-h period of post-treatment observation, and another four individuals denied withdrawal symptoms but expressed their preference to continue to use heroin. The other series, from a clinic in St. Kitts consists of 32 patients treated with a fixed dose of 800 mg of ibogaine HCl for the indication of withdrawal from heroin (Mash et al., 2001). Physician-rated structured instruments indicated resolution of withdrawal signs and symptoms at 24 h after the last use of opioids (an interval of abstinence commonly associated with significant withdrawal symptoms) that was sustained during subsequent observation for 1 week following ibogaine administration.

An unpublished Dutch doctorandus thesis (Bastiaans, 2004) presents data obtained from 21 subjects who responded to a

Web-based questionnaire adapted from the European Addiction Severity Index a mean of 21.8 months after they had taken ibogaine for treatment of a substance-related disorder. Seventeen of the 21 patients (81%) identified opioids as the primary drug of dependence for which they had sought treatment. Five individuals reported stopping the use of all substances following treatment with ibogaine, and another nine reported stopping the use of their primary drug while continuing to use alcohol or cannabis. Nineteen patients reported stopping their use of their primary drug for at least a week following treatment, suggesting frequent resolution of acute opioid withdrawal.

1.3. Preclinical research

Research utilizing animal models has involved the *iboga* alkaloids ibogaine (Alper, 2001) and its desmethylated metabolite noribogaine (Baumann et al., 2001), and a synthetic congener, 18-methoxycoronaridine (18-MC) (Maisonneuve and Glick, 2003). Eleven of the 13 published preclinical studies of *iboga* alkaloids in opioid withdrawal indicate a significant attenuation of opioid withdrawal signs in the rat (Dzoljic et al., 1988; Sharpe and Jaffe, 1990; Maisonneuve et al., 1991; Glick et al., 1992; Cappendijk et al., 1994; Rho and Glick, 1998; Parker et al., 2002; Panchal et al., 2005), mouse (Frances et al., 1992; Popik et al., 1995; Layer et al., 1996; Leal et al., 2003), and primate (Aceto et al., 1992). *Iboga* alkaloids are also reported to reduce the self-administration of morphine (Glick et al., 1991; Glick et al., 1994; Glick et al., 1996; Maisonneuve and Glick, 1999; Pace et al., 2004), cocaine (Cappendijk and Dzoljic, 1993; Glick et al., 1994), amphetamine (Maisonneuve et al., 1992), methamphetamine (Glick et al., 2000; Pace et al., 2004), alcohol (Rezvani et al., 1995; Rezvani et al., 1997; He et al., 2005) and nicotine (Glick et al., 1998; Glick et al., 2000), and to diminish dopamine efflux in the nucleus accumbens (NAc), which is regarded as a correlate of drug salience (Berridge, 2007), in response to opioids (Maisonneuve et al., 1991; Glick et al., 1994; Glick et al., 2000; Taraschenko et al., 2007b) or nicotine (Benwell et al., 1996; Maisonneuve et al., 1997; Glick et al., 1998).

1.4. Mechanisms of action

Initially, ibogaine's mechanism of action was hypothesized to involve antagonism at the *N*-methyl-D-aspartate-type glutamate (NMDA) receptor (Skolnick, 2001). However, 18-MC, which has negligible NMDA receptor affinity, also reduces opiate withdrawal and drug self-administration in the animal model (Glick et al., 2001). Antagonism of the α3β4 nicotinic acetylcholine receptor (nAChR) is a possible mechanism of action, as indicated by a series of studies of *iboga* alkaloids and nicotinic agents (Fryer and Lukas, 1999; Glick et al., 2002a,b; Pace et al., 2004; Taraschenko et al., 2005). The α3β4 nAChR is relatively concentrated in the medial habenula and interpeduncular nucleus, where 18-MC's antagonism of α3β4 nAChRs diminishes sensitized dopamine efflux in the NAc (Taraschenko et al., 2007a,b).

Ibogaine's mechanism of action has frequently been suggested to involve the modification of neuroadaptations related to prior drug exposure (Rabin and Winter, 1996b; Popik and Skolnick, 1998; Alper, 2001; Glick et al., 2001; Sershen et al., 2001; Levant and Pazdernik, 2004). Ibogaine may modulate intracellular signaling linked to opioid receptors, and potentiates the morphine-induced inhibition of adenylyl cyclase (AC) (Rabin and Winter, 1996b), an effect that is opposite to the activation of AC that is classically associated with opioid withdrawal (Sharma et al., 1975). In animals, ibogaine enhances the antinociceptive effect of morphine or other μ opioids without by itself having an effect on nociception (Schneider and McArthur, 1956; Schneider, 1957; Frances et al., 1992; Bagal et al., 1996), and inhibits the development of tolerance to morphine antinociception (Cao and Bhargava, 1997). Prior exposure to morphine potentiates ibogaine's diminution of sensitized dopamine efflux in the NAc in response to morphine (Pearl et al., 1996) or ibogaine's enhancement of morphine antinociception (Sunder Sharma and Bhargava, 1998), suggesting an effect on neuroadaptations related to opioid tolerance or dependence.

Increased glial cell line-derived neurotrophic factor (GDNF) in the ventral tegmental area has been suggested to mediate decreased ethanol consumption following the administration of ibogaine to rats (He et al., 2005; He and Ron, 2006). GDNF enhances the regeneration of dopaminergic function (Ron and Janak, 2005) and is increased by antidepressant treatment (Hisaoka et al., 2007). The hypothesis that GDNF may mediate improvement in hedonic functioning and mood in chronic withdrawal from addictive substances is appealing, but does not appear likely to explain efficacy in acute opioid withdrawal.

Although designated as a hallucinogen, ibogaine's use in opioid withdrawal distinguishes it from other compounds that are commonly termed "psychedelics", namely the serotonin type 2A receptor agonist classical hallucinogens such as lysergic acid diethylamide (LSD), psilocybin and mescaline, or the serotonin releasing substituted amphetamine 3,4-methylenedioxymethamphetamine (MDMA). In contrast with ibogaine, there is no preclinical or case report evidence that suggests a significant therapeutic effect of classical hallucinogens or MDMA in acute opioid withdrawal. Ibogaine's effects in opioid withdrawal do not appear to involve serotonin agonist or releasing activity (Wei et al., 1998; Glick et al., 2001). Serotonergic neurotransmission does not appear to play a significant role in mediating the expression of the opioid withdrawal syndrome, which remains unchanged even after extensive lesioning of the raphe (Caille et al., 2002).

The phenomenology of the subjective state produced by ibogaine has been attributed with the quality of a "waking dream" and distinguished from the state associated with classical hallucinogens (Goutarel et al., 1993; Lotsof and Alexander, 2001). The visual phenomena associated with ibogaine tend to occur with greatest intensity with the eyes closed, and to be suppressed with the eyes open, and often involve a sense of location within an internally represented visual or dream landscape, in contrast to an alteration of the visual environment experienced with the eyes open while awake which is often reported with classical hallucinogens. The occurrence of an atropine-sensitive

electroencephalogram (EEG) rhythm in animals treated with ibogaine (Schneider and Sigg, 1957; Depoortere, 1987) suggests a waking neurophysiological state with an analogy to rapid eye movement sleep (Goutarel et al., 1993; Alper, 2001).

1.5. Research objectives of this study

A previous publication provides a history and description of the ibogaine subculture in the U.S. and Europe from its origin in 1962 until early 2001 (Alper et al., 2001). The major objectives of this study are the qualitative analysis of observational and textual data (Bailey, 1994; Malterud, 2001) to provide an updated description as well as a typology of the ibogaine medical subculture, and the systematic collection of quantitative data regarding treatment and the purpose for which individuals took ibogaine.

2. Methods

The Institutional Review Board of the New York University School of Medicine approved this research.

2.1. Observational methods

The providers of ibogaine treatment were conceptualized as participants in a global medical subculture and studied from an "observing participant" research perspective (Gold, 1958). The qualitative and quantitative information was obtained from face to face discussions, phone conversations and e-mail correspondence with treatment providers and other participants.

2.2. Study sample

The study included only treatment providers who had already publicly identified their activities by maintaining Web sites, publishing in the lay or scientific press, presenting at public meetings, or posting to ibogaine list servers. Because ibogaine is not regulated in most of the world, providers are very often open about their activity.

A "scene" is defined in this study as a provider of ibogaine in an associated setting. The term "ibogaine subculture" refers to all ibogaine scenes collectively outside of Africa. The sample in this study that represented the ibogaine subculture consisted of all known presently or previously existing ibogaine scenes outside of Africa involving publicly identified providers, with the exception of a scene in Gabon which was included that involved European and US participants and African Bwiti adept providers. Otherwise no systematic attempt was made to study the Bwiti religious context in Africa. No data was encountered regarding the use of *Lambarene*, a tablet that was marketed in France between 1939 and 1970 that contained an estimated 8 mg of ibogaine (Goutarel et al., 1993).

2.3. Excluded scenes

A large ibogaine scene was alleged to have existed in the Christiana squatter community in Copenhagen but was concluded to lack corroborative evidence on the basis of communication with the Danish Drug Users Union and former Christiana residents (Alper et al., 2001). Reported ibogaine scenes in Pakistan and Thailand were not included due to lack of independent verification. Due to the inability to obtain quantitative data, the study did not include a sample of probably about 20 individuals who were provided ibogaine by Dan Lieberman, a South African ethnobotanist who died in a motor vehicle accident in August 2000. Psychologist Leo Zeff and others administered ibogaine (typically as a single doses in the range of 150–300 mg) and other hallucinogens as an adjunct to psychotherapy beginning in the 1950s in a scene that existed on the West Coast of the US (Stolaroff, 2004) that was excluded due to a lack of quantitative data.

2.4. Data collection

The data collection for this study began with a previously published description and history of the ibogaine subculture as of early 2001 (Alper et al., 2001). The authors subsequently continued their contact with the ibogaine subculture by email, phone, and in person. Quantitative information that was assessed systematically from the providers included cumulative numbers of people treated, percentage seeking treatment for addiction and specifically acute opioid withdrawal, as well as ibogaine form and dosage and the cost of treatment. The approach to pretreatment medical screening and laboratory evaluation, and monitoring during the treatment was also discussed. The estimates of cumulative numbers of subjects treated obtained from providers are current as of February 2006 except for the figure for the St. Kitts Clinic, which is taken from an abstract published in June 2005 (Mash et al., 2005).

To determine if any further scenes existed in addition to those of which the authors were aware, in May of 2005 a series of messages was posted to Mindvox (Kroupa, 2006), the most frequently used ibogaine list server. The Internet, which is an important aspect of the ibogaine subculture and comprises an extensive unpublished "grey literature" (Boukacem-Zeghmouri and Schöpfel, 2006) was searched monthly from May 2005 to February 2006 using the terms "ibogaine" or "iboga" alone, and combined with the term "treatment". The list server postings and Internet searches yielded no usable information regarding new scenes that had not already been previously obtained by longstanding, ongoing contact with subculture participants. In May of 2005, and again near the conclusion of data gathering in February 2006, all known treatment providers were systematically contacted to update the quantitative information. The typology of scenes was created between the first and second data collections.

The study also reviewed the academic literature, and the "white literature" (Boukacem-Zeghmouri and Schöpfel, 2006) including public media and officially published government or industrial documents. Databases with white literature content including ProQuest, LexisNexis, and the New York Times, and academic literature databases including PubMed, PsycInfo, JSTOR, UMI Dissertation Abstracts, WorldCat, and the SAGE Sociology Full-Text Collection were searched utilizing the terms

"ibogaine" and "iboga". The references cited by the articles retrieved utilizing the above searches were reviewed until they no longer yielded new references containing the search terms. The above searches yielded relatively little material that was new to the authors because of their extensive prior use of the *iboga* alkaloid conventional and nonconventional literature, as well as substantial access to ibogaine-related material that is not indexed in any searchable database (Lotsof, 1985; Alper, 2001; Alper et al., 2001; Lotsof and Wachtel, 2003; Lotsof, 2007).

2.5. Data validation

Triangulation of the data, i.e., viewing the data from multiple observational perspectives (Malterud, 2001; Denzin and Lincoln, 2005), was possible for all of the currently operating scenes listed in Table 1 on the basis of independent corroboration from provider and patient participants in the same scenes, providers regarding other providers, and other informants. Most treatment providers interviewed in the present study had previously supplied data that was published 5 years earlier (Alper et al., 2001) and were known to at least two of the authors. For three medical model scenes that no longer exist (Lexington 1955–1956, Santiago 1966–1967, and Zürich 1980–1989) textual evidence was used for validation. This study omitted providers who had not publicly disclosed their activity, which would tend to lead toward underestimation of the total numbers of individuals who have taken ibogaine. This is particularly likely for scenes involving small numbers of patient participants, such as individuals obtaining ibogaine from the Internet. In order to account for this effect, estimates of hidden populations were obtained from individuals with extensive contact with the subculture as described below in Section 3.2.

2.6. Data analysis

A typology of scenes was constructed (Bailey, 1994), based on the classificatory dimensions of setting and the provider's set and credentials. The *setting* is the physical and ecological location in which the treatment takes place: a clinic or hospital, a private residence or hotel, or a religious shrine. A *provider* is an individual or group that administers ibogaine to the patient participant, and specifies the form and dose to be given. The provider determines the parameters of the treatment such as setting, inclusion and exclusion criteria, and medical monitoring. Providers may or may not have a credential as a licensed physician. The provider's set consists of the beliefs, expectations, attitudes and motivation that determine the intention to provide ibogaine. Provider set subsumes beliefs and expectations regarding ibogaine as a treatment for substance-related disorders, a psychotherapeutic adjunct, or religious sacrament. Motivational aspects of set may include the giving of care, activism, or ritual.

Quantitative data included the number of individuals who took ibogaine, and the number who took it for the treatment of a substance-related disorder, and specifically for acute opioid withdrawal. This data for each scene was included in Table 1, and the totals for each of the four types of scenes are indicated in Table 2.

3. Results

3.1. Typology

As indicated in Table 1, four types of scenes were identified and classified on the basis of the features of treatment setting, provider credentials and provider set; "medical model", "lay provider/guide", "activist/self-help" and "religious/ceremonial".

3.1.1. Medical model

In this type of scene the provider is a licensed physician. In the variation of the medical model type involving clinical research, some roles of the provider are distributed among authors of the study protocol and the physician investigator who prescribes ibogaine. Settings of the medical model are medical hospitals or clinics, or clinical research facilities, which are officially credentialed according to national and local requirements in a given country, as well as offices or residential settings in the case of treatment intended as psychotherapy. The set of the treatment provider includes the aim of emulating existing conventional medical standards in the treatment of addiction, clinical research, and/or psychotherapy.

Historically, the use of ibogaine in the medical model began in the 1950s, when clinicians and researchers viewed ibogaine much as they did other compounds classified as hallucinogens. Some, such as Jan Bastiaans, M.D. (Snelders and Kaplan, 2002), Leo Zeff, Ph.D. (Stolaroff, 2004), and Claudio Naranjo, M.D. (Naranjo, 1973), were interested in ibogaine as an adjunct to psychotherapy. Ibogaine, like other hallucinogens, was of interest as an experimental model of psychosis (Turner et al., 1955; Fabing, 1956; Salmoiraghi and Page, 1957; Schneider and Sigg, 1957). As with other hallucinogens, ibogaine may have also been investigated for military or intelligence purposes as a "truth serum", or a means of "brainwashing" or incapacitating an adversary which was the focus of MKULTRA (1977), a US Central Intelligence Agency project acknowledged to have existed from 1953 until 1964. Harris Isbell, M.D., an apparent participant in the MKULTRA project, directed the Addiction Research Center in Lexington, Kentucky where he reported administering ibogaine to human subjects in a letter to the Ciba Pharmaceutical, the manufacturer at that time (Isbell, 1955).

The medical treatment model presently exists mainly in countries adjacent to the US, such as Mexico, where ibogaine is subsumed within a physician's legal prerogative to prescribe experimental treatment, or Saint Kitts, where the government includes ibogaine in its national formulary and provides specific approval to the clinic there to administer it. The most common setting is a private clinic with less frequent use of hospitals. The clinics' Web sites tend to emphasize images that suggest comfort, safety, and the experience and expertise of the clinical team.

The standard of care varies among scenes in the medical model, but typically at a minimum involves pretreatment laboratory and electrocardiogram (EKG), vital signs and evaluation

Table 1
Ibogaine scenes: quantitative and descriptive features, grouped by scene type

Scene, year began- (year ended, if applicable)	Reason for taking ibogaine: *n*[a], *n* (%)[b] [*n* (%)][c]	Other non-substance-related reason for taking ibogaine	Dose/form	Setting/provider, medical evaluation and monitoring	Cost
Medical model type					
US, 1955 Lexington, KY (Isbell, 1955)	8 (research, subjects not seeking treatment)	Research, determination of psychoactive threshold	50–300 mg ibogaine HCl	Clinical research, US Public Health Service Hospital, Lexington, KY; Harris Isbell, M.D. Subjects were prisoners with prior histories of opioid dependence who had been abstinent for periods of months	Volunteers/prisoners
Chile, 1966–1967 Santiago (Naranjo, 1973)	30 None	Adjunct to psychotherapy	3–5 mg/kg ibogaine HCl	Claudio Naranjo, M.D., psychiatrist. Ibogaine administered in office setting in context of ongoing psychotherapy	N/A
Switzerland, 1980–1989 Zürich (Prins, 1988)	34 None	Adjunct to psychotherapy	4–10 mg/kg ibogaine HCl	Peter Baumann M.D., psychiatrist. Ibogaine administered in office or residential setting, given in context of ongoing psychotherapy	N/A
US, 1994–1995 Miami FL (Mash et al., 1998)	15 (Phase I clinical trial subjects not seeking treatment)	FDA approved clinical research	1–4 mg/kg ibogaine HCl	Phase I/II dose-ranging study. Juan Sanchez-Ramos, Ph.D., M.D., Principal Investigator, Deborah Mash, Ph.D., Co-Investigator. Jackson Memorial Hospital in Miami	Volunteers
Panama, 1994–1995 Panama City (Luciano, 1998)	11, 11 (100%) [9 (82%)]	Substance dependence only	10–25 mg/kg ibogaine HCl	Hospital Centro Medico Paitilla, full medical staff. Pretreatment evaluation included EKG, blood chemistry, medical and psychiatric history	No cost to $35,000 USD
Brazil, 1994–Sao Paulo (Sandberg, 2006)	9, 9 (100%) [1 (11%)]	Substance dependence only	10–20 mg/kg ibogaine HCl	Hospital Maternidade Maria Perpetua Piedade Goncalves, full medical staff. Pretreatment evaluation includes EKG, blood chemistry, medical and psychiatric history	$3000 USD
St. Kitts, 1996- (Mash et al., 2001)	400, 400 (100%) [316 (79%)][d]	Substance dependence only	600–1200 mg ibogaine HCl	See text for description of the approach to medical evaluation and monitoring developed by Jeffrey Kamlet, M.D	$10,000–$12,500 USD
Mexico, 2001– Playas de Tijuana, Baja California (Ibogaine Association, 2006)	283, 252 (89%) [186 (74%)]	psychotherapeutic, spiritual	12–18 mg/kg ibogaine HCl	Clinic or hospital. Pretreatment evaluation includes EKG, blood chemistry, medical and psychiatric history. Continuous EKG monitoring and presence of a nurse in the room with the patient during the treatment	$4000 USD
Mexico, 2005– Cancun (villaserena.org, 2006)	34, 34 (100%) [6 (18%)]	Substance dependence only	8–18 mg/kg ibogaine HCl	Clinic, private rooms. See text regarding medical evaluation and monitoring	$6000 USD

Lay provider/guide type					
US, 1962–1963 New York City (Lotsof and Alexander, 2001)	20; none sought treatment, 7 were opioid dependent	Lay experimentation and research, Psychotherapeutic	0.14–19.0 mg/kg ibogaine HCl	Apartments, private homes. No medical support. Self-administration and systematic self-observation	$15 USD for 500 mg
Central America, Caribbean, 1993– (Taub, 2006)	607, 455 (75%) [309 (68%)]	Psychotherapeutic, spiritual	9–36 mg/kg ibogaine HCl	Rented cottages in resort settings, private residences. Pretreatment medical and psychiatric history, EKG and blood chemistry	No cost to $4000 USD
Italy/France, 1994–(Naeher, 2006)	101, 44 (44%) [34 (77%)]	Psychotherapeutic, spiritual	10–23 mg/kg ibogaine HCl	Apartment. Physician available. Pretreatment medical and psychiatric history, EKG and blood chemistry	$1500 USD
Netherlands, 1999– Breukelen (Glatt, 2006)	200, 160 (80%) [144 (90%)]	Psychotherapeutic, spiritual	2–6 g *Tabernanthe iboga* extract (estimated 15% ibogaine)	Private home. Use of other "plant medicine or fungi" in combination with ibogaine. Pretreatment medical and psychiatric history, no medical testing	No cost to $2000 USD
Czech Republic, 2000– (Mariano, 2006)	102, 94 (92%) [73 (71%)]	Psychotherapeutic, spiritual	900–1600 mg ibogaine HCl	Apartments and private homes. Medical assessment by local consulting clinic, including medical and psychiatric history, EKG and blood chemistry	£600 GBP
UK, 2000– London, West Sussex (Conn, 2006; Wells, 2006)	83, 54 (65%) [46 (85%)]	Psychotherapeutic, spiritual	14–20 mg/kg, or 250–2000 mg ibogaine HCl	Multiple Providers; apartment or private home. Pretreatment medical and psychiatric history, EKG and blood chemistry	£400–£850 GBP
Canada, 2002–Vancouver, Toronto (ibogatherapyhouse.net, 2007)	64, 52 (81%) [36 (69%)]	Psychotherapeutic, spiritual	16–23 mg/kg ibogaine HCl	Multiple Providers; dedicated clinic, private residences. Pretreatment medical and psychiatric history, EKG and blood chemistry. Emergency medical technician on premises during treatment at clinic	$1000–$3500 CAD
South Africa, 2004–Eldoraigne (Rossouw, 2006)	36, 36 (100%) [23 (64%)]	Substance dependence only	15–19 mg/kg ibogaine HCl	Treatments conducted in private residences. Pretreatment medical and psychiatric history, EKG and blood chemistry. Arrangement for very rapid response emergency medical support	$3000 USD
Activist/Self-Help type					
Netherlands, 1989–1993 Rotterdam, other Dutch cities (Alper et al., 2001)	40, 40 (100%) [37 (93%)]	Substance dependence only	10–29 mg/kg ibogaine HCl	Multiple treatment providers; private residences and hotels. Pre and post-treatment medical evaluation. Strong involvement of activist drug user network	No cost to $18,000 USD
US, 2003– New York, San Francisco, other U.S. cities (Freedomroot.com, 2007)	160, 160 (100%) [152 (95%)]	Substance dependence only	21–24 mg/kg ibogaine HCl	The "ibogaine underground"; multiple treatment providers. Private residences and hotels. Pretreatment medical and psychiatric history, EKG and blood chemistry	No cost to $1500 USD
Religious/Ceremonial type					
Slovenia/Croatia, 1995– Ljubljana (Sacrament of Transition, 2006)	433, 424 98% [403 (95%)]	Psychotherapeutic, spiritual	20 mg/kg ibogaine HCl	Religious Ritual, treatment guide/priest. The Republic of Slovenia officially recognizes the Church of the Sacrament of Transition as a religion. Private homes. Initiates are interviewed and sign a statement attesting to their good health without clinical evaluation	€750 EUR

Table 1 (*Continued*)

Scene, year began- (year ended, if applicable)	Reason for taking ibogaine: *n*[a], *n* (%)[b] [*n* (%)][c]	Other non-substance-related reason for taking ibogaine	Dose/form	Setting/provider, medical evaluation and monitoring	Cost
France, 2000- (Meyaya, 2006)	378 45 (12%) [36 (80%)][d]	Bwiti initiation, psychotherapeutic, spiritual, general health issues	Dried root bark, 6–10 teaspoons[e]	Bwiti Religious ritual. Chateau, private residences. Nganga (ritual leader or priest) with African and European assistants. Requires only a doctor's or the prospective patient's statement assuring good health without clinical evaluation.	€ 650 EUR
France/UK, 2003–(myeboga.com, 2006)	316, 32 (10%) [6 (19%)]	Bwiti initiation, psychotherapeutic, spiritual, general health issues	Dried root bark 3–4 teaspoons[e]	Bwiti religious ritual, retreat. Resort settings, private residences. European initiates of the African Bwiti tradition with African and European assistants. Pretreatment medical and psychiatric history, blood chemistry and EKG. Medical doctor in attendance throughout the treatment	€500 EUR
Gabon, 1999– (Ebando, 2006)	50, 8 (16%) [5 (63%)]	Bwiti initiation, psychotherapeutic, spiritual, general health issues, fertility	Infusion, 20–25 teaspoons of fresh root bark scrapings	Bwiti religious ritual. Bwiti chapels in which Europeans and non-Africans are accepted. Prospective interview by a Nganga, without clinical evaluation	$4000 USD (for 1 month stay)

[a] *n* = number of individuals within each scene who took ibogaine.

[b] *n* (%) = subset of *n* who took ibogaine for the treatment of any substance-related disorder, expressed as absolute number, and as (%) of *n*.

[c] [*n* (%)] = subset of *n* who took ibogaine for the treatment of opioid withdrawal expressed as absolute number, and as (%) of the number of individuals who took ibogaine for the treatment of any substance-related disorder.

[d] Data regarding the number of individuals taking ibogaine for opioid withdrawal among all those who took ibogaine for the treatment of any substance-related disorder were missing for the St. Kitts and France 2000 scenes. For these scenes, the proportion seeking treatment specifically for opioid withdrawal relative to all those seeking treatment for any substance-related disorder was assumed to be the same as the rest of the sample. This yielded estimates of ($0.79 \times 400 = 316$) for St. Kitts, and ($0.79 \times 45 = 36$) for France 2000.

[e] One teaspoon of dried *Tabernanthe iboga* root bark weighs approximately 2–3 g. Also often referenced as a "coffee spoon" by French speaking providers.

Table 2
Numbers of individuals and reason for having taken ibogaine in each the four types of scenes

Type of scene	n[a]	Non-substance-related (%)[b]	Substance-related (%)[b]	Opioid[c] (%)[b]	%Opioid[d] of substance-related (%)
Medical model	824	118 (14%)	706 (86%)	518 (63%)	74
Lay provider/guide	1213	318 (26%)	895 (74%)	665 (55%)	74
Activist/self-help	200	0	200 (100%)	189 (95%)	95
Religious/ceremonial	1177	668 (57%)	509 (43%)	450 (38%)	89
Total	3414 (=N)[e]	1104 (32%)[f]	2310 (68%)[f]	1822 (53%)[f]	79

Summary data regarding numbers of individuals who took ibogaine and their reason for taking it, from the second column of Table 1 entitled "Reason for taking ibogaine. . .". The rows in this table summarize the data from the individual scenes for each type.

[a] n = total number of individuals who took ibogaine within each of the four types of scenes indicated in the left hand column.

[b] Percentage of n.

[c] Opioid = number of individuals who took ibogaine for the treatment of opioid withdrawal in the given type of scene.

[d] %Opioid of substance-related = percentage of individuals who took ibogaine for the treatment of opioid withdrawal relative to the number of individuals who took ibogaine for the treatment of any substance-related disorder.

[e] N = the total number of individuals who took ibogaine across all scenes.

[f] Percentage of N.

of the medical and psychiatric history, and some participation of nurses and physicians. The most intensive approach appears to have been that developed at the St. Kitts clinic (see Table 1). A recently started clinic in Mexico reported a similar clinical standard (villaserena.org, 2006). Prior to treatment with ibogaine, opioid dependent patients are converted to equivalent doses of orally administered short acting opioids. All centrally acting medications are tapered and discontinued for at least three serum half lives, although no specific drug interactions with ibogaine have yet been identified. Evaluation includes pretreatment Holter monitor and 12 lead EKG, and the following continuously during the treatment: EKG, vital sign and pulse oximetry monitoring, intravenous access, and the presence on site of an emergency physician with advanced cardiac life support certification and a registered nurse in the room with the patient continuously throughout the treatment (Mash et al., 2000, 2001).

3.1.2. Lay provider/guide

The term lay provider designates a provider without an official medical credential. The set and purpose of the treatment may be the medical treatment of addiction, psychotherapy, and/or spiritual growth. The dosage utilized for "psychospiritual" goals is typically on the order of half that required for opioid withdrawal. The treatment setting is a private residence or hotel, and the provider typically functions in the role of a "guide", or in the UK, a "sitter", and manages the treatment setting and the interaction with the patient with the goal of facilitating the therapeutic process. The treatment is conducted in a quiet, darkened room over a time interval of 12–18 h. Interaction with the patient is typically minimized during the treatment unless the patient initiates verbal communication because of the importance attributed to the patient's focus on the content of the experience. Some guides view ibogaine as unlinking mental representations from the pathological salience and obsessive motivational states with which they have become associated, allowing an opportunity for insight and positive change (Stolaroff, 2004). Goutarel et al. (1993) described the use of ibogaine in dosages of 10–50 mg as an antidepressant, and some contemporary lay providers presently use similar dosages given daily over periods of several days or weeks, to which they attribute an antidepressant effect or the diminution of craving (Kroupa and Wells, 2005). Interestingly, the low dose regimen is also reportedly used to limit or reduce opioid tolerance, which is an effect attributed to ibogaine in a patent obtained by Ciba Pharmaceutical 50 years ago (Schneider, 1957), and has been observed in subsequent preclinical research (Cao and Bhargava, 1997).

Regardless of their beliefs concerning ibogaine's psychotherapeutic benefits, lay treatment providers are aware of medical risk, which they make some attempt to minimize. A downloadable manual for ibogaine treatment (Lotsof and Wachtel, 2003) reflects collective views among lay providers regarding clinical issues such as the use of exclusion criteria and pretreatment laboratory tests, assuring adequate hydration during a treatment, or contingencies for accessing emergency medical intervention. A significant consensus exists among lay providers regarding the use of EKG and liver function tests in pretreatment screening, and with respect to a set of medical and psychiatric conditions are commonly designated as exclusionary such as cardiac disease, acute hepatitis and psychotic disorders.

3.1.3. Activist/self-help

This type of scene involves a lay provider with an activist or evangelical set that prominently includes the explicit objective of gaining acceptance of the use of ibogaine. Activist self-help providers often view their activities as a form of civil disobedience affirming the right to better treatment for a stigmatized group. A nexus exists involving the harm reduction movement and the ibogaine subculture. The ibogaine scene that existed in the Netherlands from 1989 to 1993 featured strong participation of European and U.S. addict self-help including the Dutch Junkiebond, which was a model for subsequent European drug user unions and a vanguard of the harm reduction movement (Grund, 1995; De Rienzo and Beal, 1997; Alper et al., 2001; Frenken, 2001; Lotsof and Alexander, 2001). The "ibogaine underground", or "Freedomroot" (Freedomroot.com, 2007) is a scene that recently emerged in the U.S. that recalls the earlier

aggressive advocacy in the Netherlands. It is a network of individual providers, many of whom themselves are former patient participants in the subculture, who actively reach out to heroin users in New York and some other US cities.

The following quote from a post to an ibogaine list server captures some important attitudes and beliefs of the subculture associated with the activist/self-help type. These include the identification of individuals with severe opioid dependence as a marginalized population abandoned by the institution of conventional medicine, the theme of self-help, and the attribution of aspects of the medical model to "underground providers", who are referenced sympathetically as doing "most of the research".

> ". . .No one with the money and clout to do so wants to touch ibogaine. . . The reasons are numerous, from its illegal status in some places, to the stigma attached to drug addiction to begin with . . . with the result that most of the research is being done by underground providers who only have lists like this and the internet to help share information with each other. I can tell you from personal experience with an 8+ year opiate addiction . . . if it wasn't for ibogaine I doubt I would be clean today, two and a half years later. There are many more people on this list who can also tell you the same thing from their own personal experience. It's a risk to be sure. The risk of death, and the risk that it might not work . . . But for me it came down to the fact that absolutely nothing else had worked for me . . . in the end it was through ibogaine that I finally got clean."

3.1.4. Religious/ceremonial

Scenes of this type involve a lay provider and the setting of Bwiti religious shrine in Africa, or any residential, or hotel or resort setting intended to provide a religious or ceremonial context. A provider set of identification with traditional Bwiti ritual culture may exist in scenes in either Gabon or Europe. The scenes listed here are those involving participants from Europe or the US. Individuals who take ibogaine in these scenes tend to be seeking a spiritual experience, although even in the religious scene type about a third of participants primarily seek treatment for substance dependence. As in Africa, there are also those who seek to use ibogaine in a traditional context as treatment for medical illness or infertility.

In their comparative analysis of the African Bwiti religious context and an addict self-help scene, Fernandez and Fernandez (2001) identify the construct of personal transformation, guided by insight or new knowledge mediated by iboga/ibogaine, as a common feature of central importance, and reference ibogaine as a "transitional alkaloid". The similarly named Sacrament of Transition (2006) is a ritual context of Western creation that is officially recognized as a religion in Slovenia with a large proportion of participants who took ibogaine for heroin withdrawal. The Bwiti theme of personal transformation is shared among diverse religious cultures, regardless of the ritual use of hallucinogens, and in their own narratives patients in conventional treatment settings frequently characterize recovery from substance dependence as a spiritual transformation (Galanter, 2006).

3.2. Quantitative data

Table 2 summarizes the quantitative data regarding numbers of individuals taking ibogaine and their reason for taking it, totaled across each scene type from Table 1. The total number of individuals across all scenes who have taken ibogaine is 3414. This is approximately a fourfold increase relative to the estimate of 857 of 5 years before based on previously published quantitative data from early 2001 (Alper et al., 2001). As indicated in table, 68% of the total number of individuals across all scenes took ibogaine for the treatment of substance-related disorders, and 53% specifically for opioid withdrawal.

The effect of hidden populations would lead to underestimation of the true number of participants in the ibogaine subculture. In order to estimate this effect, the editors of the most frequently utilized ibogaine list server (Kroupa, 2006), and a popular ibogaine Web site (Sandberg, 2006) were asked to blindly and independently estimate the "hidden proportion", i.e. the proportion of participants in the ibogaine subculture in scenes that would have been overlooked by the criteria used in this study. Both estimates of the hidden proportion fell within a range of 20–30% (personal communication, Patrick Kroupa, December 3, 2006 and Nick Sandberg, December 4, 2006), as did the hidden proportion of an unpublished sample (Bastiaans, 2004), suggesting that most treatments involve experienced providers who are open about their activity. These sources agreed regarding the view that opioid withdrawal was the most common reason for taking ibogaine, and that the subculture had expanded greatly over the prior 5 years. Taking the hidden proportion estimates into account yields an estimated range of approximately 4300–4900 individuals who took ibogaine outside of Africa as of February 2006.

4. Discussion

4.1. A medical subculture, distinct from other drug subcultures

The clinical focus on the treatment of opioid withdrawal distinguishes the ibogaine subculture from subcultures associated with psychedelic or other illegal drugs. The reason for taking ibogaine was more frequently to alleviate the symptoms of opioid withdrawal than to pursue spiritual or psychological goals. In the US, the expansion of the ibogaine subculture coincides temporally with a substantial increase in the public health impact of opioid use disorders (Compton and Volkow, 2006). The incidence of opioid-related deaths in the US doubled between 1999 and 2004 (Fingerhut, 2007), with methadone and oxycodone accounting for most of this increase. In contrast to trends regarding opioids, there was no increase in use of hallucinogen and MDMA among young adults in the US between 2002 and 2005 (Substance Abuse and Mental Health Services Administration, 2006), suggesting that the recent expansion of the ibogaine subculture is not an epiphenomenon of popular interest in psychedelic drugs and the availability of psychoactive substances on the Internet (Schifano et al., 2006).

The ibogaine subculture is not a counterculture (Yinger, 1960) because its identity is not defined on the basis of opposition to conventional medicine. The subculture is to a significant extent an innovation by its participants in response to a demand for a treatment that is unavailable in the conventional medical setting. Although it involves alternative means, the ibogaine subculture shares with the conventional medical culture the common goal of providing treatment, which it emulates in the medical model type, or the utilization by lay treatment providers of medical tests for pretreatment evaluation. Criminality per se is not a significant focus of the subculture, which exists because of ibogaine's lack of availability within the institution of clinical medicine, and not its illegality. Ibogaine is not illegal and available by Internet in most of the world. It is illegal in the US, Australia and five EU countries, but it is available throughout Europe and the Americas including Canada and Mexico.

4.2. Study limitations and methodological concerns

The issue of observer subjectivity is an important concern regarding the participant–observer approach. The need to establish rapport and elicit collaboration and disclosure may conflict with the imperative of scientific objectivity (Jackson, 1983; Malterud, 2001), and beliefs and attitudes that motivated interest in ibogaine and provided contacts and access within the subculture are also a potential cause of bias. Qualitative methodology acknowledges that the problem of observer subjectivity always exists, and addresses it by and attempting to account for its effect by the use of multiple validating approaches (Malterud, 2002). Validating approaches utilized in this study include triangulation of the data across providers, patient participants and other informants, as well as longitudinal observation involving multiple contacts over time.

The authors' collective access and intensive observation of the ibogaine subculture suggests that this study approaches an exhaustive, and not merely representative sampling of publicly identified ibogaine scenes. The intensiveness of the sampling in this study indicates that most of the use of ibogaine outside of Africa has taken place in the scenes that are included in Table 1, even taking into account the problem of hidden populations.

4.3. Implications of the "vast uncontrolled experiment"

Frank Vocci, who oversaw NIDA's ibogaine project as the head of Medications Development (Vastag, 2005), characterized the ibogaine subculture as a "vast uncontrolled experiment". The term has significant literal merit. The data on *iboga* alkaloids collectively subsumes significant elements of a drug development process in various stages of completion, including substantial preclinical and open label study evidence, preclinical toxicological studies, and some initial Phase I safety and pharmacokinetic data.

Reports of efficacy of ibogaine in opioid withdrawal may be valid irrespective of the methodological limitations associated with the clinical settings in which ibogaine is presently used. Unlike other outcomes such as post-treatment drug abstinence or craving, the clinical expression of acute opioid withdrawal occurs within a limited time frame, is easily operationalized, tends to be robust, and can be assessed accurately by typically experienced lay providers. It appears unlikely that suggestion or placebo could solely mediate the effect attributed to ibogaine in acute opioid withdrawal. Recent Cochrane reviews on the management of acute opioid withdrawal with α_2-agonists (Gowing et al., 2004), buprenorphine (Gowing et al., 2006) or methadone taper (Amato et al., 2005) evaluated a combined total of 56 studies. Overall rates of treatment completion among studies of α_2-agonists, buprenorphine, or methadone, respectively ranged from 48 to 64%. Only 3 of the 56 studies included a placebo comparison, and all indicated a strong distinction of placebo from any active drug treatment at a level of significance of $p < .001$ on the basis of more frequent failure to complete detoxification (Benos, 1985; San et al., 1992) or higher ratings of withdrawal symptoms (Gerra et al., 1995) in the placebo group. The relatively negligible effect of placebo in acute opioid withdrawal is likely further reduced with the greater severity of physical dependence that is generally characteristic of individuals who take ibogaine, such as a series of 33 patients whose average daily heroin use was 0.64 g, mainly by the intravenous route (Alper et al., 1999; Frenken, 2001).

The authors are aware of a total of 11 individuals that are reported to have died within 72 h of taking ibogaine from the time of the first such fatality in 1990 (Alper, 2001) until February 2006. Collectively, the cases suggest that cardiac rhythm may be a particularly significant domain of medical risk. Deaths were most commonly attributed to a cardiac cause in association with significant risk factors such as a prior myocardial infarction, cardiomyopathy or valvular disease, or to pulmonary embolus. Other deaths were regarded as mixed drug overdoses involving opioids with or without the additional ingestion of cocaine (Alper et al., 1999; Marker and Stajic, 2002). Deaths not involving the above factors have been associated with the use of *Tabernanthe iboga* alkaloid extract (Alper, 2001) or dried root bark (Kontrimaviciute et al., 2006b). This subset of fatalities may reflect a general hazard associated with the use of indigenous ethnopharmaceutical forms outside of their traditional context by the uninformed or inexperienced (Callaway and Grob, 1998; Maas and Strubelt, 2006). For example, one death (Kontrimaviciute et al., 2006b) involved ingestion of an amount of powdered dried root bark that is at least twice the maximum upper limit used by the providers in this study who are traditional African Bwiti adepts. Other potential hazards may be associated with the lack of pharmaceutical standards for ibogaine, including unregulated procedures for manufacturing and storage or the possibility of naturally co-occurring toxic alkaloids (Singbartl et al., 1973; Jenks, 2002; Kontrimaviciute et al., 2006a).

Cerebellar Purkinje cell degeneration reported in rats administered ibogaine at high dosages of 100 mg/kg (O'Hearn and Molliver, 1993, 1997) prompted concern regarding potential neurotoxicity. The FDA was aware of this research at the time it approved the Phase I study; other work indicated no evidence of neurotoxicity rats at the dosage of 40 mg/kg typically used to

study drug self-administration and withdrawal (Molinari et al., 1996). Evidence of neurotoxicity due to ibogaine is reportedly absent in mice (Scallet et al., 1996), primates (Mash et al., 1998) and a postmortem neuropathological examination of a woman who had taken ibogaine four times in the prior 15 months at doses up to 30 mg/kg. In the Phase I study, quantitative dynamic measures of cerebellar motor function were unremarkable in human subjects that received low doses of ibogaine of 1 and 2 mg/kg (Mash et al., 1998). The study was never finished due to contractual disputes with eventual litigation among the study sponsors, unrelated to clinical issues. The σ_2 receptor mediates neurotoxic injury (O'Hearn and Molliver, 1997; Bowen, 2001), and is apparently not involved in effects of ibogaine on drug self-administration and withdrawal (Glick et al., 2001). This suggests that the therapeutic and neurotoxic effects of *iboga* alkaloids can be resolved from one another by rational drug design, as indicated by the example of 18-MC, which has lower affinity for the σ_2 receptor and is not associated with evidence of neurotoxicity even at very high dosages (Maisonneuve and Glick, 2003).

4.4. Suggestions for future research

Experimental pharmacologists are increasingly interested in the development of approaches to addiction that extend beyond the present repertoire of agonist or antagonist actions, and instead are targeted at effects on intracellular signaling downstream from the receptor (Bonci and Carlezon, 2005). Ibogaine may provide a prototypic example of an agent with such novel mechanisms of action. Future work should replicate and extend on prior research indicating that *iboga* alkaloids modulate signal transduction in second messenger pathways linked to G protein-coupled receptors (GPCRs) (Rabin and Winter, 1996a,b).

Constitutive spontaneous activity without the binding of an agonist (Costa and Cotecchia, 2005) occurs in GPCRs such as opioid receptors (Shoblock and Maidment, 2006). Constitutive signaling mediated by conformational states of receptor-associated proteins may be modulated relatively rapidly and span a wide signal range, consistent with a possible role in the highly dynamic neuroadaptations associated with opioid tolerance and withdrawal. It may be worthwhile to investigate the possibility that *iboga* alkaloids interact allosterically or orthosterically with GPCRs to affect constitutive signaling. A possible role of orphan receptors should be also considered (Civelli et al., 2006).

Functional and clinical evidence of muscarinic cholinergic actions of *iboga* alkaloids includes the occurrence of a state with some neurophysiological and behavioral features common to REM sleep (Schneider and Sigg, 1957; Depoortere, 1987; Goutarel et al., 1993; Alper, 2001), and recent work suggesting that muscarinic acetylcholine receptors (mAChRs) as well as nAChRs in the habenulopeduncular pathway mediate the effects of 18-MC on dopamine efflux in the NAc (Taraschenko et al., 2007a,b). Ibogaine interacts with cholinergic neurotransmission in multiple ways; as a strong antagonist at nAChRs (Daly, 2005), binding to mAChRs with affinities on the order of approximately 10 μM with actions that are not well characterized with regard to antagonist versus agonist effects, and according to an older literature, inhibition of acetylcholinesterase (Vincent and Sero, 1942). The knockout mouse, which exists for each of the five basic subtypes of mAChRs (Wess et al., 2003), provides an in vivo approach that makes it possible to study functional correlates of activity at mAChRs such as the EEG or cardiac electrophysiology, as well as the role of mAChRs in ibogaine's effects on models of substance-related disorders.

Structure–function relationships mediating toxic and therapeutic effects of *iboga* alkaloids have been identified and utilized to guide rational synthesis (Glick et al., 1994; Kuehne et al., 2003; Maisonneuve and Glick, 2003). Preclinical toxicological testing, and if appropriate, clinical research on *iboga* alkaloids will require the development of pharmaceutical synthetic and chemical manufacturing technology in order to produce adequate quantities of investigational drug in conformance with international Good Manufacturing Practice standards. The chemical, manufacturing and control stage of pharmaceutical development generally is accomplished in the private sector, but the pharmaceutical industry historically has shown less interest in developing drugs for substance-related disorders relative to other indications (Gorodetzky and Grudzinskas, 2005), indicating an important need for involvement of the public sector.

5. Conclusions

The estimated number of participants in the ibogaine subculture increased fourfold relative to the prior estimate of 5 years earlier, an average yearly rate of growth of approximately 30%. The existence and expansion of the subculture indicates a demand for new treatment, which is sought regardless of medical risk, inconvenience, expense, and in some cases legal prohibition. Across a diversity of settings, most individuals who took ibogaine did so for the treatment of a substance-related disorder, specifically for opioid withdrawal. Ibogaine's effect in opioid withdrawal is consistent with case series and preclinical evidence, and is unlikely to be mediated by placebo. The mechanism of ibogaine's action in opioid withdrawal merits further investigation as a paradigm for neurobiological research and rational pharmaceutical development.

Conflict of interest statement

We declare that we have no conflict of interest. Howard Lotsof was awarded multiple patents on the use of ibogaine in substance-related disorders, which he divested in 1998.

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