——Chapter 1——

IBOGAINE: A REVIEW

Kenneth R. Alper

Departments of Psychiatry and Neurology
New York University School of Medicine
New York, NY 10016

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I. Introduction and Historical Time Line

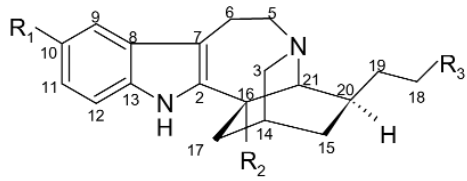
A. Introduction

Ibogaine, a naturally occurring plant alkaloid with a history of use as a medicinal and ceremonial agent in West Central Africa, has been alleged to be effective in the treatment of drug abuse. The National Institute on Drug Abuse (NIDA) has given significant support to animal research, and the U.S. Food and Drug Administration (FDA) has approved Phase I studies in humans. Evidence for ibogaine's effectiveness includes a substantial preclinical literature on reduced drug self-administration and withdrawal in animals, and case reports in humans. There is relatively little financial incentive for its development by the pharmaceutical industry because ibogaine is isolated from a botanical source in which it naturally occurs, and its chemical structure cannot be patented. This has left the academic community and the public sector with a crucial role in research on ibogaine, which was a major reason for organizing the First International Conference on Ibogaine.

A major focus of the Conference was the possible mechanism(s) of action of ibogaine. Ibogaine is of interest because it appears to have a novel mechanism of action distinct from other existing pharmacotherapeutic approaches to addiction, and it potentially could provide a paradigm for understanding the neurobiology of addiction and the development of new treatments. Another important focus of the Conference was to review human experience with ibogaine and preclinical and clinical evidence of efficacy and safety. The Conference also featured presentations related to the sociological and anthropological aspects of the sacramental context of the use of iboga in Africa and the distinctive ibogaine subculture of the United States and Europe.

B. Chemical Structure and Properties

Ibogaine (10-methoxyibogamine) (Figure 1) is an indole alkaloid with molecular formula $C_{20}H_{26}N_{20}$ and molecular weight 310.44. Ibogaine is the most abundant alkaloid in the root bark of the Apocynaceous shrub *Tabernanthe iboga*, which grows in West Central Africa. In the dried root bark, the part of the plant



Alkaloid	R_1	R_2	R_3
Ibogaine	OCH_3	H	H
Noribogaine	OH	H	H
(+)-18-Methoxycoronaridine	H	CO_2CH_3	OCH_3

FIGURE 1. CHEMICAL STRUCTURES OF IBOGAINE, NORIBOGAINE, AND 18-METHOXYCORONARIDINE. The ibogamine skeleton above is numbered using the LeMen and Taylor system in which ibogaine is designated as 10-methoxyibogamine and noribogaine as 10-hydroxyibogamine. Alternatively, according to the Chemical Abstracts numbering system for the ibogamine skeleton which is frequently encountered in the biological and medical literature, ibogaine and noribogaine have respectively been referred to as 12-methoxyibogamine and 12-hydroxyibogamine.

in which alkaloid content is highest, total alkaloid content is reportedly 5 to 6% (*1*).

Ibogaine has a melting point of 153°, a pK_a of 8.1 in 80% methylcellosolve, and it crystallizes as prismatic needles from ethanol. Ibogaine is levorotatory $[\alpha]_D$ –53° (in 95% ethanol), soluble in ethanol, ether, chloroform, acetone and benzene, but it is practically insoluble in water. Ibogaine is decomposed by the action of heat and light. Ibogaine hydrochloride decomposes at 299°, is also levorotatory $[\alpha]_D$ –63° (ethanol), $[\alpha]_D$ –49° (H_2O), and is soluble in water, methanol, and ethanol, slightly soluble in acetone and chloroform, and practically insoluble in ether (*2*). The X-ray crystal analysis that confirmed the structure of ibogaine has been described (*3*). The literature provides references to the mass spectrum of ibogaine (*4*), and the proton (*5,6*) and the ^{13}C (*7-9*) NMR spectra of ibogaine and other *iboga* alkaloids. Analytic chemical methods for extraction, derivatization, and detection of ibogaine utilizing combined gas chromatography-mass spectometry have been described (*10-13*).

Ibogaine undergoes demethylation to form its principal metabolite, noribogaine, also known as *O*-desmethylibogaine or 10-hydroxyibogamine. 18-methoxycoronaridine (18-MC, see Glick *et al*. in this volume) is an ibogaine congener that appears to have efficacy similar to ibogaine in animal models of drug dependence with evidence of less potential toxicity.

C. Historical Time Line

The following timeline outlines the historical events relating to the development of ibogaine as a treatment for drug dependence. Elsewhere in this volume, Alper *et al*. provide a more detailed contemporary history of ibogaine in the United States and Europe.

1864: The first description of *T. iboga* is published. A specimen is brought to France from Gabon. A published description of the ceremonial use of *T. iboga* in Gabon appears in 1885 (*14*).

1901: Ibogaine is isolated and crystallized from *T. iboga* root bark (*15-17*).

1901-1905: The first pharmacodynamic studies of ibogaine are performed. During this period ibogaine is recommended as a treatment for "asthenia" at a dosage range of 10 to 30 mg per day (*14*).

1939-1970: Ibogaine is sold in France as Lambarène, a "neuromuscular stimulant," in 8 mg tablets, recommended for indications that include fatigue, depression, and recovery from infectious disease (*14*).

1955: Harris Isbell administers doses of ibogaine of up to 300 mg to eight already detoxified morphine addicts at the U.S. Addiction Research Center in Lexington, Kentucky (*18*).

1957: The description of the definitive chemical structure of ibogaine is published. The total synthesis of ibogaine is reported in 1965 (*19-21*).

1962-1963: In the United States, Howard Lotsof administers ibogaine to 19 individuals at dosages of 6 to 19 mg/kg, including 7 with opioid dependence who note an apparent effect on acute withdrawal symptomatology (*22,23*).

1967-1970: The World Health Assembly classifies ibogaine with hallucinogens and stimulants as a "substance likely to cause dependency or endanger human health." The U.S. Food and Drug Administration (FDA) assigns ibogaine Schedule I classification. The International Olympic Committee bans ibogaine as a potential doping agent. Sales of Lambarène cease in France (*14*).

1969: Dr. Claudio Naranjo, a psychiatrist, receives a French patent for the psychotherapeutic use of ibogaine at a dosage of 4 to 5 mg/kg (*24*).

1985: Howard Lotsof receives a U.S. patent for the use of ibogaine in opioid

withdrawal (*22*). Additional patents follow for indications of dependence on cocaine and other stimulants (*23*), alcohol (*25*), nicotine (*26*), and polysubstance abuse (*27*).

1988-1994: U.S. and Dutch researchers publish initial findings suggestive of the efficacy of ibogaine in animal models of addiction, including diminished opioid self-administration and withdrawal (*28-30*), as well as diminished cocaine self-administration (*31*).

1989-1993: Treatments are conducted outside of conventional medical settings in the Netherlands involving the International Coalition of Addict Self-Help (ICASH), Dutch Addict Self Help (DASH), and NDA International (*22,32-35*).

1991: Based on case reports and preclinical evidence suggesting possible efficacy, NIDA Medication Development Division (MDD) begins its ibogaine project. The major objectives of the ibogaine project are preclinical toxicological evaluation and development of a human protocol.

August 1993: FDA Advisory Panel meeting, chaired by Medical Review Officer Curtis Wright, is held to formally consider Investigational New Drug Application filed by Dr. Deborah Mash, Professor of Neurology at the University of Miami School of Medicine. Approval is given for human trials. The approved ibogaine dosage levels are 1, 2, and 5 mg/kg. The Phase I dose escalation study begins December 1993, but activity is eventually suspended (*36*).

October 1993-December 1994: The National Institute on Drug Abuse (NIDA) holds a total of four Phase I/II protocol development meetings, which include outside consultants. The resulting draft protocol calls for the single administration of fixed dosages of ibogaine of 150 and 300 mg versus placebo for the indication of cocaine dependence (*37*).

March 1995: The NIDA Ibogaine Review Meeting is held in Rockville, Maryland, chaired by the MDD Deputy Director, Dr. Frank Vocci. The possibility of NIDA funding a human trial of the efficacy of ibogaine is considered. Opinions of representatives of the pharmaceutical industry are mostly critical, and are a significant influence in the decision not to fund the trial. NIDA ends its ibogaine project, but it does continue to support some preclinical research on *iboga* alkaloids.

Mid 1990s-2001: Ibogaine becomes increasingly available in alternative settings, in view of the lack of approval in the Europe and the United States. Treatments in settings based on a conventional medical model are conducted in

Panama in 1994 and 1995 and in St. Kitts from 1996 to the present. Informal scenes begin in the United States, Slovenia, Britain, the Netherlands, and the Czech Republic. The Ibogaine Mailing List (*38*) begins in 1997 and heralds an increasing utilization of the Internet within the ibogaine medical subculture.

II. Mechanisms of Action

A. Neurotransmitter Activities

1. General Comments

Elsewhere in this volume, Glick *et al*., Sershen *et al*., and Skolnick review the mechanism of action of ibogaine. Popik and Skolnick (*39*) provide a recent, detailed review of ibogaine's receptor activities. Ibogaine appears to have a novel mechanism of action that differs from other existing pharmacotherapies of addiction, and its mechanism of action does not appear to be readily explained on the basis of existing pharmacologic approaches to addiction. Ibogaine's effects may result from complex interactions between multiple neurotransmitter systems rather than predominant activity within a single neurotransmitter system (*39-42*).

Several laboratories have reported on the results of pharmacological screens of the receptor binding profile of ibogaine (*40,43-45*). Ibogaine has low micromolar affinities for multiple binding sites within the central nervous system, including *N*-methyl-D-aspartate (NMDA), kappa- and mu-opioid and sigma$_2$ receptors, sodium channels, and the serotonin transporter. Although not apparent in binding studies, functional studies indicate significant activity of ibogaine as a noncompetitive antagonist at the nicotinic acetylcholine receptor (*46-50*).

Although *in vitro* activities in the micromolar range are often described as ancillary in attempting to characterize a drug's *in vivo* mechanism of action, micromolar activity may be pharmacologically important with regard to ibogaine or noribogaine due to the relatively high concentrations reached in the brain (*40,44,51*). Hough *et al*. (*51*) noted a brain level of ibogaine of 10 µM in female rats at 1 hour after the administration of 40 mg/kg ibogaine i.p., which is the usual dosage, animal, gender and route of administration used in that laboratory to investigate ibogaine's effects on drug self-administration and withdrawal. Brain levels of ibogaine, and its major metabolite noribogaine, ranged from 1 to 17 µM between 15 minutes and 2 hours in male rats following the oral administration ibogaine at a dose of 50 mg/kg (*44*).

2. Glutamate

Elsewhere in this volume, Skolnick reviews the possible relevance of

ibogaine's activity as a glutamate antagonist to its putative effects in drug dependence. There is evidence that suggests that antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor are a potentially promising class of agents for the development of medications for addiction (*52-54*). Ibogaine's apparent activity as a noncompetitive NMDA antagonist has been suggested to be a possible mechanism mediating its putative effects on drug dependence (*39,41,55-58*).

Ibogaine competitively inhibits the binding of the NMDA antagonist MK801 to the NMDA receptor complex, with reported affinities in the range of 0.02 to 9.8 µM (*40,45,55-57,59,60*). Functional evidence supporting an antagonist action of ibogaine at the NMDA receptor includes observations of reduced glutamate-induced cell death in neuronal cultures, reduction of NMDA-activated currents in hippocampal cultures (*55,58*), prevention of NMDA-mediated depolarization in frog motoneurons (*59*), and protection against NMDA-induced convulsions (*61*). Glycine, which acts as an NMDA co-agonist by binding at the NMDA receptor, attenuates ibogaine's effect of blocking naloxone-precipitated jumping (*58*). MK801 and ibogaine do not produce identical effects, as evidenced by the observation that in the rat brain ibogaine lowered the concentration of dopamine while increasing the level of its metabolites, whereas MK801 did not have these effects (*62,63*).

3. Opioids

It has been suggested that ibogaine's or noribogaine's activity as a putative agonist at mu-opioid receptors might explain ibogaine's apparent efficacy in opioid withdrawal (*36,64,65*). Ibogaine binds to mu-opioid receptors with reported binding affinities in the range of 0.13 to 26 µM (*40,45,64,66*), with one study reporting a result in excess of 100 µM (*43*). Ibogaine behaves as an agonist in a functional assay for mu-opioid receptors, the binding of [35^S]-GTPγS (*65*). However, some observations are difficult to reconcile with a mu-agonist action of ibogaine. Ibogaine did not behave as a mu-opioid agonist in assays with isolated smooth muscle preparations (*67*). Unlike mu-opioid agonists, ibogaine (*68-70*) and noribogaine (*71*) do not appear by themselves to have antinociceptive effects.

Some findings suggest the intriguing possibility that ibogaine may act at the level of second messenger signal transduction to enhance the functional activity of mu-opioid receptors independently of any direct agonist interaction at opioid receptors. Both ibogaine and noribogaine reportedly potentiated morphine-induced inhibition of adenylate cyclase *in vitro* with opioid receptors already occupied by the maximally effective concentration of morphine, but did not affect adenylate cyclase in the absence of morphine (*72*). A similar interpretation might also explain the finding that ibogaine inhibited the development of tolerance to the antinociceptive effect of morphine in mice, without by itself affecting nociception (*73*).

Ibogaine binds to kappa-opioid receptors with reported binding affinities in the range of 2.2 to 30 μM (*43,45,56,66*). Evidence consistent with a kappa-opioid action of ibogaine includes the observation that the kappa-opioid antagonist, norbinaltorphimine antagonized some of the effects of ibogaine in morphine-treated rats (*74,75*). Kappa-opioid agonists reportedly can imitate certain effects of ibogaine, such as reduced cocaine and morphine self-administration (*76*), and reduction in locomotor activation to morphine accentuated by prior morphine exposure (*77*). Sershen, on the other hand, attributes a kappa-opioid antagonist action to ibogaine, based on the observation that stimulated dopamine efflux from mouse brain slices was decreased by a kappa opioid agonist, and the decrease was offset by the addition of ibogaine (*78*). However, ibogaine's interactions with multiple neurotransmitter systems raises the possibility that the finding could be accounted for by mechanisms that do not involve the kappa-opioid receptor, as dopamine efflux is modulated by multiple neurotransmitters.

4. Serotonin

Ibogaine and serotonin both contain an indole ring in their structure, and ibogaine has been shown to bind to the serotonin transporter and to increase serotonin levels in the nucleus accumbens (NAc) (*41,79,80*). The demonstration that ibogaine blocks serotonin uptake (*81*) suggests that the effect of ibogaine on extracellular serotonin levels may be mediated by uptake inhibition, in addition to release (*80*). The reported affinity of ibogaine for the serotonin transporter ranges from 0.55 to 10 μM (*39,44,45,79,81*), and the affinity of noribogaine for the serotonin transporter is approximately 10-fold stronger (*45,79*). The magnitude of the effect of ibogaine on serotonin release is reportedly large and is comparable to that of the serotonin releasing agent fenfluramine, with noribogaine having a lesser effect, and 18-MC no effect (*80*). Some authors suggest a role for modulatory influence of serotonin in ibogaine's effects on dampening dopamine efflux in the NAc (*41,80*).

Ibogaine's hallucinogenic effect has been suggested to involve altered serotonergic neurotransmission (*42,80*). Ibogaine is reported in some studies to bind the 5-HT_{2A} receptor, which is thought to mediate the effects of "classical" indolealkylamine and phenethylamine hallucinogens (*82*), with three studies reporting affinities in the range of 4.1 to 12 μM (*40,45,83*), one reporting a value of 92.5 μM (*84*), and with two other studies reporting no significant affinity (*43,44*). Drug discrimination studies provide some functional evidence for the action of ibogaine as an agonist at the 5-HT_{2A} receptor, which is apparently a significant, although nonessential, determinant of the ibogaine stimulus (*84*) (see Section II.B, "Discrimination Studies"). Ibogaine binds to the 5-HT_3 receptor with reported affinities of 2.6 and 3.9 μM (*40,45*), and it was without significant affinity in two other studies (*43,83*). The 5-HT_3 receptor is apparently not involved in the ibogaine discriminative stimulus (*85*).

5. *Dopamine*

Ibogaine does not appear to significantly affect radioligand binding to D_1, D_2, D_3, or D_4 receptors (*40,43,44*) and is a competitive blocker of dopamine uptake at the dopamine transporter with affinities in the range of 1.5 to 20 μM (*81*). Where affinities for the serotonin and dopamine transporter have been estimated within the same study, the reported affinity of ibogaine for the serotonin transporter has generally been 10 to 50 times stronger than its affinity for the dopamine transporter (*44,79,81*). Ibogaine does not apparently affect norepinephrine reuptake (*44,45*).

French *et al.* (*86*) studied the electrophysiological activity of dopamine neurons in the ventral tegmental area (VTA) of rats given up to 7.5 mg/kg ibogaine intravenously and found a significant increase in firing rate. Ibogaine given intraperitoneally (i.p.) at a dose of 40 mg/kg did not affect the spontaneous firing of VTA dopamine neurons or the response of VTA dopamine neurons to cocaine or morphine. Ibogaine reportedly lowers the concentration of dopamine, while increasing the level of its metabolites, indicating diminished release of dopamine in the brain of the rat (*62,63*) and the mouse (*87*). Decreased release of dopamine could possibly explain the observation of increased prolactin release following ibogaine administration (*62,63,88*). Staley *et al.* (*44*) have suggested that ibogaine might act at the dopamine transporter to inhibit the translocation of dopamine into synaptic vesicles, thereby redistributing dopamine from vesicular to cytoplasmic pools. As a result, the metabolism of dopamine by monoamine oxidase could explain the observation of decreased tissue dopamine content with increased levels of its metabolites.

The effects of ibogaine on dopamine efflux in response to the administration of drugs of abuse are described in Section III.E, "Dopamine Efflux".

6. *Acetylcholine*

Ibogaine is a nonselective and weak inhibitor of binding to muscarinic receptor subtypes. Reported affinities are 7.6 and 16 μM and 5.9 and 31 μM, respectively, for the M_1 and M_2 muscarinic receptor subtypes (*40,45*), with another study reporting no significant affinity of ibogaine for muscarinic receptors (*43*). Functional evidence consistent with a muscarinic cholinergic agonist effect of ibogaine includes the observations of the elimination of ibogaine-induced EEG dyssynchrony by atropine in cats (*89*), decreased heart rate following ibogaine administration in rats (*90*), and the attribution of the effect of cholinesterase inhibition to ibogaine in the older literature (*1,91*). The affinity of noribogaine for muscarinic receptors is apparently similar to that of ibogaine (*44,45*).

Several laboratories have reported that ibogaine produces noncompetitive functional inhibition of the nicotinic acetylcholine receptor, apparently involving open channel blockade (*46,48-50*). As with a number of other channel blockers, binding studies involving channels associated with nicotinic receptors have been

limited by the lack of appropriate ligands, and investigations of the affinity of ibogaine for the nicotinic acetylcholine receptor have mainly involved functional assays. Utilizing $^{86}Rb^{+}$ efflux assays, Fryer and Lukas (*50*) found that ibogaine inhibited human ganglionic and muscle-type nicotinic acetylcholine receptors with IC_{50} values of 1.06 and 22.3 μM, respectively. Badio *et al.* (*48*) found that ibogaine inhibited $^{22}Na^{+}$ influx through rat ganglionic and human muscle-type nicotinic acetylcholine receptors with IC_{50} values of 0.020 μM and 2.0 μM, respectively. Noribogaine was 75-fold less active than ibogaine in the rat ganglionic cell assay. In mice, ibogaine at a dose of 10 mg/kg completely blocked the central antinociceptive nicotinic receptor-mediated response to epibatidine. Ibogaine has been associated with decreased acetylcholine-stimulated nicotinic receptor mediated catecholamine release in cultured cells (*49*) and decreased dopamine release evoked by nicotine in the NAc of the rat (*46,92*).

7. Sigma Receptors

Elsewhere in this volume, Bowen discusses ibogaine's action at the sigma receptor. The affinity of ibogaine for the $sigma_2$ receptor is strong relative to other known CNS receptors, and the reported range is 0.09 to 1.8 μM (*45,60,93,94*). The affinity of ibogaine for the $sigma_1$ receptor is reportedly on the order of 2 to 100 times weaker than its affinity for the $sigma_2$ receptor (*45,60,93,94*). The neurotoxic effects of ibogaine may involve activity at the $sigma_2$ receptor, which reportedly potentiates the neuronal response to NMDA (*95*).

8. Sodium Channels

The reported affinity of ibogaine for sodium channels ranges from 3.6 to 9 μM (*40,43*). There is apparently no experimental evidence regarding the functional significance of ibogaine's action at sodium channels.

B. Discrimination Studies

Elsewhere in this volume, Helsley *et al.* discuss the topic of ibogaine and drug discrimination. Drug discrimination studies offer a possible approach to the issue of ibogaine's mechanism of action and may help resolve the distinction between ibogaine's therapeutic and hallucinogenic effects. The 5-HT_{2A} receptor appears to be a significant, but nonessential, determinant of the ibogaine stimulus (*84,96*). The ibogaine stimulus is reportedly generalized to the indolealkylamine hallucinogen D-lysergic acid diethylamide (LSD) and the phenethylamine hallucinogen 2,5-dimethoxy-4-ethylamphetamine (DOM), and this generalization is abolished by the addition of a 5-HT_{2A} receptor antagonist (*96*). The addition of a 5-HT_{2A} receptor antagonist did not attenuate stimulus control of ibogaine itself in the ibogaine-trained animals, indicating that the 5-HT_{2A} is not essential to the ibogaine discriminative stimulus. The 5-HT_{2C} receptor, which

plays a modulatory role in hallucinogenesis, is also involved, but is not essential to the ibogaine stimulus, and the 5-HT_{1A} and 5-HT_3 receptors are apparently not involved in the ibogaine stimulus (*85*). The ibogaine discriminative stimulus reportedly is potentiated by the serotonin reuptake inhibitor fluoxetine (*85*), and has an insignificant degree of generalization to the serotonin releaser D-fenfluramine (*97*).

Ibogaine showed a lack of substitution for phencyclidine (*98,99*), and substituted for MK 801 only at high (100 mg/kg) doses in mice (*58,61*), but not at lower (10 mg/kg) doses in rats (*99,100*), suggesting that the NMDA receptor is not a significant determinant of the ibogaine stimulus. $Sigma_2$, and mu- and kappa-opioid activity may be involved in the ibogaine discriminative stimulus (*99*). A high degree of stimulus generalization is reported between ibogaine and some of the Harmala alkaloids, a group of hallucinogenic beta-carbolines that are structurally related to ibogaine (*101,102*). While the discriminative stimulus for both the Harmala alkaloids and ibogaine apparently involves the 5-HT_2 receptor (*84,85,103*), it does not appear essential to generalization between ibogaine and harmaline, as generalization to the harmaline stimulus was unaffected by the addition of a 5-HT_2 antagonist in ibogaine-trained animals (*84*). Ibogaine-trained rats generalize to noribogaine (*100,104*), which in one study was more potent than ibogaine itself in eliciting ibogaine-appropriate responses (*100*).

C. Effects on Neuropeptides

Both ibogaine and cocaine given in multiple administrations over 4 days to rats reportedly increase neurotensin-like immunoreactivity (NTLI) in the striatum, substantia nigra, and NAc (*105*). However, unlike cocaine, which increased NTLI in the frontal cortex, ibogaine had no effect on frontal cortical NTLI. Ibogaine pretreatment prevented the increase of NTLI in striatum and substantia nigra induced by a single dose of cocaine. Substance P, like NTLI, was increased in the striatum and substantia nigra after either cocaine or ibogaine, with an increase in frontal cortex with cocaine and no effect with ibogaine (*106*). Ibogaine–induced increases in NTLI or substance P were blocked by administration of a D_1 antagonist.

Unlike the NTLI or substance P responses, ibogaine alone had no effect on dynorphin. However, ibogaine pretreatment dramatically enhanced cocaine-induced increases in dynorphin, a kappa-opioid agonist (*107*). The authors suggested that the increase in dynorphin related to cocaine's interaction with ibogaine could result in enhanced kappa-opioid activity. Kappa-opioid agonists reportedly decrease cocaine intake in animal models (*108,109*).

D. Possible Effects on Neuroadaptations Related to Drug Sensitization or Tolerance

There is some evidence to suggest that ibogaine treatment might result in the "resetting" or "normalization" of neuroadaptations related to drug sensitization or tolerance (*110*). Ibogaine pretreatment blocked the expression of sensitization-induced increases in the release of dopamine in the NAc shell in response to cocaine in cocaine-sensitized rats (*111*). The effect of ibogaine on diminished locomotor activity and dopamine efflux in the NAc in response to morphine is more evident in animals with prior exposure to morphine (*112,113*), which is consistent with a relatively selective effect of ibogaine on neuroadaptations acquired from drug exposure. Similarly, the observation that ibogaine inhibited the development of tolerance in morphine-tolerant mice, but had no effect on morphine nociception in morphine-naïve mice (*114*), suggests a selective effect on acquired neuroadaptations related to repeated morphine exposure.

Ibogaine appears to have persistent effects not accounted for by a metabolite with a long biological half-life (*29,115*). Ibogaine's action could possibly involve the opposition or reversal of persistent neuroadaptive changes thought to be associated with drug tolerance or sensitization. Such an action could be related to persistent effects on second messengers (*72,116*). For example, sensitization to both opiates and cocaine is thought to involve enhanced stimulation of cyclic AMP (*117*). Ibogaine has been reported to potentiate the inhibition of adenylyl cyclase by serotonin (*72*), an effect that would be expected to oppose the enhanced transduction of cyclic AMP that is reportedly associated with stimulant sensitization (*117*).

III. Evidence of Efficacy in Animal Models

A. Drug Self-Administration

Evidence for ibogaine's effectiveness in animal models of addiction includes observations of reductions in self-administration of morphine or heroin (*29,31,118-120*), cocaine (*29,31,119,121*), and alcohol (*122*), and reduced nicotine preference (*75*). According to some reports, effects of ibogaine on drug self-administration are apparently persistent. Sershen *et al.* (*121*) administered ibogaine i.p. to mice as two 40 mg/kg dosages 6 hours apart, and found a diminution of cocaine preference that was still evident after 5 days. Glick *et al.* (*29,119*) noted reductions in cocaine and morphine self-administration that persisted for at least 2 days and were dose dependent in the range of 2.5 to 80 mg/kg. ibogaine given i.p. The persistence of an effect beyond the first day

suggests a specific action of ibogaine on drug intake, as water intake was also suppressed initially by ibogaine on the first, but not the second day. Cappendijk and Dzoljic (*31*) found reductions in cocaine self-administration that persisted for more than 48 hours in rats treated with ibogaine at a dose of 40 mg/kg i.p., given as a single administration, or repeatedly on 3 consecutive days or three consecutive weeks.

In the studies by Glick *et al*. there was variation between results in individual rats with some showing persistent decreases in morphine or cocaine intake for several days or weeks after a single injection and others only after two or three weekly injections. The authors noted evidence of a continuous range of individual sensitivity to ibogaine among the experimental animals and that it appeared as if adjustments of the dosage regimen could produce long-term reductions in drug intake in most animals (*29*). Similarly, Cappendijk and Dzoljic (*31*) found the largest effects on cocaine self-administration occurred when ibogaine was given weekly for three consecutive weeks. This result suggests the possibility that the optimal schedule of ibogaine administration to limit cocaine intake may involve modification of the single dose regimen which has been used for opioid detoxification (*32,123*).

Dworkin *et al*. (*118*) found that pretreatment with ibogaine at a dose of 80 mg/kg i.p. diminished the response for heroin and cocaine, and also for food, suggesting a nonspecific confound. A 40 mg/kg intraperitoneal dose of ibogaine sharply reduced heroin self-administration in the absence of a significant effect on food response, although the effect did not persist beyond 24 hours (*118*). Dworkin *et al*. cited methodologic factors relating to differences in gender, strain, and reinforcement schedule to explain the apparent discrepancy between their results and other studies that reported persistent effects (*29,31,119,121*).

Noribogaine has also been reported to reduce cocaine and morphine self-administration (*124*). The effect of noribogaine on drug self-administration persisted for 2 days, after the response for water, which was initially suppressed on the first day, had returned to baseline. Other *iboga* alkaloids have also been reported to reduce morphine and cocaine self-administration in rats for a period of a day or longer following a single i.p dose (*119*). Some of the *iboga* alkaloids tested in this study produced tremors, which typically occurred for a period of 2 to 3 hours, and were independent of persistent effects of drug self-administration. An ibogaine congener, 18-methoxycoronaridine (18-MC) (*45*), reportedly reduces in rats the self-administration of cocaine (*120*), morphine and alcohol (*125*), and nicotine preference (*75*) without any apparent reduction in the response for water.

B. Acute Opioid Withdrawal

Dzoljic *et al*. (*28*) administered ibogaine in a dose range of 4 to 16 µg intra-

cerebroventricularly to rats and observed a dose-dependent attenuation of naloxone-precipitated withdrawal signs. This same group also found an attenuation of morphine withdrawal signs in rats with 40 mg/kg ibogaine administered i.p., and also norharman, an endogenously occurring hallucinogenic beta-carboline and a structural relative of ibogaine (*126*). Glick *et al*. have reported dose-dependent reduction of the signs of naltrexone-precipitated morphine withdrawal in rats administered ibogaine at doses of 20, 40, or 80 mg/kg i.p (*127*) or 18-MC (*128*) at doses of 20 and 40 mg/kg i.p. Attenuation of withdrawal signs was reported in morphine-dependent monkeys given 2 or 8 mg/kg ibogaine subcutaneously (*129*). In their chapter in this volume, Parker and Siegel report that 40 mg/kg ibogaine administered i.p attenuated naloxone-precipitated morphine withdrawal in rats, as well as withdrawal-induced place aversion.

Sharpe and Jaffe (*130*) reported that ibogaine in dosages ranging between 5 and 40 mg/kg administered subcutaneously failed to attenuate naloxone-precipitated withdrawal in rats, although they did find that one sign (grooming) was reduced, and noted the possible effect of methodological issues such as morphine exposure and withdrawal procedures, or the route of administration of ibogaine. Popik *et al*. (*58*) and Layer *et al*. (*56*) found that ibogaine at doses ranging from 40 to 80 mg/kg i.p. reduced naloxone-precipitated jumping in morphine dependent mice, although Francés *et al*. (*69*) found the opposite effect of 30 mg/kg ibogaine administered i.p. in mice. As pointed out by Popik and Skolnik (*39*), the divergent results in morphine dependent mice might relate to ibogaine having been given prior to the administration of naloxone in the studies by Popik *et al*. (*58*) and Layer *et al*. (*56*), whereas ibogaine was administered after naloxone in the study by Francés *et al*.

C. Conditioned Place Preference

Parker and Siegel review ibogaine and place preference in this volume. Ibogaine is reported to prevent the acquisition of place preference when given 24 hours before amphetamine (*131*) or morphine (*132*). The effect of ibogaine on blocking the acquisition of place preference was diminished across multiple conditioning trials. Ibogaine given after morphine did not apparently attenuate the expression of previously established morphine place preference (*133*).

D. Locomotor Activity

Pretreatment with ibogaine and its principal metabolite, noribogaine reportedly diminishes locomotor activation in response to morphine (*74,112,113,124,134-136*). The effect of ibogaine in reducing locomotor activity in response to morphine is reportedly greater in female than in male rats, probably reflecting the

relatively greater bioavailability of ibogaine in females (*135*). The literature on cocaine appears to be less consistent, with some reports of decreased locomotor activation (*87,137-139*), and others reporting increases (*127,137,140,141*). This apparent disparity may be related in part to the species of experimental animal that was used, as Sershen *et al*. (*137*) report increased locomotor activity in response to cocaine in the rat, with the opposite result in the mouse.

Stereotypy is a methodologic issue that might explain some of the disparate results regarding ibogaine's interaction with the locomotor response to cocaine. Higher doses of stimulants can produce strereotypy, which could decrease the amount of measured locomotion relative to an animal that is experiencing less locomotor stimulation at a lower stimulant dose. Thus, the potentiation by ibogaine of locomotor activity related to cocaine administration can result in less measured movement in animals experiencing locomotor stimulation to the point of stereotypy (*110*). Ibogaine pretreatment reportedly potentiates stereotypy in rats receiving cocaine or methamphetamine (*111,142*).

E. Dopamine Efflux

Reductions in dopamine efflux in the NAc in response to morphine have been reported in animals pretreated with ibogaine (*113,115,134*), noribogaine (*124*), or 18-MC (*120,143*). Similarly, reductions in dopamine efflux in the NAc in response to nicotine have been reported in animals pretreated with ibogaine (*46,92*) and 18-MC (*42*).

As with locomotor stimulation, methodological issues may have played a part in apparently divergent results regarding ibogaine's effect on dopamine efflux in the NAc in response to cocaine or amphetamine, which is reportedly increased as measured by microdialysis (*134*), although the opposite result was observed in a study on cocaine using microvoltammetry (*139*). Dosage is an additional consideration that might influence ibogaine's effect on dopamine efflux in the NAc in response to cocaine, with a larger ibogaine dose reportedly producing an increase and a smaller dose producing a decrease (*144*).

Dopamine efflux in response to cocaine may also depend on whether dopamine measurements are made in the NAc core versus shell. Szumlinski *et al*. (*111*) found that ibogaine pretreatment (given 19 hours earlier) abolished the sensitized dopamine efflux in response to cocaine in the NAc shell in rats that had been sensitized by repeated prior exposure to cocaine. The same ibogaine pretreatment had no apparent effect on dopamine efflux in the NAc shell in response to "acute" (administered without prior cocaine exposure) cocaine. The authors noted a prior study in their laboratory that found a potentiation by ibogaine pretreatment of dopamine efflux in response to acute cocaine in which the position of the recording probe spanned both the core and shell regions of the NAc (*134*). These results indicate the possibility of a differential effect of ibogaine on dopamine

efflux in response to cocaine between the NAc shell, which is thought to play a relatively greater role in the motivational aspects of drugs of abuse, and the NAc core, which, in turn, is thought to play a relatively greater role in motor behavior (*145*). The authors suggested that the effect of ibogaine on reduced cocaine self-administration may be mediated by the observed reduction in dopamine efflux in response to cocaine in the NAc shell in cocaine-sensitized animals (*111*). On the other hand, the enhancement by ibogaine preatreatment of locomotor activity seen in response to acute or chronic cocaine administration may be mediated by increased dopamine efflux in the NAc core. The observed increase in dopamine efflux with ibogaine pretreatment in the NAc core in response to acute cocaine (*134*) is consistent with such a formulation, although this group has yet to report on the effect in cocaine-sensitized animals.

Ibogaine and 18-MC reportedly decrease dopamine release evoked by nicotine in the NAc of the rat (*46,92*). In the study by Benwell *et al.* (*46*), the decreased NAc dopamine release following ibogaine was independent of any change in locomotor activity, which was viewed as notable given the usual association between NAc dopamine efflux and locomotor activity in response to nicotine. The authors cited previous work in which a similar dissociation between NAc dopamine efflux and locomotor activity in response to nicotine was produced by treatment with NMDA antagonists, and they suggested that their findings might be related to ibogaine's NMDA antagonist activity.

IV. Evidence of Efficacy and Subjective Effects in Humans

A. Evidence Of Efficacy

1. Acute Opioid Withdrawal

One line of clinical evidence suggesting ibogaine's possible efficacy are the accounts of the addicts themselves, whose demand has led to the existence of an "informal" treatment network in Europe and the United States. Opioid dependence is the most common indication for which addicts have sought ibogaine treatment, which has been typically administered as a single dose. Common reported features of case reports describing ibogaine treatment (*35,36,146-149*) are reductions in drug craving and opiate withdrawal signs and symptoms within 1 to 2 hours, and sustained, complete resolution of the opioid withdrawal syndrome after the ingestion of ibogaine. These case studies appear consistent with general descriptions of ibogaine treatment (*33,34,150*).

Alper *et al.* (*32*) summarized 33 cases treated for the indication of opioid detoxification in nonmedical settings under open label conditions. These cases

are a subset of those presented at the NIDA Ibogaine Review Meeting held in March, 1995 (*151*). A focus on acute opioid withdrawal may offset some of the methodological limitations of the informal treatment context because the acute opioid withdrawal syndrome is a clinically robust phenomenon that occurs within a relatively limited time frame and yields reasonably clear outcome measures. Despite the unconventional setting and the lack of structured clinical rating instruments, the lay "treatment guides" who reported on the case series might reasonably be expected to be able to assess the presence or absence of the relatively clinically obvious and unambiguous features of opioid withdrawal.

The subjects in this series of cases reported an average daily use of heroin of 0.64 ± 0.50 g, primarily by the intravenous route, and received an average dose of ibogaine of 19.3 ± 6.9 mg/kg (range of 6 to 29 mg/kg). Resolution of the signs of opioid withdrawal without further drug seeking behavior was observed in 25 patients. Other outcomes included drug seeking behavior without withdrawal signs (four patients), drug abstinence with attenuated withdrawal signs (two patients), drug seeking behavior with continued withdrawal signs (one patient), and one fatality, possibly involving surreptitious heroin use (see Section VI, "Safety"). The reported effectiveness of ibogaine in this series suggests the need for a systematic investigation in a conventional clinical research setting.

In their chapter in this volume, Mash *et al*. report having treated more than 150 subjects for substance dependence in a clinic located in St. Kitts, West Indies. A subset of 32 of these subjects was treated with a fixed dose of ibogaine of 800 mg 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 hours following ibogaine administration and 24 hours after the last use of opiates, and at 24 hours following ibogaine administration 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 (*123*). The authors noted that ibogaine appeared to be equally efficacious in achieving detoxification from either methadone or heroin. The reported efficacy of ibogaine for the opioid withdrawal syndrome observed in the St. Kitts facility appears to confirm the earlier impressions of the case study literature (*32-36,146-150*).

2. Long-Term Outcomes

There is very little data regarding the long-term outcomes in patients treated with ibogaine. Lotsof (*151*) presented a summary of 41 individuals treated between 1962 and 1993 at the NIDA Ibogaine Review Meeting held in March 1995. The data consisted of self-reports obtained retrospectively, which are essentially anecdotal, but apparently represent the only formal presentation of a

systematic attempt to determine long-term outcomes in patients treated with ibogaine. Thirty-eight of the 41 individuals presented in the summary reported some opioid use, with approximately 10 of these apparently additionally dependent on other drugs, mainly cocaine, alcohol, or sedative-hypnotics. The use of tobacco or cannabis was not apparently assessed. Across the sample of 41 individuals, nine individuals were treated twice and one was treated three times for a total of 52 treatments. The interval of time following treatment was recorded for which patients reported cessation of use of the drug or drugs on which they were dependent. Fifteen (29%) of the treatments were reportedly followed by cessation drug use for less than 2 months, 15 (29%) for at least 2 months and less than 6 months, 7 (13%) for at least 6 months and less than one year, 10 (19%) for a period of greater than one year, and in 5 (10%) outcomes could not be determined.

B. Subjective Effects

There appear to be common elements to experiences generally described by patients treated with ibogaine. The "stages" of the subjective ibogaine experience presented below are a composite derived by the author from interviews with patients and treatment guides, and general descriptions and case studies provided by the literature (*33-35,146,150*). Ibogaine has been typically given in a non-hospital setting as a single dose in the morning. Vomiting is reportedly common and usually occurred relatively suddenly as a single episode in the first several hours of treatment. Patients generally lie still in a quiet darkened room throughout their treatment, a practice that is possibly related to the cerebellar effects of ibogaine, and because vomiting tends to be more frequent with movement. Patients later in treatment often experience muscle soreness, possibly due to reduced motor activity earlier in treatment, that resolves with motion, stretching, or massage.

1. Acute

The onset of this phase is within 1 to 3 hours of ingestion, with a duration on the order of 4 to 8 hours. The predominant reported experiences appear to involve a panoramic readout of long-term memory (*152*), particularly in the visual modality, and "visions" or "waking dream" states featuring archetypal experiences such as contact with transcendent beings, passage along a lengthy path, or floating. Descriptions of this state appear more consistent with the experience of dreams than of hallucinations. Informants appear to emphasize the experience of being placed in, entering, and exiting entire visual landscapes, rather than the intrusion of visual or auditory hallucinations on an otherwise continuous waking experience of reality. Ibogaine-related visual experiences are reported to be strongly associated with eye closure and suppressed by eye

opening. The term "oneiric" (Greek, *oneiros*, dream) has been preferred to the term "hallucinogenic" in describing the subjective experience of the acute state. Not all subjects experience visual phenomena from ibogaine, which may be related to dose, bioavailability, and interindividual variation.

2. Evaluative

The onset of this phase is approximately 4 to 8 hours after ingestion, with a duration on the order of 8 to 20 hours. The volume of material recalled slows. The emotional tone of this phase is generally described as neutral and reflective. Attention is still focused on inner subjective experience rather than the external environment, and it is directed at evaluating the experiences of the acute phase. Patients in this and the acute phase above are apparently easily distracted and annoyed by ambient environmental stimuli and prefer as little environmental sensory stimulation as possible in order to maintain an attentional focus on inner experience.

3. Residual Stimulation

The onset of this phase is approximately 12 to 24 hours after ingestion, with a duration in the range of 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. It is not clear to what extent such reports might reflect a persistent effect of ibogaine on sleep or a dyssomnia due to another cause.

V. Pharmacokinetics

A. Absorption

Jeffcoat *et al.* (*153*) administered single oral doses of ibogaine of 5 mg/kg and 50 mg/kg to rats, and estimated oral bioavailabilities of 16 and 71% at the two dosages, respectively, in females, and 7 and 43% in males. The dose-dependent bioavailability was interpreted as suggesting that ibogaine absorption, and/or first pass elimination, is nonlinear, and the greater bioavailability in females was viewed as consistent with gender-related differences in absorption kinetics. Pearl *et al.* (*135*) administered ibogaine at a dose of 40 mg/kg i.p. and found whole brain levels at 1, 5, and 19 hours post-administration of 10, 1, and 0.7 μM in female rats, and 6, 0.9, and 0.2 μM in male rats, respectively. In the same study, brain levels of noribogaine at 1, 5, and 19 hours post-administration were 20, 10,

and 0.8 μM in female rats, and 13, 7, and 0.1 μM and male rats respectively. In addition to gender differences in bioavailability, the data also provide evidence for the pharmacologic relevance of micromolar activities of ibogaine and noribogaine measured *in vitro* (*40,44*).

Upton (*154*) reported on observations in rats given ibogaine in the form of oral suspension, oral solution, or via IV or intraperitoneal routes, and also reviewed data obtained in beagle dogs, cynomologous monkeys, and human subjects. Absorption of the oral suspension in rats was noted to be variable and incomplete. As in the study cited above by Jeffcoat (*153*), peak levels and bioavailability were greater in female than in male rats.

B. Distribution

Hough *et al*. (*51*) administered 40 mg/kg ibogaine by the intraperitoneal and subcutaneous routes and evaluated its distribution in plasma, brain, kidney, liver, and fat at 1 and 12 hours post-administration. Ibogaine levels were higher following subcutaneous versus intraperitoneal administration, suggesting a substantial "first pass" effect involving hepatic extraction. The results were consistent with the highly lipophilic nature of ibogaine; ibogaine concentrations at 1 hour postadministration were 100 times greater in fat, and 30 times greater in brain, than in plasma. These authors suggested that the prolonged actions of ibogaine could relate to adipose tissue serving as a reservoir with release and metabolism to noribogaine over an extended period of time (*51*). The apparently greater levels of ibogaine in whole blood versus plasma suggests the possibility that platelets might constitute a depot in which ibogaine is sequestered (*42*). If there is conversion of ibogaine to noribogaine in the brain, then the significantly greater polarity of noribogaine relative to ibogaine could prolong the presence of the more polar metabolite in the CNS after conversion from ibogaine (*42*).

C. Metabolism

The major metabolite of ibogaine, noribogaine, is formed through demethylation, apparently via the cytochrome P-450 2D6 (CYP2D6) isoform (*155*). Consistent with first pass metabolism of the parent drug, noribogaine is reportedly detectable in brain tissue within 15 minutes after oral administration of 50 mg/kg ibogaine (*44*). Noribogaine is itself pharmacologically active and is discussed in this volume by Baumann *et al.*

In pooled human liver microsomes, Pablo *et al*. identified two kinetically distinguishable ibogaine *O*-demethylase activities which corresponded, respectively, to high and low values of the apparent Michaelis constant (K_{mapp}) (*155*). The low K_{mapp} ibogaine *O*-demethylase activity was attributable to CYP2D6 and accounted for greater than 95% of the total intrinsic clearance in pooled human

liver microsomes. The authors noted that the apparent involvement of the CYP2D6 suggests possible human pharmacogenetic differences in the metabolism of ibogaine. "Poor metabolizers" who lack a copy of the CYP2D6 gene (*156*) would be expected to have relatively less CYP2D6-catalyzed activity to metabolize ibogaine to noribogaine. Consistent with such an expectation, a subject identified as a phenotypic CYP2D6 poor metabolizer possessed only the high K_{mapp} ibogaine *O*-demethylase activity, which had accounted for only a small fraction of the intrinsic clearance. In another study, analysis of ibogaine and noribogaine levels in human subjects yielded a distribution interpreted as indicating three groups of rapid, intermediate, and poor metabolizers (*157*), a pattern consistent with the observed pharmacogenetic polymorphism of CYP2D6 in human populations (*156*).

D. Excretion

Ibogaine has an estimated half-life on the order of 1 hour in rodents (*158*), and 7.5 hours in man (Mash *et al*., this volume). Ibogaine and its principal metabolite, noribogaine, are excreted via the renal and gastrointestinal tracts. In rats, Jeffcoat *et al*. (*153*) noted 60 to 70% elimination in urine and feces within 24 hours, and Hough *et al*. (*51*) found plasma and tissue levels to be 10 to 20-fold lower at 12 hours versus 1 hour post dose.

Upton and colleagues (*154*) cited several pharmacokinetic issues of potential concern based on their analysis of data obtained from rats. These include evidence for presystemic clearance potentially resulting in low bioavailability and interpatient variability, and saturable first pass clearance, which could also generate intrapatient variability. The possibility of saturable systemic clearance was also noted. Mash *et al*. (*36*) suggested the possibility of species or strain differences in ibogaine metabolism and clearance rates and cited the rapid elimination of ibogaine from the blood of primates, as opposed to rats or humans, as an example.

In human subjects, 90% of a 20 mg/kg dose of ibogaine was reportedly eliminated within 24 hours (*36*). Noribogaine is apparently eliminated significantly more slowly than ibogaine, and observations in human subjects indicate persistently high levels of noribogaine at 24 hours (*36,79,123,* Mash *et al*. in this volume). The sequestration and slow release from tissues of ibogaine or noribogaine and the slow elimination of noribogaine have been suggested to account for the apparently persistent effects of ibogaine.

VI. Safety

A. Neurotoxicity

1. Neuropathology

Multiple laboratories have reported on the degeneration of cerebellar Purkinje cells in rats given ibogaine at a dose of 100 mg/kg i.p. (*159,160*). However, the available evidence suggests that the neurotoxic effects of ibogaine may occur at levels higher than those observed to have effects on opioid withdrawal and self-administration. Molinari *et al.* (*161*) found no evidence of cerebellar Purkinje cell degeneration with 40 mg/kg i.p. administered as a single dose, which is reported to reduce morphine or cocaine self-administration or morphine withdrawal in rats (*29,119,126,161*). Xu *et al.* (*162*) evaluated biomarkers of cerebellar neurotoxicity in rats treated with single doses of ibogaine of 25, 50, 75, and 100 mg/kg i.p. The biomarkers used in this study included the specific labeling of degenerating neurons with silver, and Purkinje neurons with antisera to calbindin. Astrocytes were identified with antisera to glial fibrillary acidic protein (GFAP), a marker of reactive gliosis, a general response of astrocytes to CNS injury. The 25 mg/kg dosage was found to correspond to a no-observable-adverse-effect-level (NOAEL). Helsley *et al.* (*102*) treated rats with 10 mg/kg ibogaine every other day for 60 days and observed no evidence of neurotoxicity.

Regarding the question of neurotoxicity in brain areas outside the cerebellum, O'Hearn and Molliver (*163*) have stated, "Evidence of neuronal injury following ibogaine administration in rats appears to be almost entirely limited to the cerebellum." While the cerebellum appears to be the brain region most vulnerable to neurotoxic effects of ibogaine, some research has addressed the issue of neurotoxicity in other brain regions. O'Callaghan *et al.* (*164*) examined GFAP in male and female rats exposed to either an "acute" regimen of ibogaine administered at doses of 50, 100, or 150 mg/kg i.p. daily for 3 days or a "chronic" regimen of daily oral administration of 25, 75, or 150 mg/kg for 14 days. The acute i.p. regimen produced elevations of GFAP in animals of either gender that were not restricted to the cerebellum, and were observed in the cerebellum and hippocampus at the 50 mg/kg dosage level, and in the cortex, hippocampus, olfactory bulb, brain stem, and striatum at the 100 mg/kg level. The effect of the acute ibogaine regimen on GFAP was no longer evident at 14 days with either dosage in male rats, and was restricted to the cerebellum with the 100 mg/kg dose in female rats. GFAP levels were examined at 17 days after the completion of the chronic dosing regimen. No elevations of GFAP were found in any of the brain regions examined at any of the dosages administered utilizing the chronic regimen in males, and elevations of GFAP were found only in females, which were restricted to the hippocampus with the 25 mg/kg dosage regimen and were

present in the hippocampus, olfactory bulb, striatum, and brain stem with the 150 mg/kg dosage regimen.

O'Hearn *et al*. (*159*) found GFAP elevations in the cerebellum only, and not the forebrain of male rats administered 100 mg/kg doses i.p on up to 3 consecutive days. Elevations of GFAP are relatively sensitive, but not specific to, neuronal degeneration (*162*). Using a silver degeneration-selective stain as a histologic marker of neurodegeneration, Scallet *et al*. (*165*) examined diverse brain regions in rats and mice treated with single 100 mg/kg doses of ibogaine administered i.p. and found evidence of neurodegeneration only in the cerebellum in rats, whereas mice showed no evidence of neurodegeneration. In rats that received a dose of ibogaine of 100 mg/kg i.p., neuronal degeneration was confined to the cerebellum as revealed by staining with Fluoro-Jade, a recently developed sensitive and definitive marker of neuronal degeneration (*166,167*).

Sensitivity to ibogaine neurotoxicity appears to vary significantly between species. The monkey appears to be less sensitive to potential ibogaine neurotoxicity than the rat (*36*). Mash *et al*. observed no evidence of neurotoxicity in monkeys treated for 5 days with repeated oral doses of ibogaine of 5 to 25 mg/kg, or subcutaneously administered doses of 100 mg/kg (36). Another species difference in sensitivity is the mouse, which unlike the rat shows no evidence of cerebellar degeneration at a 100 mg/kg i.p. dose of ibogaine (*165*).

2. Mechanisms of Neurotoxicity

Ibogaine's cerebellar toxicity could be related to excitatory effects mediated by $sigma_2$ receptors in the olivocerebellar projection, which sends glutaminergic excitatory input to cerebellar Purkinje cells, whose synaptic redundancy makes them particularly vulnerable to excitotoxic injury (*160*). $Sigma_2$ agonists are reported to potentiate the neuronal response to NMDA (*95*), and potentiation of glutamatergic responses at Purkinje cells might lead to the observed neurotoxicity. $Sigma_2$ agonists have also been shown to induce apoptosis, and activation of $sigma_2$ receptors by ibogaine results in direct neurotoxicity via induction of apoptosis in *in vitro* cell culture systems (*168,169*). Elsewhere in this volume, Bowen discusses the effects of *iboga*a alkaloids at $sigma_2$ receptors. It is possible therefore that ibogaine's neurotoxic effect on the highly sensitive Purkinje neurons is the result of combined direct neurotoxicity and excitotoxicity due to the enhancement of glutamatergic activity, both effects being mediated by $sigma_2$ receptors. The agonist activity of ibogaine at the $sigma_2$ receptor might explain the apparent paradox of ibogaine-induced excitotoxicity, despite its properties as an NMDA antagonist (*42*). The neurotoxic effects of *iboga* alkaloids can apparently be dissociated from their putative effects on addiction, since $sigma_2$ receptors appear not to be involved in the suppression of drug self-administration. 18-MC, an ibogaine congener with relatively much less $sigma_2$ affinity, reportedly produces effects similar to ibogaine on morphine and cocaine

administration in rats, but has shown no evidence of neurotoxicity, even at high dosages (*42,75,120*).

Ibogaine's NMDA antagonist activity has been cited as a rationale for a patent for its use as a neuroprotective agent to minimize excitotoxic damage in stroke and anoxic brain injury (*170*). In methamphetamine-treated mice, ibogaine is reported to protect against hyperthermia and the induction of heat shock protein, which are possible mediators of methamphetamine neurotoxicity (*171*). Binienda *et al*. in this volume report an accentuation of delta amplitude in ibogaine pretreated animals given cocaine, and they suggest a "paradoxical" proconvulsant effect resulting from the interaction of cocaine and ibogaine, similar to interactions reported between cocaine and other noncompetitive NMDA antagonists. However, ibogaine is reported to protect against convulsions produced by electroshock (*61*), or the administration of NMDA (*55*). Luciano *et al*. (*148*) did not observe EEG abnormalities in five human subjects during treatment with ibogaine in the dosage range of 20 to 25 mg/kg. There is apparently no reported human data on possible differences between the pre- and post-ibogaine treatment EEG, or effects persisting into extended periods of time after treatment.

3. Tremor

Ibogaine has been noted to produce tremor at dosages of 10 mg/kg i.p. in rats (*172*) and 12 mg/kg s.c. in mice (*173*). Glick *et al*. (*119*) evaluated ibogaine and several other *iboga* alkaloids and found that their effects on drug self-administration and tendency to produce tremor were independent from one another. Studies of structure-activity relationships of the *iboga* alkaloids indicate that the tendency to cause tremor is enhanced by the presence of a methoxy group at position 10 or 11 and is diminished or eliminated by the presence of a carbomethoxy group at position 16 (*173,174*). Accordingly, tremors were not produced in rats administered noribogaine, which differs from ibogaine with respect to the absence of a methoxy group at position 10, at a dosage of 40 mg/kg i.p. (*124*). Likewise, tremors were not observed in rats administered a dosage of 18-MC as high as 100 mg/kg. 18-MC differs from ibogaine with respect to the absence of a methoxy group at position 10 and the presence of a carbomethoxy group at position 16 (*120*).

4. Observations in Humans

Concern over possible neurotoxicity led Mash *et al*. to quantitatively investigate ibogaine's effects on postural stability, body tremor, and appendicular tremor in humans (*36*). In U.S. FDA safety trials, nine subjects receiving 1 and 2 mg/kg of ibogaine showed only a statistically insignificant increase in body sway 6 hours after taking ibogaine. Ten patients evaluated 5 to 7 days after receiving doses of ibogaine ranging from 10 to 30 mg/kg showed no evidence of

abnormality on quantitative measures of static or dynamic posturography or hand accelometry, or on clinical neurologic exam.

A woman died in the United States in 1994 who had been previously treated with ibogaine 25 days earlier (*36*). This woman had undergone four separate treatments with ibogaine in dosages ranging from 10 to 30 mg/kg in the 15 months prior to her death. The cause of death was concluded to have been a mesenteric arterial thrombosis related to chronic cellulitis, and a role for ibogaine in causing the fatality was not suspected. Of interest with regard to concerns over potential neurotoxicity, was the absence of any neuropathological abnormality not associated with chronic IV drug use. Neuropathological examination revealed only slight medullary neuroaxonal dystrophy and an old focal meningeal fibrosis, which were explainable on the basis of chronic IV drug use (*36*). There was no evidence of cytopathology or neurodegenerative changes in the cerebellum or any other brain area, nor was there evidence of astrocytosis or microglial activation.

B. Cardiovascular Effects

Glick *et al*. (*45*) found no changes in resting heart rate or blood pressure in rats at the dose of 40 mg/kg of ibogaine, which was often used in that laboratory in drug withdrawal or self-administration studies. Higher doses of ibogaine (100 and 200 mg/kg) decreased the heart rate without an effect on blood pressure, and 18-MC had no apparent effect on heart rate or blood pressure at any of the above doses. Binieda *et al*. (*90*) found a significantly decreased heart rate in rats given 50 mg/kg of ibogaine.

Mash *et al*. (*175*) reported on intensive cardiac monitoring in 39 human subjects dependent on cocaine and/or heroin who received fixed doses of ibogaine of 500, 600, 800, or 1000 mg. Six subjects exhibited some significant decrease of resting pulse rate relative to baseline, one of whom evidenced a significant decrease in blood pressure, which was attributed to a transient vasovagal response. Monitoring revealed no evidence of EKG abnormalities appearing or intensifying during ibogaine treatment. No significant adverse events were seen under the study conditions, and it was concluded that the single dose of ibogaine was apparently well tolerated. In their chapter in this volume, Mash *et al*. comment further that random regression of vital signs showed no changes across time or by dosage in opiate-dependent subjects. They did however observe the occurrence of a hypotensive response to ibogaine in some cocaine-dependent subjects, which was responsive to volume repletion.

C. Fatalities

The LD50 of ibogaine is reportedly 145 mg/kg i.p. and 327 mg/kg intragastrically in the rat, and 175 mg/kg i.p. in the mouse (*158*).

In June 1990, a 44 year-old woman died in France approximately 4 hours after receiving a dose of ibogaine of about 4.5 mg/kg. The cause of death was concluded to have been acute heart failure in an autopsy carried out at the Forensic-Medical Institute in Zurich (*176*). Autopsy revealed evidence of a prior myocardial infarction of the left ventricle, severe atherosclerotic changes, and 70 to 80% stenosis of all three major coronary artery branches. This patient had a history of hypertension, and inverted T waves were noted on EKG three months prior to the patient's death. The autopsy report concluded that the patients preexisting heart disease was likely to have caused the patient's death, and it specifically excluded the possibility of a direct toxic effect of ibogaine. The report acknowledged the possibility that an interaction between ibogaine and the patient's preexisting heart condition could have been a contributing factor in the fatal outcome.

The autopsy report, which included information obtained from the patient's family physician, and the psychiatrist who administered ibogaine, makes reference to the possibility that the patient might have taken other drugs. The autopsy report noted the presence of amphetamine in the enzyme immunocytochemical (EMIT) assay of a dialysate of the kidney tissue (urine was reported not to be obtainable). This finding, however, was regarded as artifactual and possibly attributable to a false positive EMIT result due to the presence of phenylethylamine.

A fatality occurred during a heroin detoxification treatment of a 24-year-old female in the Netherlands in June 1993. This incident was a significant factor in the NIDA decision not to fund a clinical trial of ibogaine in 1995. The patient received a total ibogaine dose of 29 mg/kg and suffered a respiratory arrest and died 19 hours after the start of the treatment. Forensic pathological examination revealed no definitive conclusion regarding the probable cause of death (*177*) and cited the general lack of information correlating ibogaine concentrations with possible toxic effects in humans. The high levels of noribogaine found in the deceased patient were possibly consistent with saturation of elimination kinetics. However, the higher levels of noribogaine in heart, relative to femoral blood, also suggested significant postmortem redistribution of noribogaine. The potential artifact associated with a high volume of distribution and postmortem release of drug previously sequestered in tissue (*51,139,158*) limits the interpretability of postmortem levels of noribogaine.

Some evidence suggested the possibility of surreptitious opioid use in this case, which was noted in the Dutch inquiry (*178*) and which is another source of uncertainty in this fatality. There is evidence suggesting that the interaction of opioids and ibogaine potentiates opioid toxicity (*68,179*). Analysis of gastric contents for heroin or morphine, which might have confirmed recent heroin smoking, and analysis of blood for 6-monoacetyl morphine, a heroin metabolite whose presence indicates recent use (*180*), were not performed. This incident

underscores the need for the security and medical supervision available in a conventional medical setting, and for completion of dose escalation studies to allow systematic collection of pharmacokinetic and safety data.

In London, in January 2000, a 40-year-old heroin addict died after having allegedly taken 5 g of *iboga* alkaloid extract 40 hours prior to his death (*38*, see the chapter by Alper *et al*. in this volume). The extract was said to have contained approximately five times the alkaloid content of the dried rootbark. The official British inquest regarding this matter is still in progress as of the time of the writing of this book.

D. Abuse Liability

The available evidence does not appear to suggest that ibogaine has significant potential for abuse. The 5-HT_{2A} receptor, the primary mediator of responding for LSD and other commonly abused drugs classified as "hallucinogenic" or "psychedelic," does not appear to be essential to discriminability of the ibogaine stimulus (*84,96*). Ibogaine is reportedly neither rewarding or aversive in the conditioned place preference paradigm (*132*). Rats given either 10 or 40 mg/kg ibogaine daily for 6 consecutive days did not show withdrawal signs (*129*). Animals do not self-administer 18-MC, an ibogaine analog, in paradigms in which they self-administer drugs of abuse (*45*). None of the consultants to NIDA in the 1995 Ibogaine Review Meeting identified the possible abuse of ibogaine as a potential safety concern.

VII. Learning, Memory, and Neurophysiology

A. Learning, Memory, and Addiction

Drug abusers may be viewed as having a disorder involving excess attribution of salience to drugs and drug-related stimuli (*181*), which suggests the possibility of a role of processes subserving learning and memory in the acquisition of the pathological motivational focus in addiction (*182-185*). Learning, in the most general sense, 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 subsumes everything from social behavior to learning to read, to the neuroadaptations of drug tolerance and dependence.

Addiction can be argued to involve the pathological acquisition or "learning" of associations of drug related stimuli with motivational states corresponding to

valuation and importance (*181,183,184*). The pathological learning of addiction differs from that of normal learning in at least two important respects. First, the acquisition of drug salience in addiction does not involve learned associations between drug-related external cues or internal representations, and the experience of external events as they actually occur. Instead, the "imprinting" or "stamping in" of 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 (*183-186*). Dopamine and glutamate transmission are thought to be involved in the modulation of neural plasticity of both normal learning and the neuroadaptations of drug salience (*184*). Second, drug-related "learning" does not apparently habituate (*184*). Unlike normal learning, the drug stimulus appears to be experienced as perpetually novel and continues to command attention and be attributed with salience unattenuated by habituation (*53,182*).

B. Effects of Ibogaine on Learning and Memory

Ibogaine appears to have significant effects on brain events involved in learning and the encoding of drug salience. Ibogaine interacts significantly with the NMDA receptor (*39,58,179*), which is involved in long term potentiation (LTP), a process thought to be important in neural plasticity, memory, and learning (*182,184,187*). Experiences apparently involving memory, such as panoramic recall, are prominent in descriptions by individuals who have taken ibogaine (*14*).

The observation of an effect of ibogaine on the expression of behavioral sensitization to amphetamine, but not a conditioned place preference (*188*), raises the interesting possibility of a relatively selective effect of ibogaine on the pathological encoding of drug salience, distinguished from learning involving non-drug incentives. Ibogaine reportedly attenuates the acquisition of place preference for morphine or amphetamine (*131,132*). A general effect of interference with learning has been suggested (*189*), but studies on spatial learning show an actual enhancement by ibogaine (*102,190*). Consistent with a selective effect on neuroadaptations acquired from drug exposure are ibogaine's effects on locomotor activity and dopamine efflux in the NAc, which are relatively more evident in animals with prior experience with morphine (*112,113*) or cocaine (*111*).

C. Ibogaine and the EEG

Studies of animals treated acutely with ibogaine report a desynchronized EEG with fast low amplitude activity, a state described as "activated" or "aroused"

(*89,90,191*). Binienda *et al*. (*90*) noted a decline in delta amplitude and interpreted this as consistent with activation of dopaminergic receptors. However, observations on the interaction of atropine and ibogaine with respect to the EEG suggest the involvement of ascending cholinergic input. Depoortere (*191*) found that ibogaine enhanced an atropine-sensitive theta frequency EEG rhythm in rats. Schneider and Sigg (*89*) observed a shift toward high-frequency low-voltage EEG activity following the administration of ibogaine to cats, and they noted that this effect was blocked by the administration of atropine. Luciano *et al*. (*148*) observed no changes in the visually evaluated EEG in humans administered 20 to 25 mg/kg ibogaine.

D. Goutarel's Hypothesis

The French chemist Robert Goutarel (*14*) hypothesized that ibogaine treatment involves a state with functional aspects shared by the brain states of REM sleep, with important effects on learning and memory. During the REM state, there is believed to be reconsolidation of learned information in a state of heightened neural plasticity, with the reprocessing of previously learned information and the formation of new associations (*192,193*). Goutarel suggested that a REM-like state may be induced by ibogaine, which corresponds to a window of heightened neural plasticity, during which there may be weakening of the pathological linkages between cues and representations of the drug incentive and the motivational states with which they have become paired (*14*). Analogous to the reconsolidation of learned information that is thought to occur during the REM state (*192,193*), Goutarel theorized that the pathological learning of addiction was modified during ibogaine treatment. He appears to have based his theoretical formulation mainly on reports of the phenomenological experiences of awake ibogaine-treated subjects that share features in common with dreams. Goutarel's hypothesis is speculative, but nonetheless has an interesting apparent consistency with the literature on the relationship of learning and addiction and the physiologic function of the REM EEG state with regard to the consolidation of learned information.

There is some evidence that may be viewed as consistent with Goutarel's hypothesis. Goutarel's belief in a relationship of the ibogaine-treated EEG state to that of REM is supported by studies in animals treated with ibogaine that report an apparently activated or desynchronized EEG state consistent with arousal, vigilance, or REM sleep (*90,191*). The observation that ibogaine enhanced an atropine-sensitive theta frequency rhythm (*191*) suggests the possible involvement of ascending cholinergic input, which is an essential determinant of EEG desynchronization during REM sleep (*192*). The possible reconsolidation of learned information due to heightened plasticity during both the REM and ibogaine-induced desynchronized EEG states is suggested by the observation that

EEG dyssynchrony is associated with an increased facilitation of Hebbian covariance (*194*), which is believed to be an important determinant of the neural plasticity involved in consolidation of learning and memory. Also, with regard to a possible analogy of the REM and ibogaine induced brain states, some ibogaine treatment guides have anecdotally mentioned that they have observed REM-like eye movements in awake patients during treatments (*195,196*).

VIII. Anthropological and Sociological Perspectives

As discussed in various aspects by this volume by the Fernandezes, Frenken, and Lotsof and Alexander, ibogaine's use appears to involve distinctive interactions of psychopharmacologic effects with set and setting in both the subcultures of the United States and Europe, and the centuries older, sacramental context of the use of iboga in Bwiti, the religious movement in West Central Africa. In the Bwiti religious subculture, and arguably to some extent in the European ibogaine subculture, there is the common attribute of a group of initiates that seek to facilitate healing through the affiliation of the collective with the individual. In both the African and U.S./European contexts, the ibogaine experience has been attributed to serving the objective of facilitating personal growth and change. Use of ibogaine in both contexts has been criticized as involving the use of an "addictive" or "hallucinogenic" agent, and it appears to some extent to involve the formation of a subculture among individuals confronted with marginal social circumstances such as colonialism, or the state of addiction (*197-199*, see also Fernandez and Fernandez in this volume).

Galanter (*200*) identifies three important psychological features that he regards as descriptive of the process of charismatic groups or zealous self-help movements such as 12-step programs that appear to also be relevant to Bwiti. These three processes are group cohesiveness, shared belief, and altered consciousness, such as that of religious ecstasy or insight to which the group can attribute a new construction of reality in their life. An understanding of these powerful behavioral influences could be useful in optimizing the clinical milieu and interpersonal dynamics of present conventional treatment settings, or of future treatment settings, if ibogaine or a congener should receive official approval.

The application of ethnographic techniques to the analysis of the phenomenological features of the acute treatment experience could be informative from a neuropsychiatric, as well as from a cultural perspective. For example, similar subjective phenomena are frequently described in both ibogaine treatment and near death experiences (NDEs) (*14,152,199,201*) such as panoramic memory;

calm, detached emotional tone; specific experiences, such as passage along a long path or floating; "visions" or "waking dream" states featuring archetypal experiences such as contact with transcendent beings; and the frequent attribution of transcendent significance to the experience. Such shared features between ibogaine and NDEs suggest a common transcultural phenomenology of transcendent or religious experience or, alternatively, the possibility of a similar subjective experience due to the influence of a common underlying neurobiological mechanism such as NMDA transmission (*202*).

IX. Economic and Political Perspectives

A. Economic Incentives and the Development of Ibogaine

The academic research community working in the public sector has a crucial role in studying ibogaine as a paradigm for the development of new treatment approaches. The strategy of relying on the pharmaceutical industry to underwrite the cost of drug development works extremely well in many instances, but appears to present some limitations with regard to the development of pharmacotherapy for addiction in general, and specifically ibogaine.

In the public sector, the major economic incentives for the development of addiction treatment are the saved costs associated with preventing lost economic productivity, medical morbidity, or crime. In the private sector, decisions are based on weighing the expense of development against the expected profit, and not the magnitude of saved economic or social costs. Owing to limited financial incentives in the form of insurance reimbursements and a perceived lack of "breakthrough" compounds, the U.S. pharmaceutical industry has not generally viewed addiction as an attractive area for development (*203*), and expenditures for the development of medications for addiction are small relative to those to develop drugs for other indications. Ibogaine is particularly unattractive to industry for several reasons: its mechanism of action is apparently complex and incompletely understood, it may present significant safety issues, it is a naturally occurring alkaloid whose structure cannot itself be patented, and some of its use patent are close to expiration.

There is arguably an important role for academic/public-sector development in the case of a theoretically interesting drug with a limited profit potential and significant developmental expense such as ibogaine. However, the entire annual expenditures for medications development in NIDA, which accounts to about 90% of U.S. public sector spending on developing addiction pharmacotherapy, is on the order of approximately $60 million, a fraction of the average cost of

successfully developing a drug to market, which is estimated to exceed $300 million (*204*). Opportunities to fund research on ibogaine are limited by factors that generally affect the development of other drugs to treat addiction: a limited public sector budget in the presence of disproportionately low private-sector expenditures on the development of pharmacotherapies for addiction relative to other indications (*203*).

B. Political Issues

The chapter by Alper *et al*. in this volume describes the medical subculture of the informal ibogaine treatment scene and the political subculture of advocacy for the development and availability of ibogaine. These scenes are a distinctive and significant aspect of ibogaine's history, which arguably have impacted on decisions regarding its development. From a clinical standpoint, the informal treatment subculture has been an important source of information on human experience with ibogaine (*32*).

From a political or historical standpoint, the informal treatment subculture has viewed itself as a form of activism or civil disobedience on the part of its participants seeking a treatment, despite a lack of official approval (*34*). Ibogaine has been associated with a vocal activist subculture, which views its mission as making controversial treatments available to a stigmatized minority group of patients suffering from a life-threatening illness, and has utilized tactics intended to engage the attention of the press (*34*). These confrontational media-oriented tactics may well have provoked negative reactions at times, but may also have influenced Curtis Wright, the former FDA ibogaine project officer, to write in 1995 that ". . . a significant portion of the public we serve believes the drug merits investigation" (*205*).

X. Conclusions

Evidence that supports the possible efficacy of ibogaine as a treatment for addiction includes case reports in humans, and effects in preclinical models of drug dependence. The case report evidence has mainly involved the indication of acute opioid withdrawal, and there appears to be consistency between earlier observations derived from informal treatment contexts (*32-36,146-150*) and more recent work from a setting that appears to conform to a conventional medical model (*123*, Mash *et al*. in this volume). The continued existence of informal treatment scenes parallels case report evidence indicating possible efficacy. Animal work has provided observations of attenuation of opiate withdrawal signs

and reductions of self-administration of a variety of drugs including morphine, cocaine, alcohol, and nicotine. Preclinical models have also yielded evidence that with respect to certain abused drugs, ibogaine may dampen responses that may be associated with dependence, such as dopamine efflux in the NAc or locomotor activation.

Ibogaine's pharmacologic profile includes interactions with multiple neurotransmitter systems that could plausibly be related to addiction, including NMDA, nicotinic, mu- and kappa-opioid, and serotonergic systems. The putative efficacy of ibogaine does not appear fully explainable on the basis of interactions with any single neurotransmitter system, or on the basis of currently utilized pharmacologic strategies such as substitution therapies, or monoamine reuptake inhibition. Ibogaine's effects may result from interactions between multiple neurotransmitter systems, and might not be attributable to actions at any single type of receptor. The apparently persistent effect of ibogaine has been suggested to involve a long-lived metabolite. Some evidence suggests effects on second messenger signal transduction, an interesting possibility that could conceivably result from interactions between multiple neurotransmitter systems and produce persistent effects lasting beyond the duration of occupancy at receptor sites. Work with ibogaine congeners suggests that other *iboga* alkaloids can be developed that might minimize unwanted toxic, or possibly behavioral effects, while retaining apparent efficacy in drug dependence. In summary, the available evidence suggests that ibogaine and the *iboga* alkaloids may have efficacy in addiction on the basis of mechanisms that are not yet known and which can possibly be dissociated from toxic effects, and may present significant promise as a paradigm for the study and development of pharmacotherapy for addiction.

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