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THE USE OF IBOGAIN IN THE TREATMENT OF ADDICTIONS

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INTRODUCTION

Ibogaine is a naturally occurring *iboga* alkaloid, a chemical taxonomic category presently known to contain approximately 80 naturally occurring and synthetic compounds, some of which reportedly reduce the self-administration of drugs of abuse and opiate withdrawal symptoms in animal models and humans (Alper et al. 2001b). Ibogaine is isolated from the root bark of *Tabernanthe iboga* native to West Central Africa, where it has been used as a religious sacrament for centuries (Fernandez 1982; Goutarelet al. 1993) before it was observed in the United States and Europe to have apparent effects on opioid withdrawal and other drug dependence syndromes. As reviewed in this chapter, major published scientific evidence for ibogaine's effectiveness includes reduced drug self-administration and withdrawal in animals, and case reports and open-label trials in humans. The NIDA (National Institute on Drug Abuse) committed several million dollars of support during the term of its program of ibogaine research (Vastag 2002), and ibogaine has been administered to humans in the United States in a FDA (Food and Drug Administration) approved phase 1 study (Mash et al. 1998).

From a pharmacological standpoint, ibogaine is interesting because it appears to have a novel mechanism of action that is different from other existing

pharmacotherapeutic approaches to addiction. The question of ibogaine's mechanism of action is important because its ultimate significance may be a paradigm for understanding the neurobiology of addiction as well as the development of new medications.

Consistent with ibogaine's status as a ritual hallucinogen in Africa, there is some use of ibogaine in Europe and North America in the search for psychological insight or spiritual growth. However, the treatment of substance dependence, in particular opioid dependence, is the most common reason for which individuals outside of Africa have taken ibogaine (Alper et al. 2001a).

Ibogaine apparently is not an opiate agonist therapy, such as methadone (Dole and Nyswander 1967), nor is it an opiate antagonist. Ibogaine has activity at a variety of different receptors in the brain with effects that may result from complex interactions between multiple neurotransmitter systems (Popik and Skolnick 1998; Alper 2001). Some evidence suggests that ibogaine treatment results in the "resetting" or "normalization" of neuroadaptations thought to underlie the development of dependence and may have general neurobiological effects common to multiple types of substance dependence syndromes.

As a naturally occurring plant alkaloid whose structure cannot be patented and mechanism of action is unknown, ibogaine has been relatively unattractive to the pharmaceutical industry as a potential project for development. The research and possible development of ibogaine has largely been left to the academic community in the public sector. This has led to the existence of a distinctive unofficial network involving lay individuals, a "medical subculture" of ibogaine treatments in nonmedical settings (Alper et al. 2001a; Lotsof and Wachtel 2003), and clinics emulating the conventional medical model in countries such as Mexico and St. Kitts where ibogaine is not illegal (Mash et al. 1998).

HISTORY

The first published references to ibogaine over a century ago documented its use in what is now the Republic of Gabon in West Central Africa. Hunters used it in small doses to promote vigilance while stalking prey, and initiates and members of the Bwiti religious movement used it at much higher dosages as a sacramental hallucinogen in maturational rites of passage and to facilitate their experience of spiritual contact with their ancestors (Fernandez 1982). In Gabon, the sacred culture of ibogaine has been a major element of cultural and national unity.

Ibogaine was not a controlled substance in the United States until 1967, when the FDA assigned it to schedule I (considered to have high potential for abuse, with no recognized medical use). It remains unscheduled in most of the rest of the world, with the exception of Switzerland, Sweden, Belgium, and Denmark. Regardless of ibogaine's schedule I status, it has never been popular as an abused substance. Between 1939 and 1970, ibogaine was sold in France

as Lambarène, a “neuromuscular stimulant,” in the form of tablets that contained 200mg of root bark extract with an estimated content of ibogaine of 8mg, recommended for a variety of indications that included fatigue, depression, and recovery from infectious disease (Goutarel et al. 1993). *Iboga* alkaloids have not been observed to be self-administered or to produce withdrawal signs following chronic administration in animals (Aceto et al. 1992). Apparently only two arrests have ever occurred in the United States for possession, sale, or distribution of ibogaine (Ranzal 1967; Lane 2005). However one of these arrests occurred recently in December 2005 (Lane 2005) and involved Federal conspiracy charges that carry a possible penalty of 20 years in prison, raising the possibility that ibogaine could become targeted in the United States “War on Drugs.”

Research on ibogaine as a treatment for addiction began in New York City in 1962 with a group of lay drug experimenters organized by Howard Lotsof around a shared interest in the psychotherapeutic potential of hallucinogens. During this period, which preceded the scheduling of hallucinogenic drugs, the group ingested a variety of psychoactive agents obtained legally from botanical and chemical supply houses. The effects of ibogaine were entirely unknown to this group’s participants, who took it in escalating dosages ranging from 0.14 to 19mg/kg. A heroin-dependent subgroup, to their surprise, experienced an unexpected elimination of the physical symptoms of opioid withdrawal. Eventually, in 1985, Lotsof received a U.S. patent for the use of ibogaine in opioid dependence (Lotsof 1985), and additional patents followed for the indications of dependence on cocaine and other stimulants, alcohol, nicotine, and polysubstance abuse. Elsewhere, psychiatrist and anthropologist Claudio Naranjo had received a French patent for the psychotherapeutic use of ibogaine at a dosage of 4 to 5mg/kg in 1969 (Bocher and Naranjo 1969) and later published a detailed description of psychotherapy sessions utilizing ibogaine (Naranjo 1973).

Between 1988 and 1994, Dutch and U.S. researchers published initial findings suggestive of the efficacy of ibogaine in animal models of addiction, including diminished opioid self-administration and withdrawal, as well as diminished cocaine self-administration. At around this time, treatments of heroin-dependent individuals were conducted outside of conventional medical settings in the Netherlands. Among those treated was Nico Adriaans (Grund et al. 1991; Grund 1995), an activist who had organized the Dutch Junkiebond, an addict self-help and advocacy organization that became a model for the European drug user unions and the harm reduction movement.

In 1991, based on case reports and preclinical evidence suggesting possible efficacy, and prompted by a vocal activist political subculture, NIDA began its ibogaine research project, whose major objectives were preclinical toxicological evaluation and the development of protocols for eventual clinical trials. In 1993, the FDA approved a phase I clinical trial of ibogaine that was not completed for reasons unrelated to clinical or safety issues. NIDA elected to withhold funding for its own phase I/II protocol, and its ibogaine project effectively ended in 1995.

Regardless of the lack of official approval, ibogaine became increasingly available in alternative settings. Lay treatment providers in nonmedical settings began to appear in the mid to late 1990s in the United States, Slovenia, Britain, the Netherlands, and the Czech Republic. Treatments in settings based on a conventional medical model were conducted in Panama in 1994 and 1995 and in St. Kitts in the Caribbean from 1996 to the present (Alper et al. 2001a). Additional scenes followed in Mexico and Canada beginning in 2002, and South Africa in 2004. The first Internet message board, and the first web site devoted to ibogaine, the Ibogaine Dossier (Lots of 2006) appeared in 1997 and heralded the importance of the Internet within the ibogaine medical subculture (Kroupa 2006; Sandberg 2006). The Internet has been a significant factor in the expansion of the ibogaine subculture, with increasing numbers of participants and the appearance of new treatment scenes.

PHARMACOLOGY

Although it is designated as a hallucinogen, ibogaine differs importantly from other compounds that are commonly termed “psychedelic” such as the classical 5-HT_{2A} agonist hallucinogens, including LSD (lysergic acid diethylamide), psilocybin, and mescaline, or the serotonin releasing substituted amphetamine, MDMA (3,4-methylenedioxymethamphetamine). Ibogaine’s reported effect on opioid withdrawal or self-administration does not appear to involve 5-HT agonist or releasing activity (Wei et al. 1998; Alper 2001; Glick et al. 2001; Maisonneuve and Glick 2003). The reported affinity of ibogaine for the 5-HT_{2A} receptor is several orders of magnitude less than that of LSD (Glick et al. 2001). Both psychedelics and ibogaine have been claimed to facilitate psychotherapeutic insight (Novak 1997; Snelders and Kaplan 2002). However, the clinical focus on the treatment of opioid withdrawal distinguishes the subculture associated with ibogaine from those associated with compounds commonly designated as psychedelics. In contrast to *iboga* alkaloids, there is no preclinical or case report evidence to suggest a significant therapeutic effect of classical hallucinogens or MDMA in acute opiate withdrawal.

Chemistry and Metabolism

Ibogaine, a monoterpene indole alkaloid, is the most abundant alkaloid in the root bark of the Apocynaceous shrub *T. iboga*. In the dried root bark, the part of the plant with the highest alkaloid content, the concentration of ibogaine is approximately 2 to 4%. The extraction process is relatively simple, and a recent publication describes a method yielding adequate results using diluted vinegar and ammonia (Jenks 2002).

The two other important *iboga* alkaloids that are encountered in the literature are (using the Le Men and Taylor system¹) 18-MC (18-methoxycoronaridine)

and 10-hydroxyibogamine, also known as *O*-desmethylibogaine or noribogaine. 18-MC is of interest as a synthetic ibogaine congener that has been designed by a rational pharmaceutical process with the intention of developing a compound that is safer than ibogaine while retaining ibogaine's effectiveness (Maisonneuve and Glick 2003). Although 18-MC has been investigated to a substantial extent in animal models, it has not yet been given to humans. Noribogaine is ibogaine's principal metabolite formed by a process of demethylation involving the microsomal enzyme CYP2D6 (cytochrome P450 2D6; Mash et al. 1995). Noribogaine is less polar than the parent compound ibogaine and may be formed within the brain, in which CYP2D6 is expressed (Miksys and Tyndale 2002). Noribogaine may be "trapped" in the brain because less polar compounds do not cross the blood-brain barrier as rapidly. The possible sequestration of noribogaine in the brain and its slower clearance relative to ibogaine have been cited in support of the theory that ibogaine's effects are mediated mainly by noribogaine (Mash et al. 2000). Because ibogaine is more lipophilic, it accumulates preferentially in tissues containing high density of lipids, such as brain or fat (Hough et al. 1996). Noribogaine's relatively slower clearance suggests that ibogaine is sequestered in fat, and released slowly over time and subsequently converted to noribogaine.

Toxicology

The major safety concerns regarding ibogaine have been neurotoxicity and cardiotoxicity. The cerebellum appears to be the region that is most affected by neurotoxicity (O'Hearn and Molliver 1997; Xu et al. 2000), which has been observed in the rat at dosages exceeding those used to diminish drug self-administration and withdrawal but not in the mouse or primate (Molinari et al. 1996; Mash et al. 1998). No evidence of neurotoxicity was found in the postmortem neuropathological examination of a single female patient who had previously been treated on four occasions in 15 months prior to death with dosages ranging from 10 to 30mg/kg (Mash et al. 1998). Likewise, quantitative evaluation of posture and tremor, which are measures related to cerebellar functioning, indicated no abnormality in patients who had previously taken ibogaine at dosages ranging from 10 to 30mg/kg.

Bradycardia, or possibly some other form of cardiac arrhythmia, may be a more significant safety issue. As of 2006, we are aware of eight deaths since 1990 that are reported to have occurred within 72 hours of taking ibogaine (Alper 2001; Marker and Stajic 2002; Maas and Strubelt 2006). Possible causes of some of these deaths appear to have been related to drug use during treatment, preexisting cardiovascular disease, or pulmonary emboli. The uncontrolled settings in which ibogaine is given make the causes of these deaths difficult to evaluate. 18-MC does not reportedly affect cardiac rate (Maisonneuve and Glick 2003).

Mechanisms of Action

Initially, ibogaine's mechanism of action was hypothesized to involve antagonism at the NMDA (*N*-methyl-D-aspartate)-type glutamate receptor (Popik et al. 1995; Skolnick 2001). However, ibogaine, despite significant NMDA affinity, differs from NMDA antagonists in drug discrimination studies (see below) (Helsley et al. 2001) and some functional pharmacological assays (Alper 2001). Also 18-MC, which has negligible NMDA affinity, is equally as efficacious as ibogaine in reducing drug withdrawal in the animal model (Glick et al. 2001). Antagonism of the alpha3beta4 nicotinic receptor as a possible mechanism of action is supported by studies of *iboga* alkaloids and nicotinic agents (Maison-neuve and Glick 2003; Taraschenko et al. 2005). Some evidence supports the possibility of possible enhancement of signal transduction through opioid receptors, independent of a direct agonist effect (Rabin and Winter 1996; Alper 2001). A recent study found increased GDNF (glial cell line-derived neurotrophic factor) in the midbrain in rats following the administration of ibogaine, which was suggested to have mediated the observed decrease in ethanol consumption (He et al. 2005).

Drug Discrimination Studies

The drug discrimination paradigm is intended to study the neurotransmitter receptor actions of a drug by training animals to respond to a specific drug stimulus (Helsley et al. 2001). The discrimination paradigm involves conditioning in which the perception of a drug effect is paired with a nondrug reward. Animals can be trained to press one of a choice of bars in order to obtain a reward, such as a preferred food. The animal is trained to respond by pressing a particular bar when it experiences the effects of a given psychoactive drug, which establishes that the animal can perceive the effect of the drug. If a second drug produces the same type of responding, it is said to "substitute" for the first drug, and indicates that the animal perceives both drugs as being similar, possibly on the basis of common actions at neurotransmitter receptors.

In the discrimination paradigm, the receptor actions of ibogaine appear to differ from those of other drugs associated with hallucinogenic effects (Helsley et al. 2001). Classical hallucinogens such as LSD, psilocybin, or mescaline are agonists at the serotonin type 2A (5-HT_{2A}) receptor, which is thought to mediate their hallucinogenic effect (Nichols 2004). The 5-HT_{2A} stimulus is "non-essential" to the ibogaine stimulus. This means that although there is significant substitution for ibogaine by 5-HT_{2A} agonist classical hallucinogens in the drug discrimination paradigm, the animal can still recognize ibogaine even when the 5-HT_{2A} receptor is blocked. Actions that are not apparently involved in the ibogaine stimulus include NMDA antagonism, or kappa-opioid and sigma₁ agonist effects. Drug discrimination results for ibogaine indicate strong substitution by noribogaine for ibogaine, indicating that noribogaine may mediate the stimulus effect of ibogaine.

SUBJECTIVE EFFECTS

Patients treated for opioid withdrawal with ibogaine often describe significant attenuation of opiate withdrawal symptoms within several hours of ingestion, and lasting resolution of the acute opioid withdrawal syndrome within 12 to 18 hours. The advantages that patients commonly attribute to ibogaine are higher tolerability relative to other standard treatments for acute opioid withdrawal, and an interval of diminished drug craving that may last days to several months following a treatment. Descriptions of experiences by individuals treated with ibogaine appear to share some common features. A typology of stages of the ibogaine experience has been developed on the basis of the accounts of patients and treatment guides, as well as general descriptions and case studies provided by the literature (Lotsof 1995; De Rienzo and Beal 1997; Alper 2001). The typology consists of three stages: acute, evaluative, and residual stimulation.

Acute Phase

The onset of this phase is within one to three hours of ingestion, with duration on the order of four to eight hours. The predominant reported experiences appear to involve a panoramic readout of long-term memory, particularly in the visual modality, and visual experiences more consistent with the experience of dreams than of hallucinations. Ibogaine is commonly referred to as a hallucinogen; however, some authors prefer the term “oneiric” (Greek, *oneiros*, dream) instead of “hallucinogenic” because the visual experiences described with ibogaine appear to be more suggestive of vivid waking dreams than hallucinations (Goutarel et al. 1993). These visual phenomena appear to differ qualitatively from subjective experiences reported with classical hallucinogens. The classical hallucinogens tend to be associated with an alteration of the eyes open visual perception of patterns, colors, and textures. On the other hand, the visual phenomena associated with ibogaine tend to occur with greatest intensity with the eyes closed, and to be suppressed by opening the eyes, and they often involve a sense of location and navigation within an internally represented visual landscape as in a dream.

Descriptions of the form of visual phenomena experienced by individuals who take ibogaine emphasize an extremely high density of images, suggestive of an accelerated film presentation in which any individual frame may in turn generate another series of related images. The content may be autobiographical and often appears interpretable to individuals in the context of their life narrative. Other images have a less personal and more archetypal character, relating to themes such as creation, prehistory, and evolution. Surreal or comical cartoon-like images are also often described. As in the African Bwiti religious culture, the visual experiences may be attributed with psychological or spiritual significance, which is itself a motivation for some individuals to take ibogaine.

The effect of ibogaine on acute opiate withdrawal does not appear to correlate directly with the occurrence of visual phenomena.

Not all individuals experience visual phenomena from ibogaine, which may be related to dose, bioavailability, and interindividual variation. In some cases, visual images are reported during the actual experience but are not apparently recalled afterward. Generally, only a smaller subset of the many images seen during the acute phase is recalled later, similar to normal dreaming. Visual phenomena may not occur or be recalled later, although some individuals may deny visual experiences in order to avoid discussing them because of their personal significance. The acute visualization or dreamlike phase tends to end abruptly.

Evaluative Phase

The onset of this phase is approximately four to eight hours after ingestion and lasts approximately 8 to 20 hours. The volume of material recalled slows, and the emotional tone of this phase is generally described as neutral and reflective. Attention is focused on inner subjective experience and evaluation of the experiences of the acute phase, and not the external environment. Individuals in this phase and the acute phase above are apparently sensitive to distraction by ambient external stimuli, and prefer a quiet environment in which to maintain their focus on inner experience. The material reviewed and reported by patients during the evaluative phase may consist of recollection of material from the dreamlike experience or other memories and often concerns traumatic or emotional experiences, personal relationships, or important decisions that the patient has made. The transition from the second phase to a third phase of residual stimulation tends to be gradual.

Residual Stimulation Phase

The onset of this phase is approximately 12 to 24 hours after ingestion and may last 24 to 72 hours or longer. There is a reported return of normal allocation of attention to the external environment. The intensity of the subjective psychoactive experience lessens, with mild residual subjective arousal or vigilance. Some patients report reduced need for sleep for several days to weeks following treatment, which might reflect a persistent effect of ibogaine on sleep, or insomnia, experienced commonly by substance-dependent individuals in early stages of recovery. Also, many individuals treated for substance dependence have been accustomed to sleeping as a psychological coping style, and their complaints of insomnia may relate to the subjective discomfort and unfamiliarity of dealing with issues without the soporific effect of some drugs of abuse. The three phases combined resolve in most patients within 48 hours, and within 24 hours for a substantial subset of patients.

EVIDENCE OF EFFICACY

The evidence for effects of ibogaine on drug salience, self-administration, and withdrawal appears remarkably consistent between experimental animal models and human case reports. The apparent relevance of preclinical animal models suggests that ibogaine's reported effects in humans are not likely to be explained solely on the basis of a placebo effect or the psychological impact of the abreaction of the content of the subjective experiences associated with the use of ibogaine.

Evidence of Efficacy in the Animal Model

Proof of concept preclinical research in animals on *iboga* alkaloids has involved ibogaine (Dzoljic et al. 1988; Glick et al. 1994), noribogaine (Baumann et al. 2001), and 18-MC (Maisonneuve and Glick 2003). Four main preclinical paradigms have been used to model ibogaine's effects on addictive behavior. These paradigms are drug withdrawal, self-administration, the measurement of DA (dopamine) efflux in the NAc (nucleus accumbens), and place preference.

Opiate withdrawal is observed in rats as a constellation of signs such as "wet-dog shakes," compulsive grooming, teeth chattering, diarrhea, and flinching. The evidence for the effectiveness of ibogaine in opiate withdrawal in the animal model is particularly strong, with at least eight published independent replications (Dzoljic et al. 1988; Glick et al. 1992; Cappendijk et al. 1994; Glick et al. 1996a; Rho and Glick 1998; Parker and Siegel 2001; Leal 2003; Panchal et al. 2005). In this regard, it is interesting that opiate withdrawal is the specific indication for which treatment with ibogaine is most commonly sought (Alper et al. 1999; Alper et al. 2001a; Mash et al. 2001).

Drug self-administration can be instated in animals as a model of human substance abuse and dependence. It is of interest that some strains of rats will self-administer more readily than others (Kruzich and Xi 2006), which appears to model the phenomenon of apparent genetic determinants of vulnerability toward substance dependence in humans (Nestler 2000). In animal models, *iboga* alkaloids are reported to reduce the self-administration of morphine (Glick et al. 1991, 1994, 1996b; Maisonneuve and Glick 1999; Pace et al. 2004), cocaine (Cappendijk and Dzoljic 1993; Glick et al. 1994), amphetamine (Maisonneuve et al. 1992), methamphetamine (Glick et al. 2000; Pace et al. 2004), alcohol (Rezvani et al. 1995, 1997; He et al. 2005), and nicotine (Glick et al. 1998, 2000).

Iboga alkaloids are also reported to diminish DA efflux in the NAc in response to opioids (Maisonneuve et al. 1991; Glick et al. 1994, 2000) or nicotine (Benwell et al. 1996; Maisonneuve et al. 1997; Glick et al. 1998). DA efflux in the NAc is a model of drug salience, which is the ability of drug-related stimuli to command attention and motivate behavior related to obtaining and using drugs (Robinson and Berridge 1993). The NAc is a critical anatomical locus of drug-seeking behavior that receives input of neurons containing

DA from the midbrain. DA efflux in the NAc is the result of the release of DA from neurons that originate from the midbrain and terminate in the NAc, and occurs with either exposure to perceptual cues or ingestion of substances of abuse.

An exception to the tendency of the *iboga* alkaloids to reduce DA efflux in the NAc is seen with stimulants such as cocaine or amphetamine. For stimulants, the reported effects on DA efflux are variable, which might be related to differences across studies, the timing and sequence of administration, the method for measuring DA, and the region of NAc in which measurements are made. These variable results might be due to opposing effects of both the removal of tolerance to stimulants and the dampening of DA efflux generally seen with *iboga* alkaloids. Stimulants cause DA release, and a loss of tolerance would tend to oppose the dampening of DA efflux due to treatment with *iboga* alkaloids. Nonetheless, there are multiple reports of reduction in stimulant self-administration in animals following treatment with *iboga* alkaloids (Maisonneuve et al. 1992; Cappendijk and Dzoljic 1993; Glick et al. 1994, 2000; Pace et al. 2004)

Place preference is a phenomenon based on associative learning. If an animal is administered a rewarding or reinforcing substance when it is in a particular location, such as one compartment or corner of its cage, it will tend to spend more time in that location. The place preference paradigm is a model of drug craving and drug seeking behavior elicited by cues associated with the drug of abuse. The prevention of place preference in animals treated with *iboga* alkaloids may model a reduction of the salience of drug-related stimuli (Parker and Siegel 2001).

Evidence of Efficacy in Humans

Ibogaine is the only *iboga* alkaloid that has reportedly been taken by humans. Although noribogaine is formed from ibogaine by a single synthetic step, its administration to humans has not yet been reported. 18-MC has only been given to animals. The two case series that provide evidence for efficacy of ibogaine in opioid withdrawal involve a total of 65 patients. One series consists of 33 treatments for the indication of opioid withdrawal performed in nonmedical settings in the United States and the Netherlands (Alper et al. 1999). The other case series consists of 32 opioid-dependent patients treated at a clinic in St. Kitts (Mash et al. 2001). An additional 18 case reports, some overlapping with the U.S./Netherlands series, provide additional descriptive detail regarding treatment with ibogaine (Alper 2001).

The individuals treated for opioid withdrawal in the U.S./Netherlands series were generally severely dependent on heroin, and eight subjects were additionally taking methadone (Alper et al. 1999). Their average daily use of heroin was 0.64g, primarily by the intravenous route. Full resolution of the signs of opioid withdrawal without further drug-seeking behavior was observed within 24 hours in 25 patients and was sustained for 72 hours following treatment. Four

other individuals were reportedly without withdrawal signs but continued to seek heroin. In three other patients withdrawal signs were significantly attenuated but still present. This series also included one fatality, the cause of which was undetermined, but was viewed as possibly having involved surreptitious heroin use during the treatment.

The other case series, by Mash et al. (2001), reported on 32 patients in the clinic located in St. Kitts, treated with a fixed dose of ibogaine of 800mg for the indication of opioid withdrawal. Physician ratings utilizing structured instruments for signs and symptoms of opioid withdrawal indicated resolution of withdrawal signs and symptoms at time points corresponding to 12 and 24 hours following ibogaine administration, and 24 and 36 hours after the last use of opiates. The resolution of withdrawal signs and symptoms was sustained during subsequent observations over an interval of approximately one week following ibogaine administration. Reductions of measures of depression and craving remained significantly reduced one month after treatment. The authors noted that in their experience ibogaine appeared to be equally efficacious in treating withdrawal from either methadone or heroin.

The case reports of ibogaine treatment performed in nonmedical settings in the United States and the Netherlands were important to NIDA's decision to pursue an ibogaine project. Data regarding a total of 52 treatments involving 41 individuals were presented to NIDA in 1995 (Alper 2001). These treatments had been conducted mainly for opiate withdrawal, but also for other conditions such as stimulant or alcohol dependence. With regard to follow up after treatment, Table 4.1 presents a summary of outcomes following a treatment with ibogaine in this series on the basis of patient self-report.

The case reports and case series originating from the ibogaine subculture should be considered seriously as a possibly valid source of clinical evidence. The consistency of ibogaine's reported effects in interviews and the "grey literature" including the Internet appear to suggest a significant pharmacological effect. From a methodological standpoint, it appears reasonable that the lay individuals involved in the subculture could make valid clinical observations regarding the absence or presence of the signs of acute opioid withdrawal, the indication for which ibogaine has most frequently been given. Acute opioid withdrawal is a clinically robust phenomenon that can be appreciated by a lay clinical observer and produces a relatively clear outcome occurring within a limited time frame.

Table 4.1 Drug Abstinence Following Ibogaine Treatment
(Presented to NIDA, March 1995)

<2 months	15 (29%)
2 to <6 months	15 (29%)
6 months to <1 year	7 (13%)
>1 year	10 (19%)
Not determined	5 (10%)

The typically high levels of physical dependence in patients seeking treatment with ibogaine suggest that a placebo response is unlikely to explain its apparent clinical effect in opioid withdrawal.

LEARNING, MEMORY, AND ADDICTION

The excessive attribution by drug abusers of salience to drugs and drug-related stimuli suggests a possible role of processes subserving learning and memory. Learning can be viewed as the modification of future brain activity, of which thought, motivation, consciousness, or sensory experience are emergent properties, on the basis of prior experience. This broad definition relates to approach and avoidance behavior, the acquisition of cognitive skills and factual knowledge, as well the neuroadaptations of drug tolerance and dependence.

Addiction may involve the pathological acquisition or “learning” of associations of drug-related stimuli with motivational states corresponding to valuation and importance. The pathological learning of addiction differs from that of normal learning. The behavior of individuals who are dependent on drugs and persist in using them despite a variety of serious negative consequences does not appear to reflect the experience of external events as they actually occur. Instead, the attribution of salience to drug incentives appears to involve alterations of neural plasticity in processes that subserve motivation, memory, and learning, resulting in neural behavior that to a significant extent has escaped the constraint of validation by experience with external reality.

Ibogaine and Neuroadaptations Related to Substance Dependence

There is evidence for a relatively selective effect of ibogaine on the pathological “learning” encoding of drug salience, distinguished from learning involving nondrug incentives. Such evidence includes ibogaine’s effect on diminishing the acquisition of place preference associated with drugs of abuse (Parker and Siegel 2001), but not place preference associated with a sweet taste (Blackburn and Szumlinski 1997). A general effect of interference with learning has been suggested, but studies on spatial learning show an actual enhancement by ibogaine (Popik 1996; Helsley et al. 1997). Ibogaine’s effects on DA efflux in the NAc in response to morphine are relatively more evident in animals with prior exposure to morphine (Pearl et al. 1995, 1996), suggesting a specific effect on neuroadaptations related to prior drug exposure.

Goutarel’s Hypothesis

Robert Goutarel, a French chemist, was impressed with the similarity of the experiences described by individuals who had taken ibogaine to dreams and

hypothesized that these experiences were relevant to ibogaine's apparent effects on addiction (Goutarel et al. 1993). Dreaming is associated with REM (rapid eye movement) sleep, which is thought to play an important role in the consolidation of learned information and memories (Stickgold and Walker 2005).

Although Goutarel's hypothesis was based mainly on the phenomenology of description of individuals who had taken ibogaine, it receives some support from studies involving the EEG (electroencephalogram). In the awake animal model, ibogaine has been reported to produce atropine sensitive theta (Depoortere 1987) and low-voltage fast (Schneider and Sigg 1957) EEG activity, both of which are EEG rhythms characteristically seen in REM sleep (Marrosu et al. 1995). Atropine is an antagonist of the neurotransmitter acetylcholine, and ascending cholinergic input from the brainstem to the cerebral cortex and hippocampus is an essential determinant of REM sleep. Thus, it would appear that in awake animals, ibogaine produces an EEG state with pharmacological as well as electrophysiological similarity to REM sleep, consistent with Goutarel's concept of ibogaine producing a "waking dream" state. It is hypothesized that a state of plasticity during that waking dream state occurs that allows the reconsolidation of learning, permitting the separation of drug-related cues and representations from the obsessive motivational states with which they have become linked, an "unlearning" of the pathological salience that substances of abuse appear to encode in the structures and systems of the brain involved in learning and motivated behavior.

CLINICAL USE OF IBOGAINE

There is substantial variety regarding the clinical contexts in which ibogaine is used. Some clinics exist in which providers have official medical credentials, and provide treatment in settings that emulate the conventional medical model. A majority of providers lack official medical credentials and conduct treatments in apartments or hotel rooms, or in religious settings such as a Bwiti chapel. Among lay treatment providers, there has been an activist element that viewed treatment not only from the perspective of providing care but also with an evangelical intention of gaining official acceptance of ibogaine.

Dosage and Management During the Treatment

Ibogaine is most often given for the indication of acute opioid withdrawal or other drug dependence syndromes typically as a single oral dose in the range of 10 to 25mg/kg of body weight, usually given in the morning. Dosages of individuals without substance dependence who take ibogaine are usually on the order of one half the dosage used for the treatment of opioid withdrawal. Although the single large dose has been the modal dosage schedule, there has been some use of smaller dosages given on a more frequent basis (Kroupa and Wells 2005),

for example, daily regimens of as little as 25 to 50mg/day. There is also use of “booster” dosages on the order of half of those typically used in opioid withdrawal, given months after an initial high-dose treatment. The psychologist Leo Zeff utilized ibogaine as well as the classical hallucinogens and MDMA in a psychotherapeutic context. In a personal communication to one of the authors (Lotsof), Zeff described a case of a patient with a history of cocaine use who ceased using cocaine after a week of intranasally self-administered doses of ibogaine of 50 to 150mg/day.

Treatments involving the single full dose are generally conducted with the patient lying down and still, a practice that is related to the cerebellar effects of ibogaine and because vomiting tends to be more frequent with movement. The room is darkened as ibogaine produces sensitivity to light. Interaction with the patient is generally minimized during the treatment unless the patient initiates verbal communication because sound is experienced with greater acuity and because of the importance attributed to the patient’s attention to the content of the experience. Vomiting is reportedly common and often occurs relatively suddenly as a single episode in the first several hours of treatment.

Setting

The environments in which ibogaine is administered are diverse. Ibogaine treatment providers view ibogaine from perspectives as diverse as varieties of clinical research, shamanism, self-help, and African religious practices. Settings may vary from clinics that emulate the conventional medical model to Bwiti chapels.

Experienced treatment providers generally view it is important to maintain a treatment environment free of distracting sensory stimuli such as loud noises, discussions, arguments, strong or irritating odors, and bright lights (Lotsof and Wachtel 2003). This is especially the case during the first three to four hours of the ibogaine experience, during which many providers recommend that patients should not be compelled to open their eyes or respond to staff any more than is absolutely necessary. A small subset of patients may want to talk or move about, which may represent an attempt to resist ibogaine’s psychological effects. They may fear of loss of control or become uncomfortable with the content of experience.

For individuals being treated with ibogaine for substance-related disorders, the involvement of persons who have themselves previously taken ibogaine for a substance-related disorder is regarded as very useful (Lotsof and Alexander 2001). Patients find their presence reassuring, knowing that these individuals may uniquely understand what the patient is experiencing during the procedure. Dole and Nyswander, the developers of methadone maintenance therapy, incorporated methadone patients as “research assistants” for similar reasons in early methadone research (Nyswander 1967).

The standard of care varies greatly across the settings in which ibogaine is administered. In the medical model, the most intensive approaches can include a pretreatment Holter monitor to evaluate the presence of arrhythmias by recording continuous EKG (electrocardiogram) for 24 hours or longer, and 12-lead EKG. Additional evaluative procedures such as an echocardiogram are performed for patients with a question of a prior history of endocarditis, an infection that often affects the valves of the heart, and is relatively common in intravenous drug users. Monitoring and safety procedures during the treatment can include EKG and vital signs, and pulse oximetry monitoring (a method of measuring blood oxygenation). Other procedures utilized in the medical model may include the routine provision of intravenous access, the presence on-site of an emergency physician with ACLS (advanced cardiac life support) certification, and a registered nurse in the room with the patient continuously during the treatment.

Lay treatment providers must make decisions regarding medical exclusion criteria or pretreatment medical tests, or the level of availability of emergency medical support and when it should be accessed. The downloadable *Manual for Ibogaine Therapy* (Lotsof and Wachtel 2003) is informative regarding representative views among many lay providers. To a significant extent, it represents a literal consensus among the lay providers who function in nonreligious settings. The *Manual* recommends pretreatment evaluation that includes liver function tests, EKG, and some form of medical and psychiatric history, and to access medical consultation for questions related to medical conditions or psychiatric medications. Most treatment guides are aware of medical dangers but feel that risk can be minimized to some extent by measures such as excluding patients with histories of cardiac disease, assuring adequate hydration, and prospective consideration of the contingencies for accessing emergency medical intervention. The *Manual* advises, “if you are not prepared to call for emergency medical help you should not be providing ibogaine therapy.”

Set

Patients may regard the process of visualization and subsequent abreaction related to the use of ibogaine as a window of opportunity to access issues that might have been determinants of their drug use, and may be more open and able to make use of the psychotherapeutic process. Patients treated with ibogaine frequently regard the dreamlike visual experiences as providing psychological insight into issues associated with their drug use. This view is similar to that of individuals without substance use disorders who take ibogaine for psychological or spiritual reasons. A common view of treatment providers and patients is that the waking dreams and other subjective ibogaine effects are valuable in overcoming psychological blocks (Alper et al. 2001a; Stolaroff 2004). That being said, developers of *iboga* alkaloid congeners such as noribogaine and 18-MC believe these compounds might not be associated with visual experiences, an attribute that could prove valuable in gaining acceptance and support for development.

Some take the view that the visual experiences of ibogaine treatment are essential to its effectiveness. However, the effect of interrupting the motivational focus on drugs or alcohol is itself often viewed as a spiritual experience. In their own narrative, patients very commonly experience successful recovery from substance dependence as a spiritual transformation (Galanter 2006). The experimental pharmacologists tend to view the neurobiology as mediating spirituality, and patients may often perceive the direction of causality as the reverse. Both views associate an antiaddictive effect with a spiritual experience. The diminution of obsession in favor of true intention is both a cardinal spiritual value and a desired end point in pharmacological clinical trials of a medication for addiction.

There is great diversity among ibogaine providers and those who seek to be treated or initiated with the drug. Each provider group and provider brings a set of beliefs, expectations, attitudes, motivations, and skills to their intention to provide ibogaine. Providers may come from clinical medical practice or medical research, but at the present most have no medical background whatsoever. Some may view ibogaine within the context of a shamanic belief system, and others from a perspective of advocacy and addict self-help. An element of sectarian rivalry sometimes exists among some groups and individuals. Lay treatment providers may view those in the medical model as obtuse reductionists, while providers in the medical model may view lay treatment providers as irresponsible outlaws who are ignorant of the medical risks involved. The desire for control and power are ubiquitous human traits in settings ranging from academic medical research to the street.

FUTURE RESEARCH

Frank Vocci, Director of the NIDA Division of Pharmacotherapies and Medical Consequences of Drug Abuse, who directed NIDA's ibogaine project, has described the ibogaine subculture as a "vast uncontrolled experiment" (Vastag 2005). To a significant extent, this statement is literally true. The existing literature on *iboga* alkaloids indicates aspects of a drug development project in various stages of completion, including a significant body of preclinical proof of concept and case report evidence, some preclinical toxicological evaluation, and some initial phase I FDA clinical trial safety pharmacokinetic data.

An experimental evidence basis for structure–function relationships mediating therapeutic and toxic effects has existed for some time and has provided a basis for the development of evidently safer congeners such as 18-MC (Glick et al. 1994; Kuehne et al. 2003; Maisonneuve and Glick 2003). There is a need to develop techniques of practical synthesis and manufacturing of the *iboga* alkaloids for the purpose of clinical research and for further rational design utilizing known structure–function relationships mediating therapeutic and toxic effects in this richly varied chemical taxonomic category.

It appears that the actions of *iboga* alkaloids do not involve mechanisms that are presently used in the treatment of addiction, and it is therefore likely that an understanding of these actions may lead to insight into the nature of addiction and the possibilities for its treatment. More research is needed to identify the mechanism that mediates ibogaine's therapeutic effects. It would be desirable to attract more state-of-the-art laboratory investigators to address this very interesting problem. Methodological perspectives that may prove particularly worthwhile include gene transcription, constitutive receptor activity, and signal transduction.

Gene transcription refers to the alteration of the expression of gene products, for example, GDNF, which as mentioned above has produced interesting initial results (He et al. 2005). Constitutive activity is the phenomenon of receptors producing effects without binding neurotransmitters (Kenakin 2002). Constitutive activity might explain actions of *iboga* alkaloids that cannot be easily accounted for on the basis of their receptor-binding profiles. Likewise, exploration of the events of the signal cascade that proceeds from the binding of the drug to a receptor might help explain the evidence that ibogaine appears to enhance signal transduction through opioid receptors, independent of a direct agonist effect (Rabin and Winter 1996; Alper 2001). This action would oppose the tolerance associated with the opioid dependent state.

Some evidence indicates that *iboga* alkaloids may have antimicrobial, or possibly immunomodulatory properties. 18-MC shows *in vitro* activity against the human immunodeficiency type 1 virus (Silva et al. 2004) and the tropical parasite *Leishmania amazonensis* (Delorenzi et al. 2002). Ibogine is reportedly active against *Mycobacterium tuberculosis* (Rastogi et al. 1998) *in vitro* and *Candida albicans* (Yordanov et al. 2005) in an animal model. Other *iboga* alkaloids are reported to reverse multidrug resistance against a line of cultured human cancer cells of a type that often occurs in the esophagus or lung (Kam et al. 2004). The effects of *iboga* alkaloids on both immunity and neurobiology possibly suggest the existence of a mechanism at a very early stage of phylogenetic development that may have been common to both the evolving brain and the immune system. The study of the immunomodulatory effects of *iboga* alkaloids may provide a research paradigm for the study of an evolutionarily ancient communality of immune and neural functioning.

CONCLUSIONS

Acute opioid withdrawal is the indication for which ibogaine has most frequently been given (Alper et al. 1999; Alper et al. 2001a; Frenken 2001), which distinguishes the ibogaine subculture from subcultures involving other hallucinogenic drugs. It is a clinically robust phenomenon that can be appreciated by a lay clinical observer and produces a relatively clear outcome occurring within a limited time frame. The lay individuals involved in the ibogaine

subculture are very likely to be capable of making valid clinical observations regarding the absence or presence of the signs of acute opioid withdrawal. To apply the term “triangulation” as a validating principle in the clinical medical context, it is interesting that a similar effect of ibogaine in acute opiate withdrawal is evident in the animal model, the numerous and consistent accounts of subculture participants, and published case series. The ibogaine medical subculture reflects that drug users actively seek alternatives to present treatment options despite medical risk, expense, and possible legal prosecution.

The patient has primacy in the moral and ethical hierarchy of medicine, and it is fitting to end this chapter with a quote posted to an Internet message board from a patient reflecting on ibogaine treatment. The sense of marginalization, and affirmation of a belief in a real pharmacological effect, is familiar to anyone experienced with talking with ibogaine treatment providers or individuals who have been treated:

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

The existence and present expansion of the subculture, based on the word of mouth accounts of those treated, may itself also indicate the possibility of a real pharmacological effect that merits further investigation. Should that investigation prove productive in the understanding of the neurobiology of addiction or the development of innovative treatment, it would be a remarkable instance of a central dictum of clinical medicine, namely that “our patients are our greatest teachers.”

NOTE

1. To avoid possible confusion, it should be noted that there are two systems for numbering the carbon and nitrogen atoms of the monoterpene indole alkaloids (Alper and Cordell 2001). The reader may encounter either the Chemical Abstracts system, which is common in the medical literature in which ibogaine is referred to as 12-methoxyibogamine, or the Le Men and Taylor system, which is more commonly used among synthetic chemists in which ibogaine is referred to as 10-methoxyibogamine.

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