

Ibogaine in the Treatment of Substance Dependence

Thomas Kingsley Brown*

University of California, San Diego, 9500 Gilman Drive, Mail Code 0311, La Jolla, CA 92093-0311, USA

Abstract: Ibogaine is a psychoactive alkaloid derived from *Tabernanthe iboga*, a plant used in initiatory rituals in West Central Africa. Largely because of ibogaine's status as a Schedule I substance in the U.S., the development of ibogaine's use in the treatment of drug addiction took place outside conventional clinical and medical settings. This article reviews the history of ibogaine's use in the treatment of drug addiction, and discusses progress made towards, and obstacles blocking, the establishment of controlled clinical trials of ibogaine's efficacy. Preclinical research has generally supported anecdotal claims that ibogaine attenuates withdrawal symptoms and reduces drug cravings. Concerns about ibogaine's safety, as well as a dearth of solid data from human studies, have hampered progress in its development as an approved medication. This article outlines major findings from preclinical studies, discusses concerns about ibogaine's safety, and details previous and ongoing research on ibogaine's use as an anti-addictive treatment for humans.

Keywords: Addiction, addiction treatment, drug abuse, ibogaine, iboga alkaloid, psychedelics, substance-related disorders.

INTRODUCTION: BACKGROUND AND HISTORY

Ibogaine is a naturally occurring psychoactive indole alkaloid, one of at least a dozen alkaloids found in the rainforest shrub *Tabernanthe iboga*. Scrapings from the root bark of the plant have been used in low doses to combat fatigue, thirst, and hunger and in higher doses as a sacrament in religious and initiatory ceremonies, likely for many centuries, by people in West Central Africa [1]. Ibogaine is the most studied of the alkaloids present in the iboga shrub, having been used as an adjunct to psychotherapy as early as the 1950's and, in more recent decades, having been the subject of biological and clinical research investigating its purported efficacy for the treatment of addiction to opiates and other substances [2-4].

Although there is substantial evidence from preclinical studies and open-label clinical studies supporting the anecdotal reports of ibogaine's ability to interrupt addiction to opiates and other substances of abuse, there have not as yet been any complete controlled clinical trials, in part because side effects and safety concerns have hampered ibogaine's development as a therapeutic medicine [2]. What follows here is an historical overview of the emergence of ibogaine as an anti-addictive medicine within the "ibogaine medical subculture" [5] and of the barriers that have blocked its development as a legally available medicine in the U.S. and several other nations, as well as an overview of the evidence, from preclinical studies and from studies of treatments by ibogaine providers, of the drug's efficacy.

In West Central Africa, primarily in Gabon and Cameroon, initiates of the Bwiti religion chew preparations of iboga root bark during overnight rituals [1]. Iboga usually facilitates for the initiate a visionary experience having as

common themes travel along the path of birth and death, often to ordinarily unseen realms, and contact with the dead or with higher powers.

According to the timeline constructed by Dr. Kenneth Alper [2], *T. iboga* was first introduced to the Western world in 1864, when samples of the plant were brought to France from Gabon, and its ritual usage was first described in print in 1885 [6]. Ibogaine was first crystallized from extracts of the shrub's root bark in 1901 [2], and its pharmacodynamic properties were first explored in the first decade of the 20th Century; during that same time was recommended as a treatment for "asthenia" at a dosage of 10 to 30 mg per day. From 1939 to 1970 ibogaine was marketed in France as "Lambarene," a "neuromuscular stimulant" in the form of 8 mg tablets, for conditions including fatigue, depression, and infectious disease [6].

Nowadays ground, dried iboga root bark is sometimes used clinically by ibogaine providers in Mexico and elsewhere, as is an alkaloid extract of the root bark, in treatments for indications of substance use disorders [7]. However, the form most commonly used at ibogaine clinics is the ibogaine hydrochloride salt [5].

The serendipitous discovery of ibogaine's anti-addictive properties is attributed to Howard Lotsof [3, 4, 8, 9]. Lotsof was a habitual user of heroin who organized and participated with a group in New York City that met occasionally during the period of 1962-1963 to study the subjective effects and possible psychotherapeutic benefits of a wide variety of psychoactive drugs [3]. Lotsof and other members of the group, twenty individuals in all, ingested ibogaine at dosage levels up to 19 mg/kg. Of those twenty individuals, seven were dependent on heroin; following their initial ingestion of ibogaine, 5 of those 7 reported that they entirely abstained from heroin use for at least 6 months thereafter [8-10]. Lotsof notes that, in the aftermath of an initial ibogaine experience that lasted for more than 30 hours, he became aware that he did not suffer from heroin withdrawal, nor did he crave the opiate despite not having used it since ingesting

*Address correspondence to this author at the University of California, San Diego, 9500 Gilman Drive, Mail Code 0311, La Jolla, CA 92093-0311, USA; Tel: (619) 823-0069; Fax: (858) 534-8895; E-mail: tkbrown@sea.ucsd.edu

the ibogaine. The other heroin-dependent members of the group reported a similar absence of cravings and withdrawal symptoms. Sensing the possibility that the group had discovered an important medicinal use for ibogaine, Lotsof eventually made it his life's work to advocate for policy changes and research geared towards making ibogaine available as an anti-addictive medicine [8, 10]. He eventually patented the use of ibogaine to treat dependence on opiates [11] and also for the treatment of dependence on cocaine and amphetamine, alcohol, nicotine, and poly-substance abuse [12 - 15].

In 1957, prior to ibogaine's use in the treatment of drug addiction, Ciba Pharmaceutical patented its use for the purpose of enhancing the analgesic effects of opiates [16]. The mechanism by which Ibogaine potentiates the analgesia of opiates is apparently by an enhancement in opiate signaling and not because of agonistic or antagonistic binding at opiate receptors [7].

In the late 1950's and 1960's ibogaine was utilized as an adjunct to psychiatric treatment, most famously by Chilean psychiatrist Claudio Naranjo, who reported that ibogaine's tendency to enhance the retrieval of personal subjective memories and fantasies on the part of his patients helped to facilitate the closure of unresolved conflicts [17], but also by Leo Zeff and other psychotherapists on the West Coast of the U.S. who worked with a variety of psychedelic substances including ibogaine [8, 18, 19]. Zeff characterized ibogaine as particularly effective in enabling patients to recognize psychological "blocks" that they had previously denied [18, 19]. In 1969 Naranjo received a French patent for the psychotherapeutic use of ibogaine in the dosage range of 4 to 5 mg/kg [2].

Possession of ibogaine was made illegal in the U.S. in 1967. In 1970 the U.S. Food and Drug Administration classified ibogaine as a Schedule I drug along with scores of other psychoactive substances, including the better known and more widely used tryptamines LSD and psilocybin [2]. Today ibogaine is unregulated in most nations but is illegal in the U.S., Australia, Belgium, Denmark, France, Sweden, and Switzerland [5].

In 1982, Lotsof created the Dora Weiner Foundation, a nonprofit corporation dedicated to the goal of legitimizing the use of ibogaine for the treatment of substance abuse disorders, and in 1986 he launched a private company called NDA International, which provided funds to support research in Rotterdam and New York testing ibogaine with animal models of opiate addiction and withdrawal [8]. The research in Rotterdam led to the first publication showing evidence of ibogaine's efficacy in attenuating withdrawal-like symptoms in animals [20]. Soon thereafter, Dr. Stanley Glick's research team at Albany Medical College demonstrated that ibogaine produced a reduction in morphine self-administration by rats [21, 22].

Lotsof's efforts to legitimize ibogaine's medical use over the next few years nevertheless failed to elicit interest and investment by the pharmaceutical industry, perhaps due to a number of considerations including the unconventional developmental setting of the drug [8], Lotsof's lack of medical or scientific credentials [10], the fact that ibogaine is a naturally occurring compound and thus cannot itself be

patented, or the pharmaceutical industry's view that addiction was an unprofitable area for drug development [23].

Starting in 1989, ibogaine treatments for drug dependence took place in non-medical settings in the Netherlands with support from NDA International and DASH, the Dutch Addict Self-Help organization, as well as ICASH, the International Coalition of Addict Self-Help [2]. Roughly 40 to 45 patients were treated in the period from 1989 through 1993 [8]. Also during this period, based on the early preclinical evidence and case reports suggesting ibogaine's possible efficacy, the Medication Development Division of the US National Institute on Drug Abuse (NIDA) began supporting preclinical toxicological research on ibogaine and the development of human clinical trials [2]. In 1993, the Drug Abuse Advisory Panel of the US FDA granted Deborah Mash's team at the University of Miami a phase I pharmacokinetics and safety trial of ibogaine in male subjects, and in 1995 the FDA approved a revised protocol to conduct such a study with cocaine-dependent subjects [4]. During that same period (1993-1994), NIDA developed a phase I/II protocol involving fixed dosages of 150 mg and 300 mg of ibogaine HCl versus placebo for the indication of cocaine dependence [2]. Meanwhile plans were afoot at Erasmus University in Rotterdam to develop a human clinical trials protocol [8].

Within a few short years, however, these promising avenues were all blocked. In 1993 the death of a female patient in the Netherlands effectively brought an end to the NDA-funded treatments in the Netherlands and severely dampened Dutch enthusiasm for further funding and research on ibogaine treatment. Development of the clinical trial in Rotterdam was halted even though the official Dutch inquiry found no conclusive role for ibogaine in the patient's death [8].

The dose escalation trials at the University of Miami were cut short in 1995 due to a lack of sufficient funds to complete the study [4]. Also in 1995, significantly influenced by the critical opinions of consultants from the pharmaceutical industry, NIDA opted not to fund its proposed phase I/II clinical trials, though they continued to support preclinical research on ibogaine [2, 8].

In the wake of the denial of official approval for the study of ibogaine in Europe and in the United States, ibogaine became increasingly available in alternative settings [2, 5], effectively launching what science journalist Brian Vastag [24] referred to as a "vast, uncontrolled experiment." Treatment based on a conventional medical model was available in Panama in 1994-1995 and in St. Kitts from 1996 until at least 2001 [5], while treatments in informal settings became available in many countries, including the U.S., the Netherlands, Britain, Slovenia, and the Czech Republic [2] and, in later years, also including Mexico, Canada, and South Africa [5].

The far-flung, mostly informal network of ibogaine providers grew with increasing rapidity over the following decade or so. An exhaustive ethnographic study of this "ibogaine medical subculture" [5] estimated that 3,414 individuals (plus the "hidden population" accounting for approximately an additional 20 to 30%) had taken ibogaine

outside of West Central Africa as of February of 2006, a roughly fourfold increase relative to the cumulative total 5 years earlier [2, 5]. Of the total, 68% had ingested ibogaine for the treatment of a substance-abuse disorder, and 53% specifically for treatment of opioid dependence [5]. A sizeable minority had taken ibogaine for the purpose of promoting personal psycho-spiritual growth.

The study identified four distinct “scenes” or providers with an associated setting, including the “medical model” scene, in which the provider is a licensed physician, and the setting is a medical hospital or clinic or a clinical research facility, with credentials appropriate for the governmental jurisdiction, in the case of treatment for substance abuse disorders; the “lay provider/treatment guide” scene, in which the provider lacks official medical credentials, and the setting is usually a private residence or hotel; the “activist/self-help” scene, involving a provider with an activist or evangelical mindset holding the explicit goal of gaining wider acceptance for the use of ibogaine and providing better treatment for a socially stigmatized group; and the “religious/spiritual” scene involving a lay provider, a setting intended to provide a spiritual or ceremonial context, and usually a participant ingesting the ibogaine for purposes of psycho-spiritual growth rather than for treatment of a substance-related disorder [5].

Most Ibogaine clinics operating in countries where ibogaine use is allowed can be discovered and contacted via the Internet by individuals in other countries, most commonly residents of the U.S., seeking treatment [5]. Such clinics usually maintain a web presence to attract clients. Pages dedicated to information on and discussions of ibogaine and support for patients exist on Internet social media sites. For example, Erowid.org maintains pages that provide a collection of personal experiences submitted by people who have used ibogaine, information on the history and chemistry of the drug, and a bibliography of literature about ibogaine [25, 26]. Based on information volunteered by approximately 40 individuals receiving ibogaine treatment for opiate dependence in Mexico, each of whom travelled from the U.S. to Mexico for treatment [27, 28], many people treated at ibogaine clinics first learn about ibogaine treatment via the Internet.

Typical clinical usage for interrupting addiction involves the ingestion of the hydrochloride salt of ibogaine (ibogaine HCl) at a dosage of 15 to 20 mg/kg of the patient’s body weight [29], whereas usage for psycho-spiritual purposes typically involves dosages roughly half as strong [5]. The form of ibogaine used most often in the clinical setting is ibogaine HCl of 95 to 98% purity prepared from extracts of the root bark and available at a cost of about \$125-\$250 USD per gram [7]. A 13-step synthesis of ibogaine from nicotinamide has been described [30, 31] but ibogaine can also be produced by semi-synthesis from voacangine, an alkaloid found in *Voacanga Africana* [32].

For the treatment of substance dependence, ibogaine has most commonly been administered in a non-hospital setting in the morning, most commonly in the form of a single dose of ibogaine HCl [2]. The patient lies still and awake in a quiet, darkened room for the duration of the treatment. Reports of ataxia and sudden vomiting within the first several hours are common.

Following the administration of the ibogaine, the subject experiences a sharp reduction in drug cravings and signs of withdrawal within 1-2 hours [2]. Patients commonly report sustained resolution of the withdrawal syndrome within 12-18 hours [3] and a reduction in or absence of drug cravings lasting for at least a few days and sometimes up to two months [10].

Based on interviews of patients and treatment providers and on case reports and general descriptions available in the literature, the typical subjective experience following ibogaine ingestion has been characterized as occurring in 3 distinct “stages” [2, 3]. The onset of the “acute” phase occurs within 1-2 hours of ingestion and lasts for 4-8 hours and is often marked by emotional intensity and the experience of location and interaction within a “waking dream.” The visions produced by ibogaine tend to be most intense when the subject’s eyes are closed and to be suppressed when eyes are open, in contrast to the visual stimuli produced by the “classical” hallucinogens such as LSD and psilocybin, which generally impose themselves onto the subject’s normal visual field. Citing the dream-like quality of the ibogaine experience, some authors prefer to refer to ibogaine as an oneirophrenic substance rather than a hallucinogen [6]. With ibogaine, commonly reported themes during the acute stage include visions of, and interrogatory exchanges with, ancestral or archetypal persons or beings; placement in and movement within a dream-like visual landscape; and panoramic recall of personal experiences or past events. Some reports indicate that these visions appear only when the viewer’s eyes are closed, and that when the eyes are open, people and things in the surrounding environment appear normal. Typically, an abrupt cessation of these visions marks the conclusion of the acute phase. There is wide variation among individual experiences, and not everyone experiences strong visual stimuli with ibogaine. The visual experience (or lack thereof) does not seem to correlate with the ibogaine’s effect on acute opiate withdrawal [3].

The “evaluative” stage begins 4-8 hours after ingestion and lasts for 8-20 hours [2, 3]. During this phase the subject’s attention continues to be inwardly directed rather than towards external stimuli, and the emotional tone tends to diminish in intensity. Stimuli from the external environment may be experienced as distracting and annoying, and so the patient usually prefers to remain in a quiet environment at this time. The panoramic recall slows considerably or entirely as the patient reflects upon and evaluates the experiences of the acute phase. The material contemplated during this stage may consist of experiences from the dreamlike period as well as recollections of other memories and often concerns traumatic or highly emotional experiences, important personal relationships, or impactful decisions the patient has made [5].

The onset of the final stage, called the “residual stimulation” phase is roughly 12 to 24 hours after ingestion; this period generally lasts for 24-72 hours or even longer. Reports of this phase suggest that the patient returns to a normal state of attention to the external environment during this time. Meanwhile the subjective intensity of the experience subsides, though there is a lingering state of arousal or vigilance. Patients receiving ibogaine for drug

dependence often report a significantly diminished need for (or ability to) sleep, and sometimes report a period of a reduced need for sleep lasting for days or weeks. In all, the three phases resolve for most patients within 48 hours of ingestion, and for a substantial proportion within 24 hours [3].

The subjective experience of ibogaine is often described as unpleasant or even harrowing by patients receiving the drug in the treatment setting [27, 28]. It has been referred to as “brutal and unpleasant” [33] in the context of treatment for opiate dependence and as a “rough trip” in an exploratory, non-treatment context [31]. The psychologically and physically difficult nature of the experience renders ibogaine unappealing as a recreational substance [3]. For patients treated for drug addiction, the difficulty may be accentuated when they are compelled during the ibogaine experience to contend with the psychological and social consequences of a long term pattern of substance abuse; when interviewed, many such patients report having to contend with deep feelings of regret and remorse when confronted with the impact of their addictions upon their own lives and on relationships with friends and family members [27, 28]. The experience appears to reap psychological benefits for at least some people, though; reports by drug dependent patients in a study of the psychotropic effects of ibogaine [34, 35] reveal that the most common themes emerging from the interpretation of the experience included a sense of insight into destructive behaviors (86.7% of respondents), a felt need to become abstinent (68.3%), the experience of having been cleansed, healed, and reborn (50.0%), and the sense of having a second chance at life (40.0%) [4].

The question of whether or not the visions and self-reflection produced by ibogaine have an impact on substance use in the weeks and months following treatment is one that remains to be answered or even directly addressed by researchers. Indeed, for reasons discussed below there have been few rigorous studies of treatment outcomes for patients at ibogaine clinics. A few studies, discussed in detail below, have examined outcomes of such treatment. These studies provide some important data on short-term outcomes, in particular regarding the resolution of withdrawal signs, but their usefulness is limited by, in some instances, a lack of rigorous methods, short observational periods (one month or less), and the absence of controls for comparison.

EVIDENCE FOR EFFICACY: PRECLINICAL RESEARCH, PHARMACOLOGY, AND MECHANISMS OF ACTION

Beginning in the mid-1980's, scientists began using animal models of addiction to test the claims made within Lotsof's patents, specifically that ibogaine eliminates withdrawal symptoms and drug cravings and that it interrupts opiate, stimulant, nicotine, and alcohol addictions for several days or possibly for months following the administration of a single dose. Those claims have largely been supported by preclinical studies, most of which took place in the late 1980's and the 1990's, demonstrating in animal models of addiction that ibogaine significantly attenuates withdrawal signs and reduces drug self-administration [2, 7]. A detailed examination of the

preclinical evidence, as well as of the pharmacokinetics and proposed mechanisms of actions of ibogaine, exists elsewhere [2] as does a summary that includes the more recent preclinical studies [7]. An extensive review of the pharmacology of ibogaine is available as well [36]. A relatively brief overview of these topics is provided here.

Ibogaine and two closely related compounds have been studied for their anti-addictive effects in animals: noribogaine, the *O*-demethylated metabolite of ibogaine [36, 37], and 18-methoxycoronaridine (18-MC), a structurally related congener to ibogaine which was developed by way of a rational pharmaceutical approach [37] with the intention of creating a medicine with the anti-addictive efficacy of ibogaine but lacking the aversive and dangerous side effects of ibogaine [38]. There are no reports of 18-MC having been tried in humans [39] but this compound, like noribogaine, has been shown to be equally as effective as ibogaine with respect to attenuating withdrawal-like symptoms and reducing drug self-administration [37].

Evidence from animal models of addiction includes studies for ibogaine's efficacy in reducing self-administration of morphine or heroin [21, 40-43], cocaine [21, 40, 44], alcohol [45, 46] and preference for nicotine [47]. There is also evidence for persistent reductions, lasting for a few days or more after administration of ibogaine, in the preference for cocaine [40, 44] and in the self-administration of cocaine or morphine [21, 42]. Results from studies in which the standard single-dose regimen was modified (for example, when 2 doses of ibogaine were administered 6 hours apart [44] or when ibogaine was administered weekly for three consecutive weeks [40]) suggest that optimal persistence in reductions in the self-administration of drugs by animals, or persistent reductions in drug cravings by humans, may be achieved with a regimen of multiple doses over a period of time rather than with a single dose [2]. The cumulative preclinical data from four studies [21, 40, 42, 48] indicates that for some individual animals the duration of reduction in drug self-administration extended well beyond the 48-72 hour average [7].

The serum half-life of ibogaine in rats is about 1-2 hours, indicating that the prolonged effect on self-administration of drugs outlasts the presence of ibogaine and suggesting that the effect might be mediated by ibogaine's longer-lived metabolite, noribogaine [34, 35, 49, 50]. Indeed, noribogaine has also been reported to reduce self-administration, by rats, of cocaine and morphine [51] and alcohol [52]. However to date there is no compelling evidence confirming the idea that noribogaine mediates this suppression following ibogaine administration [7, 53].

18-MC has been shown to reduce self-administration of cocaine and morphine [38], methamphetamine and nicotine [54] and alcohol [55]. Ibogaine and related compounds have also been shown to alleviate withdrawal-like symptoms in animal models. Among the earliest studies showing such results were those by Djoljic, *et al.* [20] demonstrating ibogaine's dose-dependent diminution of naloxone-precipitated withdrawal signs in rats, and Glick, *et al.* [22] reporting ibogaine's attenuation of naltrexone-precipitated morphine withdrawal signs in rats. The Glick group later

showed, using the same method, similar dose-dependent attenuation of morphine withdrawal by 18-MC [56].

A summary of findings across studies [7] reported that in studies using the naloxone-precipitated model of opiate detoxification, iboga alkaloids (specifically ibogaine, noribogaine, and 18-MC) have attenuated withdrawal signs in 13 of 14 independent investigations involving two rodent and two primate species [20, 22, 56-67].

Many independent studies have established that ibogaine and noribogaine interact in a complex manner with many receptor systems in the central nervous system [36]. 18-MC has also been shown to act at many types of receptors in the brain [38]. The pharmacological bases of ibogaine's anti-addictive properties are not fully understood [36, 68, 69], nor are those of 18-MC [70], but they appear to involve complex interactions across multiple receptor systems [2, 36, 70]. In any event, the study of the mechanisms of efficacy of iboga alkaloids promises to provide an increasingly clear understanding of substance dependence and its treatment [3, 49].

Multiple reviews have detailed the pharmacology of ibogaine [2, 36, 49, 71]. Ibogaine's actions are pharmacologically distinct from those of the opioid replacement drugs such as methadone, as ibogaine is not an agonistic opiate replacement therapy, nor does it produce its activity through opioid antagonism [2, 7].

Ibogaine and its active metabolite, noribogaine, present substantially different pharmacological profiles from each other [2, 36, 49] and both appear to have multiple and complex mechanisms of action within the central nervous system [2, 72], as does the ibogaine congener 18-MC [38].

Ibogaine has a low micromolar affinity for several binding sites within the central nervous system, including N-methyl-D-aspartate (NMDA) glutamate, kappa- and mu-opioid, and sigma₂ receptors, sodium channels, and the serotonin reuptake transporter. Functional studies indicate that ibogaine is a noncompetitive antagonist at the nicotinic acetylcholine receptor [2, 36]. Ibogaine produces the presynaptic release of serotonin; inhibits the serotonin reuptake transporter; and acts as a 5HT_{2A} and 5HT₃ agonist, an NMDA antagonist, a muscarinic agonist and a nicotinic antagonist [35, 68].

Ibogaine has a greater potency at NMDA receptors than does noribogaine [36]. Initially it had been thought that ibogaine's noncompetitive antagonism at the NMDA-type glutamate receptors might underlie its anti-addictive efficacy [2, 3, 73]. However there is evidence strongly suggesting that this is not the case [3]: other NMDA antagonists differ from ibogaine in some functional pharmacological assays [2] and do not substitute for ibogaine in drug discrimination studies [74]. Furthermore, 18-MC, which has demonstrated similarly efficacious anti-addictive activity in animal models, has negligible NMDA affinity [70].

Noribogaine has a much greater affinity for mu-opioid receptors than does the parent compound and is a full opioid agonist [36, 51, 75]. Ibogaine is more highly lipophilic than noribogaine and is concentrated in the brain and fatty tissue, from which it is slowly released and then converted to noribogaine by demethylation [49]. It has been suggested

that this slow release of ibogaine along with the complex interactions of ibogaine and noribogaine at multiple receptor types accounts, in ways that have yet to be elucidated, for prolonged anti-addictive effects [35, 49].

Others have suggested, as a possible mechanism of ibogaine's therapeutic activity, the modification of signal transduction through opiate receptors, independent of direct agonistic effects [2, 3, 36].

Recently, ibogaine and noribogaine have been shown to increase GDNF (glial cell-line-derived neurotrophic factor) activity in the ventral tegmental area (VTA); this activity has been suggested to be a mediator of the action of these compounds in reducing alcohol self-administration [46, 52] but has not been linked to their effects in attenuating withdrawal symptoms [7]. 18-MC apparently differs from ibogaine and noribogaine in this respect as it has been shown that 18-MC does not promote increased GDNF activity in the VTA, hinting that if the alteration of GDNF activity is involved in ibogaine's effects on alcohol self-administration, ibogaine and 18-MC may produce their effects on drug craving and self-administration at different sites and by way of different mechanisms [52].

Like the classic "hallucinogens" such as LSD, psilocybin, and mescaline [76], ibogaine acts to increase brain serotonin levels, and its hallucinogenic effects are thought to be mediated at least in part by its activity at 5-HT_{2A} and 5-HT_{2C} receptors.¹ However, drug discrimination studies [74] show that other receptor activity (sigma-2 and possibly opiate receptors) also contributes to ibogaine's discriminatory stimulus. It is possible that ibogaine's hallucinogenic effects may be mediated by its activity at 5-HT_{2A} and 5-HT_{2C} receptors and that its activity at sigma-2 and opiate receptors are responsible for its therapeutic activity; alternatively, if ibogaine's hallucinogenic properties underlie its anti-addictive efficacy, then 5HT-2 receptors may mediate its therapeutic effects [74].

Other evidence indicates another possibility: based on comparisons with 18-MC it has been suggested elsewhere [36] that ibogaine's activity at sigma-2 sites is responsible for its neurotoxicity (discussed below under "Safety"), as ibogaine exhibits a 30-fold greater affinity for the sigma-2 sites than does 18-MC (which demonstrates similar anti-

¹In his review on the topic [76], Dr. David Nichols defines "hallucinogens" as "those substances with psychopharmacology resembling that of" psilocybin, mescaline, and LSD-25, and "that principally exert their central nervous system (CNS) effects by agonist (or partial agonist) action on serotonin (5-HT)_{2A} receptors." Nichols notes that many of these substances produce hallucinations, but only at doses higher than typically used, and so the term "hallucinogen" is a misnomer. As mentioned above, ibogaine is sometimes referred to as an "oneirophrenic" (dream-like-state inducing) drug owing to the fact ibogaine, at dosages typically used for addiction treatment and for psycho-spiritual growth purposes, induces dream-like panoramic visions that can be seen when the eyes are closed but which are usually suppressed when the eyes are open. The various hallucinogens each induce their own characteristic states (with wide variation across individuals), but, as Nichols [76] explains, there are some general commonalities including the tendency to produce somatic, perceptual, and psychic symptoms in the user. In recent decades the term "psychedelic" (mind-manifesting) has entered common parlance to refer to the common tendency of these substances to promote self-reflection and self-realization. It is this trait that presumably underlies their reported usefulness as aides in psychotherapy, as noted in the case of ibogaine by Naranjo [17] and Zeff [19].

addictive efficacy but lacks ibogaine's neurotoxicity), and there is evidence linking ibogaine's neurotoxicity to its sigma-2 activity [77].

Also on the basis of drug discrimination studies it appears that noribogaine may be largely responsible for the psychoactive effects of ibogaine and that it may be more potent in producing discriminative stimuli than is the parent compound [78]. 18-MC does not alter serotonin levels in the brain and so it is predicted to have no hallucinogenic activity [38].

SAFETY

Despite its association with the psychedelic counterculture of the 1960's and its classification as a Schedule I substance in the U.S., there is no evidence to suggest that ibogaine is physiologically or psychologically addictive in animals or in humans, or that it is a substance with a high potential for abuse [2]. Aversive side effects such as ataxia and nausea limit the potential for ibogaine's abuse [7], as does the often unsettling or disturbing nature of the subjective experience of the drug [27, 28].

Evidence from preclinical studies and from clinical reports suggests that there may be significant health risks associated with ibogaine use, at least in cases in which ibogaine is used to treat substance abuse disorders when there are pre-existing medical comorbidities (such as poor cardiac health or a history of myocardial infarction), when dosages far beyond those typically used for the treatment of substance abuse disorders are ingested, or when opioids or cocaine are used in close temporal proximity with ibogaine [2].

Multiple studies have shown that ibogaine administered to rats at dosages of 100 mg/kg causes the degeneration of cerebellar Purkinje cells [2]. However, these dosages are considerably higher than the dosages demonstrated to significantly reduce withdrawal symptoms and drug self-administration in animal models (40 mg/kg); and such degradation of neuronal cells seen in rats has not been found after the administration of similar dosages of ibogaine in other species, including mice and primates [2, 5].

Other effects of Ibogaine have been summarized elsewhere, and include a tendency to produce body tremor in rats and in mice [2] and bradycardia in humans in medical and non-medical settings, and in animals in pre-clinical studies [7]. The tendency of iboga alkaloids to cause tremor has been shown to be independent of their capacity to reduce drug self-administration in rats [42]. Both noribogaine [35] and 18-MC [38] have demonstrated these anti-addictive activities in animal models without producing body tremors or bradycardia.

The most serious of the complications with a possible causal link to ibogaine is the risk of sudden death [70]. In at least 19 cases since 1990, individuals have died suddenly within 76 hours of ingesting ibogaine [5, 7]. The first such reported case occurred in 1990. The decedent was a 44-year-old woman who had received a dose of ibogaine of 4.5 mg/kg four hours prior to death. The woman had a history of hypertension; autopsy further revealed evidence of a prior myocardial infarction, severe atherosclerotic changes, and 70

to 80% stenosis of all three major coronary artery branches. The autopsy report concluded that the woman's preexisting heart disease was the likely cause of death, and specifically excluded ibogaine intoxication as a cause; it was however deemed possible that an interaction between ibogaine and the patient's preexisting heart disease may have contributed to the sudden fatality [2].

The death of a 24-year-old woman shortly after her treatment of ibogaine for detoxification from heroin in the Netherlands in 1993 reportedly led to the cessation of treatments in that country by NDA International and dampened Dutch enthusiasm for the further investigation of ibogaine as a medicine [8]; the death also contributed to NIDA's 1995 decision not to move forward with its plan to conduct controlled human clinical trials of ibogaine for the treatment of substance dependence [2]. The patient suffered respiratory arrest and died 19 hours after the start of treatment in which she received a total ibogaine dose of 29 mg/kg [2]. The Dutch investigation of the death revealed no conclusive determination of the cause of death [2, 8]. The inquiry found evidence suggesting the possibility of surreptitious opiate use but there was no postmortem analysis to determine the presence of opioids [2].

A recent study [7] examined all available autopsy, toxicological, and investigative reports, in addition to interviews with treatment providers and other firsthand observers, to assess the possible role of ibogaine in each of the 19 deaths known to have occurred in close proximity of its ingestion (within 1.5 to 76 hours post-ingestion) outside of West Central Africa in the period from 1990 through 2008. Of the 19 individuals, 15 took ibogaine for the purpose of detoxification from opiates, 2 ingested ibogaine for psycho-spiritual purposes and had no history of substance dependence, and 2 took ibogaine for unknown reasons and had a history of substance dependence. The study determined that, in 12 of the 14 cases for which there was adequate postmortem data, a pre-existing medical (usually cardiac) condition or the concurrent use of other drugs (usually opiates or cocaine) in addition to ibogaine, adequately explained or contributed to the sudden death. It was determined that there was no clinical or postmortem evidence indicating a characteristic syndrome of neurotoxicity.

Cardiac disease was a contributing factor or proximate cause in 6 of the deaths, indicating the importance of heart problems as a risk factor in sudden deaths following the ingestion of ibogaine [7]. In this regard the authors discuss the possible relevance of the fact that prolongation of the QT interval has been observed during ibogaine treatments with continuous EKG monitoring [79] and in the case of one woman who had been hospitalized following the ingestion of an iboga alkaloids preparation [80]. QT prolongation, they note, is correlated with cardiac instability and with risk factors of particular relevance to their study of the deaths of patients receiving ibogaine for the treatment of substance abuse disorders -- including bradycardia, coronary disease, recent myocardial infarction, and liver disease [7]. Moreover, the nutritionally compromised state typical of people with long-term addictions to opiates puts them at risk for conditions associated with QT prolongation, and the use

of methadone, cocaine, and alcohol is also associated with prolongation of the QT interval [7].

The potentiation by ibogaine of both the analgesia and the toxicity of opiates (and possibly the toxicity of stimulants such as cocaine) may have been a causal factor in some of the deaths [7]. Postmortem toxicological analysis revealed the presence of commonly abused drugs in 8 of the 11 cases for which a toxicological investigation was performed. The authors explain that in cases in which multiple drugs are known to have been present at the time of death, the determination of the role of any one drug or of the interactions of multiple drugs is speculative.

Of the cases for which there were adequate postmortem examination and toxicological analysis, only two cases appear not to have involved co-intoxicants or significant medical comorbidities [7]. One case involved the ingestion of a crude alkaloid extract of unknown potency, and the other case involved the use of iboga root bark at an apparently higher dosage than that used in Bwiti initiatory rituals [5]. The study cited as possible risk factors the user's lack of experience or knowledge regarding the use and dosage of such preparations [7].

Patients in the ibogaine medical subculture are at significant risk, in part due to the lack of clinical and pharmaceutical standards and the absence of regulations pertaining to the manufacture and storage of ibogaine [5]. Providers, particularly those in the clinical setting, have become increasingly aware of the risks to patients and of practices for minimizing such risks, possibly helping to explain the apparent decrease in the rate of sudden deaths by patients since 2006, as measured by the number who have died (apparently related to treatment) versus the approximate entire number treated globally [7]. A manual available for free download on the internet [29] takes into account the collective knowledge of many providers in outlining exclusionary criteria and pretreatment laboratory tests as well as procedures for monitoring patients during treatment and for emergency medical intervention. Nowadays there is broad agreement among providers regarding the importance of pretreatment EKG and liver function tests, medical and psychiatric exclusionary criteria, and the presence of physicians or trained emergency medical technicians [5, 28, 79].

EVIDENCE FOR EFFICACY: STUDIES WITH HUMANS

The earliest evidence for the efficacy of ibogaine treatment for drug addiction in humans came from the informal experiments by the focus group organized by Howard Lotsof in New York City in 1962 and 1963 [8, 10]. The group, consisting mostly of college-educated Caucasian men in their late teens and 20's, shared an interest in exploring the psychotherapeutic potential of mind-altering drugs, and met frequently for the purpose of experimentation with a variety of such substances. During each session the role of one individual was to observe the proceedings and to take notes. Afterwards, the primary form of evaluation was the discussion of the subjective effects of the drugs.

In all, twenty group participants, all ibogaine-naïve, ingested ibogaine HCl in doses ranging from 0.14 to 19

mg/kg [10]. Seven of those 20 were heroin dependent, and all seven reported an alleviation of opiate withdrawal symptoms and cravings in the days immediately following the ingestion of ibogaine. Five of those seven maintained abstinence for six months or longer afterwards; the other two individuals similarly experienced an alleviation of withdrawal symptoms and cravings but reportedly resumed heroin use because they identified as heroin addicts and did not wish to remain abstinent [8].

The fact that the outcomes results of this study are based entirely on self-report from a small subject pool constitutes a significant weakness of this study. A presumable strength of this initial study was the likelihood that the subjects had little or no reason to dissemble. As Lotsof notes [9], the group was non-judgmental about the use of drugs and so respondents and so the subjects had little or no reason to hide their substance use from others in the group, among whom were the people soliciting and recording the data. Also, at that time ibogaine was legal to obtain and use in the U.S., and so participants were not subject to legal persecution for using ibogaine or for admitting such use.

For over thirty years the only support for that informal study, as far as usage in humans is concerned, came from reports derived from the small, informal international ibogaine treatment network. As of 1998, a total of 13 case studies of treatments, all of which took place in the U.S. or in the Netherlands, had been reported by four authors [81-84].

Members of a small independent research group in Amsterdam documented the immediate and long-term (up to 14 weeks) antecedents of ibogaine treatment for seven opiate-dependent individuals (six heroin and one codeine-dependent patients) [83]. The patients were treated with ibogaine HCl (11.7-25.0 mg/kg). At the conclusion of the 24-38 hour psychoactive period of the ibogaine, none of the subjects showed any signs of opiate withdrawal. Follow-ups with the patients at irregular intervals revealed that two relapsed to opiate usage within two days post-treatment and then fell back to regular heroin usage within a matter of weeks; two others relapsed within a few months; and the remaining three remained abstinent for at least 14 weeks post-treatment.

Neurologist Daniel Luciano [84] observed and reported on three cases of persons treated with ibogaine for cocaine dependence (one also involving heroin dependence, 1 gram/day IV). Medical and psychological tests, including EEG, ECG, and MRI scans were performed in a pre-screening examination prior to the administration of ibogaine HCl (20-25 mg/kg). Medical monitoring was continuous following ingestion, and neurologic exams and EEG scans were performed intermittently for 24 hours post-ingestion. Tremor and ataxia were observed for all three patients within the first few hours. There were no subjective or objective signs of drug withdrawal for any of the patients, and no medical, EEG, or ECG abnormalities were seen within the 24 hours.

Bob Sisko, the Director of the International Coalition for Addict Self-Help (ICASH), the organization that "pioneered the para-clinical application of ibogaine by addicts for addicts" discussed four case studies of New York City

residents who were treated for heroin and cocaine addiction in the Netherlands [82]. Sisko reviewed the case studies with particular consideration of a question central to ibogaine treatment for substance dependence: what constitutes a successful treatment? He states that, contrary to sensationalist claims found in popular media, ibogaine is not a “cure” for addiction but is, as Lotsof says elsewhere [29] an “addiction interrupter” that is particularly useful for facilitating detoxification. He further argues that success should be defined not by a “drug-free” life but by an “addiction-free” life in which the individual has the ability to choose whether or not to use drugs.

Dr. Charles Kaplan reported on some of the significant themes that had emerged from a study of an unstated number of heroin addicts treated with ibogaine and participating in a focus group in the Netherlands [85]. The study’s methodology combined an ethnographic approach with an experience-sampling methodology involving the completion of questionnaires at times determined by the random beeps, during waking hours, of a wrist terminal worn by the subject. The author states that the questionnaire responses provide a “thick description” of the subject’s lived experience over the course of a 7-day period. Each member of the focus group reported an extended period of abstinence following treatment from ibogaine, “a state that they never thought they would reach given their former nihilistic, depressed view of life” [85]. Kaplan contends that the results of the study show that the patients felt a sense of belonging to a group focused on achieving wellness, and suggests that the group provides an “exogenous” means of effecting positive health outcomes that are reflected in correlated “endogenous” states such as changes in neuronal receptors and brain pathways.

The seven cases from the early work by the Lotsof group were later combined, into a larger retrospective study, with the results from 26 patients treated in the Netherlands between 1989 and 1993 for purposes of opioid detoxification [86]. The data on these 33 subjects was a subset of the data presented by Howard Lotsof at the 1995 NIDA hearing to consider moving forward with human clinical trials of ibogaine. Data on eight other subjects presented at that hearing were excluded from the retrospective study because they were not opiate-dependent (five subjects) or because there was inadequate follow-up data (three subjects) [2].

At the time of treatment the 33 subjects reported an average daily use of heroin of $.64 \pm .50$ grams, primarily by the intravenous route ($n = 26$; four subjects reported intranasal ingestion and three reported smoking as route of ingestion) [86]. Eight of the subjects were concurrently undergoing methadone maintenance, and eight were concurrently using cocaine on a daily basis. Opioid withdrawal was chosen as the study’s focus due to the clinical robustness, clearly measurable signs, and limited time course of the phenomenon.

Eight to ten hours after each subject’s most recent use of heroin (and roughly 24 hours after the most recent methadone usage for the eight subjects concurrently undergoing methadone maintenance), ibogaine HCl was administered to the subjects at an average dosage of 19.3 ± 6.9 mg/kg (with a range of from 6 to 29 mg/kg). Self-reports of withdrawal signs and drug craving, along with overt signs

of opioid withdrawal and drug seeking behavior, were observed and recorded during a 72-hour post-treatment period.

Complete resolution of opiate withdrawal, without drug-seeking behavior, was observed in 25 (76%) of the patients. Four patients (12%) showed no signs, nor complained, of withdrawal but nonetheless sought and used opiates within 72 hours of treatment. Two other patients showed and reported attenuated signs of opiate withdrawal but refrained from drug seeking behavior. In only one case did the ibogaine treatment fail to provide significant relief from withdrawal symptoms. This patient, a 27-year-old female, complained of, and showed clear signs of, opiate withdrawal symptoms and used heroin within about eight hours following treatment. The study’s investigators suggested that the ibogaine dosage administered in this case (10 mg/kg) was insufficiently strong to counter the subject’s intravenous heroin habit of 0.4 grams daily [86].

The authors acknowledge that the assessment of the resolution of withdrawal signs rested upon the expertise and knowledge of two of the investigators, both of whom were qualified, based on their experience with observations of opiate withdrawal, to make such assessments; and that the use of a structured methodology for the assessment of withdrawal signs would improve the validity of the results [86]. Despite the study’s limitations, it provided much needed support for claims of ibogaine’s efficacy in the attenuation of withdrawal symptoms and cravings.

In his report at the NIDA Ibogaine Review Meeting in March of 1995, Howard Lotsof addressed the question of the efficacy of ibogaine for facilitating long-term reductions in, or abstinence from, drug usage. Lotsof based his report on data gleaned from the same cases discussed above [86] in addition to the eight cases that were excluded from that retrospective study. These data are largely retrospective and anecdotal but represent the only formally presented attempt to assess the long-term efficacy of ibogaine [2].

Thirty-eight of the 41 individuals in the study reported at least some use of opiates, and ten of those were also dependent on other substances, primarily cocaine, alcohol, and sedatives. Thirty-one of the participants were treated just once with ibogaine, nine were treated twice each, and one was treated three times. Individuals were contacted and asked to report the length of time they remained abstinent from the drugs of dependence following each ibogaine treatment. Fifteen (29%) of the treatments were reportedly followed by periods of abstinence of less than two months in duration; 15 (29%) for at least two months and less than six months; Seven (13%) for at least 6 months and less than 1 year; 10 (19%) for longer than 1 year; whereas for 5 (10%) the outcomes could not be determined [2].

Deborah Mash’s team treated more than 150 patients at a freestanding clinic in St. Kitts, West Indies [35]. The studies conducted with those patients constitute the earliest research in a conventional research setting on ibogaine administration in humans [2]. One subset of patients comprised of twenty-seven heroin- or cocaine-dependent individuals participated in a 12-14 day inpatient Phase I dose escalation study to determine the safety and efficacy of ibogaine for the treatment of drug dependence [72]. Upon admission each

subject was administered the Addiction Severity Index (ASI) [87] and received structured psychiatric evaluations by means of the Structured Clinical Interview for DSM Disorders (SCID I and II). These patients were randomly assigned to receive single fixed doses of 500, 600, or 800 mg of ibogaine HCl under open-label conditions. Patients were also required to complete, at three times during the inpatient stay and once at one month after discharge from the program, structured self-reports relating to mood (the Beck Depression Inventory [88] and drug craving (the Heroin (HCQN-29) [89] or Cocaine (CCQN-45) Craving Questionnaire [90]).

Compared to pre-treatment scores, self-report depression scores were reduced at post-treatment and at discharge, and significantly reduced at the 1-month follow-up for both the opiate- and cocaine-dependent groups. For the opiate-dependent group, measures of opiate craving were significantly reduced for each of five sub-scores at both the 36-hour post-treatment assessment and at the 1-month follow-up. For the cocaine dependent group, measures of cocaine craving were significantly reduced on three of the five sub-scores at the 36-hour post-treatment assessment and at discharge. At one month following discharge, self-ratings continued to show a reduction in opiate and cocaine cravings [72].

Another subset of those patients, comprised of 32 opiate users (each heroin- or methadone-dependent), was given a single fixed dose of 800 mg and was studied to observe ibogaine's effect on withdrawal symptoms. Physicians used the Objective Opiate Withdrawal Scale (OOWS) to mark the presence or absence of 13 overt signs of opiate withdrawal at 3 different points: 1 hour before the administration of ibogaine, 12 hours after administration of ibogaine (24 hours after the patient's most recent ingestion of opiates), and 24 hours after administration of ibogaine (36 hours after the most recent ingestion of opiates). The post-ibogaine OOWS ratings obtained at 12 hours and 24 hours after the administration of ibogaine were significantly lower than the OOWS ratings obtained 1 hour before the administration of ibogaine. Patient self-reports of withdrawal symptoms were significantly decreased shortly after treatment (<72 hours after ibogaine administration) and remained at a comparable level at discharge about one week later. These patients also showed significant reductions in heroin craving scores at discharge and in mean Beck Depression Inventory scores at discharge and at the 1-month follow-up [35].

The 12-14 day treatment program also aimed to provide motivational counseling and referrals to aftercare programs and community support groups (12-step programs) [35]. The report asserts that all patients in the opiate detoxification study were successful in the detoxification process and that many were able to maintain abstinence for a period of months following treatment. However, supporting data regarding post-treatment substance use has not been published, and so the only follow-up data relating to outcomes beyond the treatment period pertains to self-report depression and craving scores.

An unpublished Dutch doctorandus thesis by Ehud Bastiaans, available on the Internet [91] sought to assess the long-term outcomes for individuals who had taken ibogaine to treat drug dependence, citing a dearth of data in this

regard. The study collected outcomes data from 21 subjects who responded to an online questionnaire based on the European Addiction Severity Index. Outcomes data were collected in several areas relating to overall quality of life including substance use, medical condition, legal status, employment status, and social and psychological well being. In these respects the study differentiated itself from all previous studies that focused on only on a few short-term outcomes directly related to drug use, or, in one study [86] solely on long-term substance use post-treatment.

The questionnaires were answered retrospectively by respondents an average of 21.8 months after they had taken ibogaine for treatment of a substance use disorder. Eighteen of the twenty-one respondents stated that opiates were the primary drug of abuse (14 heroin, 2 methadone, and 2 other opiates such as oxycontin or codeine). Ten of the participants (48%) were treated twice with ibogaine and 3 (14%) were treated a total of three times.

Nineteen of the respondents (90%) indicated that they abstained from all drug use for at least 1 week following treatment, thereby corroborating data from previous studies showing ibogaine's capacity to attenuate withdrawal symptoms and to reduce cravings for drugs.

Based on the reports the respondents were categorized into three groups. One group, consisting of five participants (24%) had entirely quit all substance use (including illicit drugs, prescription medications, tranquilizers, and alcohol). The average period of post-treatment abstinence for members of this group was 3.5 years and the median period was 24 months. A second group (9 people, 43%) quit using their primary and secondary drugs of abuse for an average of 1.5 years (median of 4.5 months) but either continued to use other substances (typically cannabis and/or alcohol) or started using other drugs instead (most commonly cannabis or opiate pain medications). Seven respondents (33%) returned to using their primary and secondary drugs of abuse shortly after treatment; the average time of abstinence for this group was about 1 week. Six of those seven individuals reported a reduction in the quantity of consumption of the primary and secondary drugs of abuse.

Most of the participants reported post-treatment improvements (as compared with pre-treatment conditions) in medical health (58%), relationships with significant others (88%), and psychological well being (96%). Using contact information supplied along with the responses to the questionnaires, Bastiaans attempted to reach each respondent one year after they had completed the initial survey, but managed to reach only six of the participants for a follow-up interview.

The limitations of this study, some of which are discussed by Bastiaans, include the fact that the respondents were self-selected and that there was no method for confirming the veracity of their statements. However, because the survey was voluntary and anonymous, the respondents had no reason to lie about their substance use.

DISCUSSION

The ibogaine medical subculture [5] continues to grow. Since the beginning of enrollment into the current study of

clinical treatment in Mexico in September of 2010, at least seven ibogaine clinics have operated in Mexico. Two new clinics have opened in Baja California, Mexico within the past nine months (as of July, 2012). Public awareness of ibogaine is expanding too, as more and more stories about ibogaine appear in the popular news media and as the ibogaine subculture's Internet presence grows. The subculture gained an important measure of legitimacy in July of 2010 when New Zealand categorized ibogaine as a non-approved prescription medicine. As several authors have noted [8, 24, 82] the fact that ibogaine is illegal in the U.S. and other nations has not stopped the spread of the "vast, uncontrolled experiment." [24]. Still, the recent development in New Zealand is likely to further empower and embolden those wishing to see wider acceptance of ibogaine treatment for addiction.

Though we have learned much about the iboga alkaloids as anti-addictive agents, there is a clear need for further research into the safety and efficacy of ibogaine treatment. The substantial body of preclinical evidence strongly supports the claims made regarding ibogaine's efficacy for attenuating withdrawal symptoms and reducing drug cravings (on the short term) in humans, as do the few scientific studies with humans, namely the retrospective study by Alper, *et al.* [86] and the work by Mash's group in St. Kitts [35, 72]. The latter studies demonstrate significant effects by ibogaine - resolution of withdrawal and relief from cravings for opiates and cocaine on the short term - capable of facilitating a relatively smooth detoxification process. The case study reports and the retrospective studies discussed above are in consistent agreement about ibogaine's efficacy in this regard.

We have also learned much about the complex pharmacology of the iboga alkaloids. However, in contrast to substitution therapies questions about the mechanism of action of these substances remain to be answered. The fact that ibogaine and 18-MC, two compounds very similar in structure, both appear effective in attenuating withdrawal and reducing drug self-administration and yet seem to act by different mechanisms is intriguing in this regard. More research is certainly needed in this area, although it is known that the iboga alkaloids interact in complex ways with many receptor systems in the brain.

As mentioned above, ibogaine's serotonergic activity appears to account, at least in part, for its hallucinogenic properties, although other receptor systems also seem to be involved in producing an altered state of consciousness that can be distinguished, in drug discrimination studies [74] from those generated by other hallucinogens such as LSD, psilocybin, and DMT (a key psychoactive component of ayahuasca, a brew central to some Amazonian religious traditions). Interestingly, other hallucinogens are purported to have efficacy as adjuncts in the treatment of substance abuse [92, 93], even though they apparently lack ibogaine's ability to attenuate withdrawal symptoms. There is at least some evidence to support such claims - for example, regarding LSD for opiate addiction [94] and for alcohol abuse [95]. Evidence of this sort is discussed in detail by other authors in the present volume.

It is not currently known whether ibogaine's psychoactive effects play an important therapeutic role, or

whether they are, as Glick and Maisonneuve [38] put it, a "liability" hampering the development of ibogaine as a medicine. However, ibogaine and other hallucinogens are thought to share a capacity to generate introspection and to facilitate psychological growth [17, 96]. Recent research has shown that psilocybin-induced experiences are attributed with meaning and spiritual significance 14 months afterwards [97] and are associated with positive long-term changes in behaviors, attitudes, and values [98]. If it is demonstrated that the visions and altered states produced by ibogaine and other psychedelics have anti-addictive therapeutic value, this finding would have implications for addiction therapy and for the rational design of anti-addiction drugs.

Even if its psychoactive properties are determined to be therapeutically useful, lingering questions regarding the safety of ibogaine treatment may continue to hamper progress towards its development as a certified medicine for the treatment of substance use disorders. If indeed noribogaine, which is also thought to be psychoactive, is found to be safer than ibogaine and yet efficacious in the treatment of addiction in humans, this drug may move more quickly than ibogaine to the point of becoming a prescription medication in the USA. On the other hand, particularly if a non-psychoactive alternative such as MC-18 is shown to be effective in humans, such a drug might clear the legislative hurdles even more quickly. It is worth noting that both noribogaine and MC-18 are already patented, whereas ibogaine, as a naturally occurring substance, cannot be patented. If one or more patented ibogaine congeners eventually prove successful in human clinical trials, it is easy to envision a future in which patients seeking treatment have the choice between ibogaine treatment in certain countries, such as Mexico and New Zealand, where ibogaine treatment is permitted and treatment with a patented congener in other countries, such as the USA, in which ibogaine usage is prohibited.

The dangers of ibogaine must be taken seriously but should also be weighed against the inherent dangers of chronic addiction to substances such as heroin and the problems associated with commonly attendant conditions such as malnutrition, depression, and social and legal difficulties. The benefits and potential dangers of ibogaine treatment should also be compared with those related to current treatments for opiate addiction. The most common treatment for opiate addiction is replacement therapy using methadone or buprenorphine. When successful, these treatments typically involve several years of daily administration of the replacement opiate. Problems with patient compliance often lead to the failure of such treatments. Furthermore, the replacement therapies themselves are highly addictive and are subject to misuse and abuse (see for example Yokell, *et al.* [99]). Perhaps most seriously, methadone use and abuse is increasingly associated with deadly outcomes. The number of annual poisoning deaths related to methadone in the U.S. surpassed those related to heroin in 2002, and doubled heroin-related poisoning deaths in 2005 and 2006 [100]. In New Zealand, dependence on methadone is the most common indication for which people seek ibogaine treatment; and part of the rationale for re-scheduling ibogaine as a non-approved prescription drug is the high rate of methadone poisoning

deaths.² In any case, regardless of the risks associated with currently legitimate therapies, the better the risks of ibogaine are understood, minimized, and managed, the smoother ibogaine's path to medical legitimacy will be.

Despite the limitations of the research to date, we have gained a great deal from the studies of ibogaine treatment, including a greater awareness of the questions that remain unanswered and a better sense for how to move ahead in our ongoing research on this topic. Bastiaan's study [91], for example, is valuable in large part because it explores questions that have otherwise been virtually unexamined. The only other data on long-term outcomes for ibogaine treatment comes from Lotsof's 1995 report at the NIDA hearings, discussed above; that data was also based on retrospective reports but was narrower in scope than Bastiaan's data as it only dealt with length of time before relapse. Because Bastiaans also collected data on types and amounts of substances used both pre- and post-treatment, his data provide a clearer sense of the wide degree of variation in long-term outcomes following ibogaine treatment, and, perhaps more importantly, they also suggest that it would be worthwhile to re-examine of the notion of relapse as an absolute indicator of treatment failure or success. In particular, as Bastiaans notes, the fact that 85% of the respondents who reported continuation of their use of drugs said that they had significantly reduced their daily consumption of such drugs suggests that the definition of success of addiction treatment should be re-examined. This sentiment echoes the idea put forth by Bob Sisko [82] who provided and witnessed the results of many ibogaine treatments for substance dependence, and who argued that the success of treatments for addiction should be measured by their capacity to provide the individual with a sense of control over his or her drug use, and not by whether or not an addict achieves perfect abstinence.

Bastiaan's study also broke new ground in considering the importance of assessing the efficacy of ibogaine treatment not only in terms of substance use, but also in terms other measures of overall quality of life that are often related to substance use and that are incorporated within such instruments as the Addiction Severity Index [91]. In the past few decades, interest in quality of life issues in addiction studies has grown immensely [101] but so far there have been no published studies of quality of life changes associated with ibogaine treatment for addiction [27].

The St. Kitts study [35] however, did examine one aspect of psychiatric health, and found significantly reduced self-report scores on measures of depression at discharge from the clinic and at 1 month after discharge. This study utilized a more rigorous methodology in that data were collected at baseline and at consistent post-treatment time points using validated instruments. Unfortunately none of the ASI data have been published, nor have any data from follow-up measurements beyond the first month post-treatment.

In sum, the human studies of ibogaine treatment provide some preliminary support for the efficacy of ibogaine in alleviating the considerable discomforts of withdrawal from opiates and other addictive drugs, and thereby in facilitating

detoxification from these substances in a comparatively painless manner. Further research is needed to test these preliminary findings and to determine whether or not ibogaine consistently reduces cravings for opiates and cocaine (as the work of Mash, *et al.* [72] strongly indicates) and perhaps also for other substances such as alcohol and nicotine. It is possible that research will eventually show that ibogaine is an "addiction interrupter" for many substances of abuse, as Howard Lotsof [10] and others have insisted.

The limited research results achieved so far suggest that opiate and cocaine cravings are significantly reduced for up to 1 month following treatment [35] and that a substantial minority of patients remain abstinent for several months [83, 86, 91]. We must clarify the short-term picture and carefully document long-term outcomes to see what becomes of patients beyond the first few days and weeks after treatment. If the individual results are as varied as Bastiaans [91] and others suggest, it is important that we look carefully to see what makes a positive difference in long-term outcomes [102].

Careful documentation of treatment measures and of long-term outcomes regarding substance use and related quality of life measures (psychological and social well being, medical health, and life satisfaction, for example) and close examination of attitudes and conditions before, during, and after treatment may yield invaluable information about the predictors of optimal long-term success. Hittner and Quello [102] discuss a number of pre-treatment and post-treatment strategies for optimizing treatment success, and suggest that the patient's pre-treatment expectations might play an important role in determining outcomes. Set and setting at time of treatment, as well as the interactions of the treatment team with the patient [9, 82, 103], may also be significant determinants of treatment outcomes. Though some have suggested [9, 17, 104] that the altered-state experience and visions induced by ibogaine, and the patient's evaluations of the experience, are keys to promoting positive psychological and behavioral changes, it remains to be demonstrated whether or not the oneirophrenic and psychedelic qualities typical of the ibogaine-induced state of consciousness are related to treatment success. If the altered states, visions, and consequent psychological changes are important (as many people treated with ibogaine attest) then the ritualistic nature of the treatment, the authority of the healer/provider, and the ongoing social support of a community oriented towards wellness [84] may also prove to be helpful in achieving long-term treatment success [103].

The patient's stay at the clinic is typically one week or less; the conditions to which the patient returns after treatment are likely to have an impact on outcomes as well. The assistance of the patient's social support network may be a key to the ongoing success of treatment [9, 27, 102, 103] as might some sort of structured aftercare, be it residential rehabilitation, a halfway house, regular NA/AA meetings [102], or a longer stay at an ibogaine clinic or aftercare facility run by people who themselves have undergone ibogaine treatment and who are knowledgeable about the ongoing process of recovery³.

²Personal communication with Dr. Geoff Noller, Director, Substance Use and Policy Analysis, Dunedin, New Zealand.

³The importance of aftercare following ibogaine treatment was discussed by Sandi Hartman on December 10, 2010 in Los Angeles at a conference

Two research studies currently underway aim to address some of the unanswered questions about ibogaine treatment for opiate dependence. Both studies set out to observe and to measure outcomes for 20 to 30 patients monthly over the course of one year following initial treatment with ibogaine. The first study is an observational outcomes study of patients treated at two ibogaine clinics in Baja California, Mexico [105], and the second study is following outcomes for patients treated by either of two ibogaine providers in New Zealand [106].

Subject enrollment for the Mexico study began in September of 2010, and data collection from follow-up visits will be completed in September of 2012. Thirty subjects were obtained through continuous enrollment attempts for all eligible patients seeking treatment at the clinics. To be included in the study, patients had to be ibogaine-naïve and seeking treatment primarily for purposes of treatment of opioid dependence. Both clinics performed pre-treatment medical and psychological screening of all patients. Subject enrollment for the New Zealand study began in June of 2012 and is anticipated to continue for 18-24 months. In both studies, patients seeking ibogaine treatment but who are denied treatment will be asked to enroll in the study as members of a control group.

The primary objective for both studies is to assess the effectiveness of ibogaine-assisted treatment for opiate addiction by tracking changes in substance use and related quality of life measures using the ASI-Lite, a shortened version of the Addiction Severity Index [107]. Secondary objectives include the post-treatment assessment of the intensity of withdrawal symptoms by means of the Subjective Opioid Withdrawal Scale (SOWS) [108]; the determination of the effectiveness of ibogaine to alleviate symptoms of depression for extended periods, as measured by the Beck Depression Inventory—II [88]; and the investigation of the correlation between post-treatment ASI-lite scores and the intensity of the altered state produced by ibogaine during treatment, as measured by the States of Consciousness Questionnaire (SCQ) [109]. Additionally, the New Zealand study will assess patients' expectations of treatment at enrollment and will determine whether or not those expectations have been met in the months following treatment.

Baseline measures on the ASI-lite, BDI—II, and SOWS are gathered by investigators prior to treatment. At a second visit, taking place about two to three days after treatment, the SCQ will be administered and the SOWS and BDI—II will be completed by the patient again. Patients are contacted monthly for twelve months after treatment. At these monthly follow-up visits, investigators administer the ASI-lite (usually by telephone). Designated family members or friends of the patient are also contacted monthly to verify the patient's substance use or abstinence. Drug screenings are conducted at random and pre-set monthly follow-up visits as an objective measure of substance use. The BDI—II is also administered at various monthly follow-up visits to monitor self-report depressive symptoms on an on-going basis.

The data from these two studies should provide much-needed information about the long-term efficacy of ibogaine and about the variability among individual outcomes. They may also provide some indications regarding the determinants of treatment success. Hopefully they will represent a step towards a clearer understanding of effective treatment of drug addiction.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Fernandez JW. *Bwiti: an ethnography of the religious imagination in Africa*. Princeton, New Jersey: Princeton University Press 1982.
- [2] Alper KR. Ibogaine: a review. *Alkaloids Chem Biol* 2001; 56: 1-38.
- [3] Alper KR, Lotsof HS. The use of ibogaine in the treatment of addictions. In: Winkelman WJ, Roberts TB, Eds. *Psychedelic medicine*. Westport, Connecticut: Praeger 2007; pp 43-66.
- [4] Mash DC. Ibogaine therapy for substance abuse disorders. In: Brizer D, Castaneda R, Eds. *Clinical addiction psychiatry*. Cambridge: Cambridge University Press 2010; pp 50-60.
- [5] Alper KR, Lotsof HS, Kaplan CD. The ibogaine medical subculture. *J Ethnopharmacol* 2008; 115(1): 9-24.
- [6] Goutarel R, Gollnhoffer O, Sillans R. Pharmacodynamics and therapeutic applications of iboga and ibogaine. *Psychedelic Monographs and Essays* 1993; 6: 71-111.
- [7] Alper KR, Stajic M, Gill JR. Fatalities temporally associated with the ingestion of ibogaine. *J Forensic Sci* 2012; 57(2): 398-412.
- [8] Alper KR, Beal D, Kaplan CD. A contemporary history of ibogaine in the United States and Europe. *Alkaloids Chem Biol* 2001; 56: 249-81.
- [9] Lotsof HS, Alexander NE. Case studies of ibogaine treatment: implications for patient management strategies. *Alkaloids Chem Biol* 2001; 56: 293-313.
- [10] Lotsof HS. Ibogaine in the treatment of chemical dependence disorders: clinical perspectives. *Newsletter of the Multidisciplinary Association for Psychedelic Studies (MAPS)* 1995; 5(3): 16-27.
- [11] Lotsof HS, inventor. Rapid method for interrupting the narcotic addiction syndrome. United States patent US 4499096 1985.
- [12] Lotsof HS, inventor. Rapid method for interrupting the cocaine and amphetamine abuse syndrome. United States patent US 4587243 1986.
- [13] Lotsof HS, inventor. Rapid method for attenuating the alcohol dependency syndrome. United States patent US 4857523 1989.
- [14] Lotsof HS, inventor. Rapid method for interrupting or attenuating the nicotine/tobacco dependency syndrome. United States patent US 5026697 1991.
- [15] Lotsof HS, inventor. Rapid method for interrupting the poly-substance abuse syndrome. United States patent US 5152995 1992.
- [16] Schneider JA, inventor; Ciba Pharmaceutical Products Inc, Summit, NJ, assignee. Tabernanthine, ibogaine containing analgesic compositions. United States patent US 2817623 1957.
- [17] Naranjo C. *The healing journey: new approaches to consciousness*. New York City: Pantheon Books, Division of Random House 1974.
- [18] Stolaroff M. *The secret chief: conversations with a pioneer of the underground psychedelic therapy movement*. Charlotte, North Carolina: Multidisciplinary Association for Psychedelic Studies 1997.
- [19] Stolaroff M. *The Secret Chief Revealed: conversations with Leo Zeff, pioneer in the underground psychedelic therapy movement*. Sarasota, Florida: Multidisciplinary Association for Psychedelic Studies 2004.

- [20] Dzoljic ED, Kaplan CD, Dzoljic MR. Effect of ibogaine on naloxone-precipitated withdrawal syndrome in chronic morphine-dependent rats. *Arch Int Pharmacodyn Ther* 1988; 294: 64-70.
- [21] Glick SD, Rossman K, Steindorf S, Maisonneuve IM, Carlson JN. Effects and aftereffects of ibogaine on morphine self-administration in rats. *Eur J Pharmacol* 1991; 195: 341-5.
- [22] Glick SD, Gallagher CA, Hough LB, Rossman KL, Maisonneuve IM. Differential effects of ibogaine pretreatment on brain levels of morphine and (+)-amphetamine. *Brain Res* 1992; 588: 173-6.
- [23] Schmidt WK, Gorodetzky CW, Teti NL, Vocci F, Grossman SA, Mansbach RS. Drug abuse pharmacotherapy development in the private sector. Proceedings of the 60th Annual Meeting, The College of Problems on Drug Dependence; 1998 June; Scottsdale, Arizona. Bethesda, Maryland: US Department of Health & Human Services 1999; p 20.
- [24] Vastag B. Ibogaine therapy: a 'vast, uncontrolled experiment.' *Science* 2005; 308(5720): 345-6.
- [25] Erowid.org [homepage on the Internet]. [cited 2012 June 11]. Available from: <http://www.erowid.org>
- [26] Montagne M. Sites of substance: internet "drug" resources. *Substance Use and Misuse* 2008; 43: 17-25.
- [27] Brown TK and Gorenflo K. Ibogaine treatment for drug dependence: a study of quality of life [video on the Internet; cited 2012 May 30]. Presentation at Psychedelic Science in the 21st Century; 2010 April 15-18; San Jose, CA. Available from <http://www.maps.org/videos/source5/>
- [28] Brown TK. Ibogaine research in opiate addicts [video on the Internet; cited 2012 July 3]. Presentation at Cartographie Psychedelica Conference; 2011 Dec 8-12; Oakland, CA. Available from http://www.maps.org/media/videos_25/
- [29] Lotsof HS, Wachtel B. Manual for ibogaine therapy screening, safety, monitoring, and aftercare. [monograph on the Internet; © 2003; cited 2012 July 12]. Available from <http://www.ibogaine.desk.nl/manual.html>
- [30] Biichi G, Coffen DL, Kocsis K, Sonnet PE, Ziegler FE. The total synthesis of iboga alkaloids. *J Amer Chem Soc* 1966; 88(13): 3009-108.
- [31] Shulgin A, Shulgin A. TiKHAL: the continuation. Lafayette, CA: Transform Press 1997.
- [32] Janot MM, Goutarel R. Derivatives of the ibogaine alkaloids. Unites States patent US 2813873 1957 Nov 19.
- [33] Halpern JH. Hallucinogens: an update. *Current Psychiatry Reports* 2003; 5(5): 347-54.
- [34] Mash DC, Kovera CA, Buck BE, *et al.* Medication development of ibogaine as a pharmacotherapy for drug dependence. *Ann NY Acad Sci* 1998; 844: 274-92.
- [35] Mash DC, Kovera CA, Pablo J, *et al.* Ibogaine in the treatment of heroin withdrawal. *Alkaloids Chem Biol* 2001; 56: 155-71.
- [36] Maciulaitis R, Kontrimaviciute V, Bressolle FM, Briedis V. Ibogaine, an anti-addictive drug: pharmacology and time to go further in development. A narrative review. *Hum Exp Toxicol* 2008; 27(3): 181-94.
- [37] Maisonneuve IM, Glick SD. Anti-addictive actions of an iboga alkaloid congener: a novel mechanism for a novel treatment. *Pharmacol Biochem Behav* 2003; 75(3): 607-18.
- [38] Glick SD, Maisonneuve IM. Development of novel medications for drug addiction. The legacy of an African shrub. *Ann N Y Acad Sci* 2000; 909: 88-103.
- [39] Vastag, Addiction Treatment Strives for Legitimacy. *Journal of the American Medical Association* 2002; 288: 3096-101.
- [40] Cappendijk TSL, Dzoljic MR. Inhibitory effects of ibogaine on cocaine self-administration in rats. *Eur J Pharmacol* 1993; 241(2-3): 261-5.
- [41] Dworkin SI, Gleeson S, Meloni D, Koves TR, Martin TJ. Effects of ibogaine on responding maintained by food, cocaine and heroin reinforcement in rats. *Psychopharmacol* 1995; 117(3): 257-61.
- [42] Glick SD, Kuehne ME, Raucci J, *et al.* Effects of iboga alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum. *Brain Res* 1994; 657(1-2): 14-22.
- [43] Glick SD, Kuehne ME, Maisonneuve IM, Bandarage UK, Molinari HH. 18-Methoxycoronaridine, a non-toxic iboga alkaloid congener: effects on morphine and cocaine self-administration and on mesolimbic dopamine release in rats. *Brain Res* 1996; 719: 29-35.
- [44] Sershen H, Hashim A, Lajtha A. Ibogaine reduces preference for cocaine consumption in C57BL/6By mice. *Pharmacol Biochem Behav* 1994; 47(1) 13-9.
- [45] Rezvani AH, Overstreet DH, Lee YW. Attenuation of alcohol intake by ibogaine in three strains of alcohol-preferring mice. *Pharmacol Biochem Behav* 1995; 52(3): 615-20.
- [46] He DY, McGough NN, Ravindranathan A, *et al.* Glial cell line-derived neurotrophic factor mediates the desirable actions of the anti-addiction drug ibogaine against alcohol consumption. *J Neurosci* 2005; 25(3): 619-28.
- [47] Glick SD, Maisonneuve IM, Visker KE, Fritz KA, Bandarage UK, Kuehne ME. 18-Methoxycoronaridine attenuates nicotine-induced dopamine release and nicotine preferences in rats. *Psychopharmacology* 1998; 139(3): 274-80.
- [48] Glick SD, Maisonneuve IM, Pearl SM. Evidence for roles of kappa-opioid and NMDA receptors in the mechanism of action of ibogaine. *Brain Res* 1997; 749(2): 340-3.
- [49] Zubaran C. Ibogaine and noribogaine: comparing parent compound to metabolite. *CNS Drug Reviews* 2000; 6(3): 219-240.
- [50] Baumann MH, Rothman RB, Pablo JP, Mash DC. *In vivo* neurobiological effects of ibogaine and its O-desmethyl metabolite, 12-hydroxyibogamine (noribogaine), in rats. *J Pharmacol Exp Ther* 2001; 297(2): 531-9.
- [51] Glick SD, Pearl SM, Cai J, Maisonneuve IM. Ibogaine-like effects of noribogaine in rats. *Brain Res* 1996; 713(1-2): 294-7.
- [52] Carnicella S, He DY, Yowell QV, Glick SD and Ron D. Noribogaine, but not 18-MC, exhibits similar actions as ibogaine on GDNF expression and ethanol self-administration. *Addict Biol* 2010; 15(4): 424-33.
- [53] Pearl SM, Hough LB, Boyd DL, Glick SD. Sex differences in ibogaine antagonism of morphine-induced locomotor activity and in ibogaine brain levels and metabolism. *Pharmacol Biochem Behav* 1997; 57(4): 809-15.
- [54] Glick, SD, Maisonneuve, IM, Dickinson HA. 18-MC reduces methamphetamine and nicotine self-administration in rats. *Neuroreport* 2000; 11: 2013-15.
- [55] Rezvani AH, Overstreet DH, Yang Y, *et al.* Attenuation of alcohol consumption by a novel nontoxic ibogaine analogue (18-methoxycoronaridine) in alcohol-preferring rats. *Pharmacol Biochem Behav* 1997; 58: 615-9.
- [56] Rho B, Glick SD. Effects of 18-methoxycoronaridine on acute signs of morphine withdrawal in rats. *Neuroreport* 1998; 9(7): 1283-5.
- [57] Maisonneuve IM, Keller RW Jr, Glick SD. Interactions between ibogaine, a potential anti-addictive agent, and morphine: an *in vivo* microdialysis study. *Eur J Pharmacol* 1991; 199(1): 35-42.
- [58] Frances B, Gout R, Cros J, Zajac JM. Effects of ibogaine on naloxone-precipitated withdrawal in morphine-dependent mice. *Fundam Clin Pharmacol* 1992; 6(8-9): 327-32.
- [59] Aceto MD, Bowman ER, Harris LS, May EL. Dependence studies of new compounds in the rhesus monkey and mouse. *NIDA Res Monogr* 1992; 119: 513-58.
- [60] Sharpe LG, Jaffe JH. Ibogaine fails to reduce naloxone-precipitated withdrawal in the morphine-dependent rat. *Neuroreport* 1990; 1(1): 17-9.
- [61] Cappendijk SL, Fekkes D, Dzoljic MR. The inhibitory effect of norharman on morphine withdrawal syndrome in rats: comparison with ibogaine. *Behav Brain Res* 1994; 65(1): 117-9.
- [62] Popik P, Layer RT, Fossom LH, *et al.* NMDA antagonist properties of the putative anti-addictive drug, ibogaine. *J Pharmacol Exp Ther* 1995; 275(2): 753-60.
- [63] Layer RT, Skolnick P, Bertha CM, Bandarage UK, Kuehne ME, Popik P. Structurally modified ibogaine analogs exhibit differing affinities for NMDA receptors. *Eur J Pharmacol* 1996; 309(2): 159-65.
- [64] Koja T, Fukuzaki K, Kamenosono T, Nishimura A, Nagata R, Lukas SE. Inhibition of opioid abstinent phenomena by Ibogaine. *Jpn J Pharmacol* 1996; 71(S1): 89.
- [65] Parker LA, Burton P, McDonald RV, Kim JA, Siegel S. Ibogaine interferes with motivational and somatic effects of naloxone-precipitated withdrawal from acutely administered morphine. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26(2): 293-7.
- [66] Leal MB, Michelin K, Souza DO, Elisabetsky E. Ibogaine attenuation of morphine withdrawal in mice: role of glutamate N-

- methyl-D-aspartate receptors. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27(5): 781-5.
- [67] Panchal V, Taraschenko OD, Maisonneuve IM, Glick SD. Attenuation of morphine withdrawal signs by intracerebral administration of 18- methoxycoronaridine. *Eur J Pharmacol* 2005; 525(1-3): 98-104.
- [68] Ross S, Peselow E. Pharmacotherapy of addictive disorders. *Clinical Neuropharmacology* 2009; 32(5): 277-89.
- [69] Ward J, Rosenbaum C, Hernon C, McCurdy CR, Boyer EW. Herbal medicines for the management of opioid addiction: safe and effective alternatives to conventional pharmacotherapy? *CNS Drugs* 2011; 25(12): 999-1007.
- [70] Glick SD, Maisonneuve IM, Szumlinski KK. Mechanisms of action of ibogaine: relevance to putative therapeutic effects and development of a safer iboga alkaloid congener. *Alkaloids Chem Biol* 2001; 56: 39-53.
- [71] Popik P, Layer RT, Skolnick P. 100 years of ibogaine: neurochemical and pharmacological actions of a putative anti-addictive drug. *Pharmacol Rev* 1995; 47(2): 235-53.
- [72] Mash DC, Kovera CA, Pablo J, *et al.* Ibogaine: complex pharmacokinetics, concerns for safety, and preliminary efficacy measures. *Ann N Y Acad Sci* 2000; 914: 394-401.
- [73] Skolnick P. Ibogaine as a glutamate antagonist: relevance to its putative anti-addictive properties. *Alkaloids Chem Biol* 2001; 56: 55-62.
- [74] Helsley S, Rabin RA, Winter JC. Drug discrimination studies with ibogaine. *Alkaloids Chem Biol* 2001; 56: 63-77.
- [75] Pablo JP, Mash DC. Noribogaine stimulates naloxone-sensitive [35S]GTPgammaS binding. *Neuroreport* 1998; 9(1): 109-14.
- [76] Nichols DE. Hallucinogens. *Pharmacology and Therapeutics* 2004; 101: 131-81.
- [77] Bowen WD, Vilner BJ, Williams W, *et al.* Ibogaine and its congeners are s_2 receptor-selective ligands with moderate affinity. *Eur J Pharmacol* 1995; 271: R1-3.
- [78] Zubaran C, Shoaib M, Stoleran IP, Pablo J, Mash DC. Noribogaine generalization to the ibogaine stimulus: correlation with noribogaine concentration in rat brain. *Neuropsychopharmacol* 1999; 21(1): 119-26.
- [79] Kamlet J. Safety issues and cardiac side-effects in the administration of ibogaine HCl [video on the Internet; cited 2012 Jun 15]. Presentation at International Drug Policy Reform Conference; 2009 Nov 14; Albuquerque, NM. Available from <http://vimeo.com/7843758>
- [80] Hoelen DW, Spiering W, Valk GD. Long QT syndrome induced by the anti-addiction drug ibogaine. *N Engl J Med* 2009; 360(3): 308-9.
- [81] Cantor M. Ibogaine: miracle cure? *Truth Seeker* 1990; 117(5) 23-6.
- [82] Sisko B. Interrupting drug dependency: a summary of 4 case histories. *Bulletin of the Multidisciplinary Association for Psychedelic Studies (MAPS)* 1994; 4(2) 15-23.
- [83] Sheppard SG. A preliminary investigation of ibogaine: case reports and recommendations for further study. *J Subst Abuse Treat* 1994; 11(4): 379-85.
- [84] Luciano D. Observations on treatment with ibogaine. *Am J Addictions* 1998; 7(1): 89-90.
- [85] Kaplan CD, Ketzner E, de Jong J, de Vries M. Reaching a state of wellness: multistage explorations in social neuroscience. *Social Neuroscience Bulletin* 1993; 6(1): 6-7.
- [86] Alper KR, Lotsof HS, Frenken GM, Luciano DJ, Bastiaans J. Treatment of acute opioid withdrawal with ibogaine. *Am J Addict* 1999; 8(3): 234-42.
- [87] McClellan AT, Kushner H., Metger D., *et al.* The fifth edition of the Addiction Severity Index. *J Subst Abuse Treat* 1992; 9: 199-213.
- [88] Beck AT, Ward CH, Mendelson J., Mock J, Erbaugh J. An interview for measuring depression. *Arch Gen Psychiatry* 1961; 4: 561-71.
- [89] Singleton EG. The HCQN-29: a short version of the Heroin Craving Questionnaire. Unpublished research 1996; Available from the Clinical Pharmacology and Therapeutics Research Branch, Intramural Research Program NIDA, 55 Nathan Shock Drive, Baltimore, MD 21224, USA.
- [90] Tiffany ST, Singleton E, Haertzen CA, Henningfield JE. The development of a cocaine craving questionnaire. *Drug Alcohol Depend* 1993; 34: 19-28.
- [91] Bastiaans E. Life after ibogaine: an exploratory study of the long-term effects of ibogaine treatment on drug addicts. Science Internship Report, Vrije Universiteit Amsterdam, 2004. [monograph on the Internet; cited 2012 May 30]. Available from http://www.ibogaine.org/ibogaine_udi_bastiaans
- [92] Krupitsky EM, Burakov AM, Romanov TN, Grinenko AY, Strassman RJ. Ketamine-assisted psychotherapy (KPT) of heroin addiction: immediate effects and six months follow-up. *Hefter Review of Psychedelic Research* 2001; 2: 88-101.
- [93] McKenna DJ. Clinical investigations of the therapeutic potential of ayahuasca: rationale and regulatory challenges. *Pharmacology and Therapeutics* 2004; 102(2): 111-29.
- [94] Savage C, McCabe OL. Residential psychedelic (LSD) therapy for narcotic addicts. *Arch Gen Psych* 1973; 28: 808-14.
- [95] Krebs TS, Johansen PO. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. *J Psychopharmacol* 2012; 26(7): 994-1002.
- [96] Friedman H. The renewal of psychedelic research: implications for humanistic and transpersonal psychology. *Humanistic Psychologist* 2006; 34(1): 39-58.
- [97] Griffiths RR, Richards WA, Johnson MW, McCann UD, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol* 2008; 22: 621-32.
- [98] MacLean KA, Johnson MW, Griffiths RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *J Psychopharmacol* 2011; 25: 1453-61.
- [99] Yokell MA, Zaller ND, Green TC, Rich JD. Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: an international review. *Curr Drug Abuse Rev* 2011; 4(1): 28-41.
- [100] Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, US Department of Health and Human Services. Methadone mortality - a 2010 reassessment. Briefing paper delivered 2010 July 29-30; Washington, DC. Available from dpt.samhsa.gov/pdf/Methadone_Briefing_Paper.pdf; cited 2012 Jun 17.
- [101] De Maeyer J, Vanderplasschen W, Broekaert E. Quality of life among opiate-dependent individuals: a review of the literature. *Int J Drug Policy* 2010; 21(5): 364-80.
- [102] Hittner JB, Quello SB. Combatting substance abuse with ibogaine: pre- and post-treatment recommendations and an example of successive model fitting analyses. *J Psychoactive Drugs* 2004; 36(2): 191-9.
- [103] Fernandez JW, Fernandez RL. "Returning to the path": the use of iboga[ine] in an equatorial African ritual context and the binding of time, space, and social relationships. *Alkaloids Chem Biol* 2001; 56: 235-47.
- [104] Naranjo, C 1969. Psychotherapeutic possibilities of new fantasy-enhancing drugs. *Clin Toxicol* 2 (2): 209.
- [105] Mojeiko V, Brown TK, Gargour K, Jordan M. Observational study of the long-term efficacy of ibogaine- assisted treatment in participants with opiate addiction. Available from www.maps.org/research/ibogaine/
- [106] Noller G. Observational study of the long-term efficacy of ibogaine-assisted therapy in participants with opioid addiction. Available from www.maps.org/research/ibogaine/
- [107] McLellan AT, Cacciola JC, Alterman AI, Rikoon SH, Carise D. The Addiction Severity Index at 25: origins, contributions, and transitions. *Am J Addictions* 2006; 15(2): 113-24.
- [108] Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987; 13(3): 293-308.
- [109] Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacol* 2006; 187(3): 268-83.