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Ibogaine offers an alternative approach for treating opiate addiction

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IBOGAINE OFFERS AN ALTERNATIVE APPROACH FOR TREATING OPIATE ADDICTION

by

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ABSTRACT

Substance use disorders (SUDs) such as opioid addiction account for a large portion of the total global burden of disease. Nearly 5% of all disability-adjusted life years and 4% of overall mortality appear to be attributed to SUDs. An SUD, such as opioid use is often characterized by its addictiveness and frequent relapse among those who attempt quitting. Despite traditional methods of treatment, 5-year relapse rates are as high as 97% for opioid dependence. Alternative or novel forms of treating opioid addiction should be investigated and adopted, especially in countries which face an "epidemic" of opioid use and dependence, such as the United States.

Ibogaine is a naturally occurring indole alkaloid that may be an effective alternative form of treatment for individuals struggling with opiate addiction and/or withdrawal. Preliminary research has found that iboga alkaloids such as ibogaine are effective at reducing morphine self-administration in rats. An elaborate history of human case reports has found ibogaine to be successful at reducing drug self-administration, withdrawal symptoms, and ceasing opioid cravings. The complex pharmacological profile of ibogaine is mediated by several classes of neurological receptors and transporters, including the sigma-2, kappa- and mu-opioid, 5HT2 and 5HT3 receptors, 34 nicotinic receptors, and the N-methyl-d-aspartic acid ion channel. Ibogaine's combined interaction with all of these receptors has been suggested to reset or normalize neuroadaptation

related to drug sensitization and tolerance. The resulting anti-addictive physiological and psychological properties appear to persist beyond pharmacokinetic elimination from serum or brain tissue, but may also cause unwanted side effects such as cardiovascular and neurologic toxicity. Developing a safe and effective standard dosing regimen has proven to be difficult in humans.

The controversial therapeutic use of ibogaine in medical and nonmedical settings has been called a “vast uncontrolled experiment” or “medical subculture”, and ibogaine remains unscheduled in much of the world. However, ibogaine does not appear to have potential for recreational or other forms of abuse. During the 1995 Ibogaine Review Meeting, none of the consultants to NIDA were concerned about the abuse of ibogaine. Opiate users struggling with addiction and also interested in ibogaine therapy prompted the formation of “informal” treatment networks. Ibogaine therapy clinics catering to foreigners have also become more common in the Caribbean and Latin America. In order to clarify ibogaine’s clinical safety and therapeutic use against opiate dependence, the following thesis will investigate and analyze the ibogaine literature. Areas of focus for future ibogaine research will be identified, such as the invention of ibogaine congeners that retain efficacy against opioid dependence, but minimize unwanted toxic or psychological effects.

TABLE OF CONTENTS

TITLE……...i

COPYRIGHT PAGE……...ii

READER APPROVAL PAGE……...iii

ABSTRACT..... iv

TABLE OF CONTENTS..... vi

LIST OF TABLES..... ix

LIST OF FIGURES x

LIST OF ABBREVIATIONS..... xi

INTRODUCTION 1

Chemical Structure and Properties..... 2

SPECIFIC AIM..... 6

MECHANISMS OF ACTION..... 6

General..... 6

Glutamate 7

Opioid..... 8

Serotonin..... 10

Acetylcholine 16

Sigma Receptors..... 17

Sodium Channels 17

Effects on Neuropeptides 17

PHARMACOKINETICS 18

Absorption 18

Distribution 19

Metabolism 20

Excretion 21

EVIDENCE OF EFFICACY IN ANIMAL MODELS 22

Opioid Self-Administration 23

Acute Opioid Withdrawal 24

Locomotor Activity 25

UTILITY AND DESCRIPTIVE EFFECTS IN HUMANS 25

Evidence of Utility 25

Activist/Self-help Clinics 27

Long-Term Outcomes 29

THE IBOGAINE EXPERIENCE 30

Acute 31

Evaluative 31

Residual Stimulation 32

SAFETY 32

Neurotoxicity in Animal Models 33

Tremor in Animal Models 35

Mechanisms of Neurotoxicity 35

Cardiovascular Toxicity 39

DISCUSSION 41

Ibogaine's action on Learning and Memory 41

Safety Trials 42

Potential for Abuse 42

Case Reports of Toxicity and Fatalities in Humans 43

CONCLUSION 44

REFERENCES 47

CURRICULUM VITAE 59

LIST OF TABLES

Table	Title	Page
1	Historical Time Line of Ibogaine	3
2	Estimated extracellular basal values of DA, DOPAC and HVA in prefrontal cortex, nucleus accumbens and striatum in naive and ibogaine-pretreated rats	14
3	Demographic and Drug Use Characteristics of an Ibogaine Study Sample	27
4	ASIC scores at pretreatment baseline and 1, 3, 6, 9, and 12 months, and opioid free days	30

LIST OF FIGURES

Figure	Title	Page
1	Chemical Structures of Ibogaine, Noribogaine, and 18-Methoxycoronaridine	3
2	Effect of ibogaine, noribogaine, and 18-MC on [35S]GTPγS binding in HEK 293-mMOR cells compared with full agonist DAMGO and partial agonist buprenorphine	10
3	Changes in dopamine in the striatum and nucleus accumbens following a morphine challenge	15
4	Time course of extracellular dopamine in the nucleus accumbens and striatum after administration of noribogaine	16
5	Effects of noribogaine on morphine and cocaine self-administration and on bar-press response for water	20
6	Noribogaine blood levels versus brain levels	24
7	Ibogaine causes degeneration of Purkinje cells and activation of microglia in discrete radial bands of cerebellar cortex	39

LIST OF ABBREVIATIONS

18-MC……18-methoxycoronaridine

BU…….Boston University

BUP……Buprenorphine

CNS…….Central Nervous System

CYP2D6……...Cytochrome P-450 2D6

DA…….Dopamine

DAT……...…Dopamine Transporter

FDA…….Food and Drug Administration

GDNF……..Glial-derived Neurotrophic Factor

GFAP…….Glial Fibrillary Acidic Protein

hERG…….Human Ether-a-go-go-related Gene

HVA……Homovanillic Acid

IBO……...Ibogaine

IKr…….....Rapid Delayed Rectifier Current

Kmapp…….Michaelis Constant

LTP……..Long-Term Potentiation

MOR……Mu-opioid Receptors

nAChR……....α3β4 Nicotinic Acetylcholine Receptor

NAC……..Nucleus Accumbens

NIDA…..……...National Institute on Drug Abuse

NMDA……..N-methyl-d-aspartic Acid

PFC…….....Prefrontal Cortex

PVT……...Polymorphic Ventricular Tachycardia

SAL…….....Saline

SERT…….....Serotonin Transporter

STR…….....Striatum

SUDs……..……Substance Use Disorders

TdP……..Torsade de Pointes

VTA……Ventral Tegmental Area

INTRODUCTION

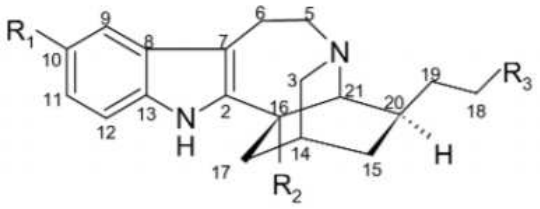
A naturally occurring indole alkaloid called ibogaine may offer an effective alternative treatment for individuals struggling with opiate addiction and/or withdrawal (K R Alper et al. 1999). Iboga alkaloids are defined by having an indole nucleus and isoquinuclidine system (Lavaud and Massiot 2017). This type of alkaloid is found naturally in plants of the family *Apocynaceae*, which includes the genera Catharanthus, Tabernaemontana, Corynanthe, Voacanga, and Aspidosperma (Lavaud and Massiot 2017). Historically, this family of plant has been used for its psychoactive nature during ceremonies of the mythic Bwiti cult of Gabon and Mbiri cults of Central Africa (Lavaud and Massiot 2017) (S D Glick et al. 1991). In addition to ibogaine's use in religious ceremonial rituals, African hunters found the stimulant effect of the iboga extracts useful for keeping them awake and motionless while stalking prey (S D Glick et al. 1991). These psychoactive properties prompted research regarding the pharmaceutical and allopathic application of iboga alkaloids.

Preliminary research found that iboga alkaloids such as ibogaine are effective at reducing morphine self-administration in rats (S.D. Glick et al. 1994). At one time, iboga root extracts were also available as anti-fatigue and stimulant agents (Lavaud and Massiot 2017). Despite these uses, ibogaine (illicit or pharmacological) never became widespread in the USA (S D Glick et al. 1991). However, it was found on the illicit market in the 1960s and classified as a Schedule I substance by the FDA (Food and Drug Administration) (S D Glick et al. 1991). All non-research use was forbidden by the 1970s (S D Glick et al. 1991). Since then, the NIDA (National Institute on Drug Abuse) has

offered support for Ibogaine animal research, and Phase I studies in humans were at one point approved by the FDA (Ibogaine Scientific Literature Overview 2012). However, the studies were then suspended, additional research considered, but funding not approved. Foreign ibogaine treatment centers continue to attract opiate dependent users to countries where the drug is unregulated, other users seek treatment from black market sources. The continuation of ibogaine research and its therapeutic use is supported by preclinical literature findings of drug abstinence and diminished withdrawal symptoms in animals, as well as successful human case reports (Ibogaine Scientific Literature Overview 2012).

Chemical Structure and Properties

Ibogaine (10-methoxyibogamine) is an indolomonoterpene alkaloid, and has a molecular formula of C20H26N2O, molecular weight of 310.44, melting point of 153°C, pKa of 8.1 in 80% methylcellosolve, crystallizes as prismatic needles from ethanol, and decomposes by the action of heat and light (Ibogaine Scientific Literature Overview 2012). It is levorotatory [α]D –53° (in 95% ethanol), soluble in ethanol, ether, chloroform, acetone and benzene, but is practically insoluble in water (Ibogaine Scientific Literature Overview 2012). Ibogaine is found at an abundance of 5 to 6% in the root bark of the Apocynaceous shrub Tabernanthe iboga, which grows in West Central Africa (Ibogaine Scientific Literature Overview 2012), (Kenneth R. Alper and Glick 2001). Only the R-enantiomer of ibogaine (Figure 1) had significant aftereffects on drug self-administration, whereas S-ibogaine had no significant effects (Lavaud and Massiot 2017).



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 (Ibogaine Scientific Literature Overview 2012). Figure and description adapted from (Ibogaine Scientific Literature Overview 2012).

Table 1. Historical Time Line of Ibogaine.The following time line provides the historical context of ibogaine's development as a treatment for drug dependence (Ibogaine Scientific Literature Overview 2012)**. Adapted from** (Ibogaine Scientific Literature Overview 2012)**.**

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 (Kenneth R Alper, Beal, and Kaplan 2001).
1901	Ibogaine is isolated and crystallized from T. iboga root bark (Piotr Popik and Wróbel 2001).
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 (Kenneth R Alper, Beal, and Kaplan 2001).
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 (Kenneth R Alper, Beal, and Kaplan 2001).

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 (Kenneth R Alper 2001).
1957	The description of the definitive chemical structure of ibogaine is published. The total synthesis of ibogaine is reported in 1965 (Ibogaine Scientific Literature Overview 2012).
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 (Ibogaine Scientific Literature Overview 2012).
1967-1970	The World Health Assembly classifies ibogaine with hallucinogens and stimulants as a "substance likely to cause dependency or endanger human health." The FDA assigns ibogaine Schedule I classification. The International Olympic Committee bans ibogaine as a potential doping agent. Sales of Lambarène cease in France (Kenneth R Alper, Beal, and Kaplan 2001).
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 (Ibogaine Scientific Literature Overview 2012).
1985	Howard Lotsof receives a U.S. patent for the use of ibogaine in opioid withdrawal (Ibogaine Scientific Literature Overview 2012). Additional patents follow for indications of dependence on cocaine and other stimulants, alcohol, nicotine, and polysubstance abuse (Ibogaine Scientific Literature Overview 2012).
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, as well as diminished cocaine self-administration (Dzoljic, Kaplan, and Dzoljic n.d.);(S D Glick et al. 1991);(S D Glick, Gallagher, et al. 1992).
1989-1993	Treatments are conducted outside of conventional medical settings in the Netherlands involving the International Coalition of Addict Self-Help, Dutch Addict Self Help, and NDA International (K R Alper et al. 1999);(Ibogaine Scientific Literature Overview 2012).
1991	Based on case reports and preclinical evidence suggesting possible efficacy, NIDA Medication Development Division begins its ibogaine project. The major objectives of the ibogaine project are preclinical toxicological evaluation and development of a human protocol (Ibogaine Scientific Literature Overview 2012).
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 (Ibogaine Scientific Literature Overview 2012), (D C Mash et al. 1998).
October 1993-December 1994:	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 (Ibogaine Scientific Literature Overview 2012).
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 (Ibogaine Scientific Literature Overview 2012).
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 begins in 1997 and heralds an increasing utilization of the Internet within the ibogaine medical subculture (Ibogaine Scientific Literature Overview 2012).

The controversial therapeutic use of ibogaine in medical and nonmedical settings has been called a “vast uncontrolled experiment” or “medical subculture” (Brown and Alper 2017). Ibogaine is unregulated in much of the world; the US, Belgium, Denmark, France, Sweden, Switzerland, and Australia have made it illegal (Kenneth R. Alper, Lotsof, and Kaplan 2008). It is recognized as a pharmaceutical substance in New Zealand, Brazil, and South Africa, but only allowed by prescription from licensed medical practitioners (Brown and Alper 2017). Most commonly used in the hydrochloride form, ibogaine is given orally at a dose in the range of 10–25 mg⁄kg of body weight at a cost of $125–$250 USD per gram (Noller, Frampton, and Yazar-Klosinski 2017). Successful administrations

have reduced opioid withdrawal symptoms and achieved cessation or sustained reduced use in dependent individuals over a 12-month study period (Noller, Frampton, and Yazar-Klosinski 2017). Regardless of ibogaine's legal status, its use as a recreational drug has never been and continues to be uncommon (Kenneth R. Alper, Lotsof, and Kaplan 2008).

SPECIFIC AIMS

Specific aims of the following thesis include:

1. Comprehensive review of the literature to analyze the therapeutic use and safety of ibogaine for treating opioid addiction.
2. Investigation of the evidence from animal models and case reports.
3. Conclusion of the findings offering final thoughts regarding the clinical use of ibogaine.

MECHANISMS OF ACTION

General

Ibogaine's pharmacological profile is mediated by a multitude of neurological receptors and transporters, including the sigma-2, kappa- and mu-opioid, 5HT2 and 5HT3 receptors, 34 nicotinic receptors, and the N-methyl-d-aspartic acid (NMDA) ion channel (Schep et al. 2016). Low concentration radio-ligand binding has been experimentally demonstrated at kappa- and mu-opioid receptors. Antagonistic action was found at nicotinic and NMDA receptors (Schep et al. 2016). Ibogaine's combined interaction with all of these receptors results in its novel physiological and psychological anti-addictive properties that appear to persist beyond pharmacokinetic elimination from serum or brain

tissue (Schep et al. 2016)-(Layer et al. 1996). Ibogaine's persistent effects of reduced drug self-administration and withdrawal symptoms are likely due to its major metabolite, noribogaine (Ibogaine Scientific Literature Overview 2012). Noribogaine has a longer half-life than ibogaine (Ibogaine Scientific Literature Overview 2012).

Glutamate

Excitatory neurotransmission is mediated by glutamate in the mammalian brain, however, it also plays a role in pathological processes (Leal et al. 2001; Ozawa 1998). Both ionotropic (ligand-gated ion channel) and metabotropic (coupled to cellular effectors) NMDA receptors mediate glutamatergic neurotransmission (Leal et al. 2001; Ozawa 1998). This type of neurotransmission is linked to the neuroplasticity of learning and memory, which may be associated with addictive behaviors (Epstein, Lipton, and Rosenberg 1994). Acute neurological disorders and neurodegenerative diseases are often found to be a result of excessive glutamate in the nervous system's synapses (Leal et al. 2001; Ozawa 1998). Excessive glutamate concentrations may result if neuronal or glial cells are no longer maintaining the concentration within a narrow range (Epstein, Lipton, and Rosenberg 1994). Inhibition of glial glutamate re-uptake, and NMDA receptor antagonism has been observed after ibogaine administration in animal models and humans (Brown and Alper 2017)-(Koenig and Hilber 2015). NMDA antagonists such as memantine have been reported to reduce signs of opioid withdrawal in animal models and case reports (Antonio et al. 2013). However, NMDA antagonism does not appear to be related to ibogaine's (Antonio et al. 2013). 18-MC, a pharmaceutical congener designed after ibogaine's structural motif is similarly effective as ibogaine at reducing

opioid use, but does not have NMDA receptor affinity (Antonio et al. 2013). By inhibiting glutamate neurotransmission in cortical and cerebellar synaptosomes, as well as in cortical astrocyte cultures from mice and rats, evidence supports ibogaine inhibition of cell death caused by excessive glutamate (Pearl, Maisonneuve, and Glick 1996). Evidence of ibogaine's NMDA antagonism include: a lessened current in hippocampal cells (Chen et al. 1996),(P Popik et al. 1995), inhibition of frog motor neuron activation (D C Mash, Staley, Pablo, et al. 1995), and the prevention of NMDA-induced convulsions (Geter-Douglass and Witkin 1999). Conversely, noribogaine lacks affinity for the NMDA transporter (Deborah C Mash et al. 2016).

Opioid

Ibogaine activates mu-opioid receptors (MOR), with an affinity for the receptor ranging from 0.13 to 26 μM (Sweetnam et al. 1995),(Skolnick 2001),(Pearl et al. 1995) sometimes at affinities as great as 100 μM (Deecher et al. 1992). Ibogaine was found to potentiate the pain reducing properties of morphine, but have no effect when given independently (Antonio et al. 2013; Corkery et al. 2004). In mice that have developed a tolerance to morphine, noribogaine and ibogaine have been shown to reduce this tolerance, and increase the pain-reducing effect of morphine in these same mice, but not in morphine-naïve mice (Antonio et al. 2013). However, neither ibogaine nor its metabolite noribogaine potentiate G protein stimulation by morphine (Antonio et al. 2013; Corkery et al. 2004). This finding implies neuroadaptation associated with chronic morphine exposure rather than allosteric MOR agonism (Antonio et al. 2013; Corkery et al. 2004). [^{35}S]GTPγS binding assays in MOR expressing cells show that ibogaine does not exhibit

allosteric MOR properties, but instead reduces the action of morphine and DAMGO, and does not activate [35S]GTPγS binding (Ibogaine Scientific Literature Overview 2012),[15,](Antonio et al. 2013). In cells that express MOR, noribogaine sometimes elicited activation, but did not stimulate [35S]GTPγS binding (Ibogaine Scientific Literature Overview 2012),(Antonio et al. 2013). Ibogaine may not activate at the level of MOR, but may cause second messengers to be activated instead (Ibogaine Scientific Literature Overview 2012). Both ibogaine and noribogaine had no action on adenylyl cyclase without morphine, but potentiated morphine or serotonin stimulated reduction of adenylyl cyclase when MOR were bound to the highest effective physiologic level of morphine (Ibogaine Scientific Literature Overview 2012),(Rabin and Winter 1996b). Noribogaine is reported to dose-dependently decrease opiate withdrawal, and to penetrate into the brain with a brain/blood ratio of 7±1 (Antonio et al. 2013). 18-MC does not have the effect of an MOR agonist, and offers equal utility to ibogaine during a naloxone precipitated withdrawal paradigm experiment on rats (Antonio et al. 2013).

Some studies report that noribogaine, but not ibogaine shows evidence of kappa-opioid agonist action, while others have demonstrated that ibogaine has an affinity for kappa opioid receptors (Deborah C Mash et al. 2016),(Schneider and McArthur 1956). Kappa-opioid agonists have been observed to mimic specific actions of ibogaine, for example, the decreased self-administration of morphine (S D Glick et al. 1995) or locomotor activity (Pearl and Glick 1996). Ibogaine's effectiveness at detoxification does not appear to be a result of a MOR agonist pathway (Antonio et al. 2013). Furthermore, ibogaine

does not cause overdose of opioids in nontolerant subjects such as Bwiti tribe initiates, or other first-time ibogaine users (Antonio et al. 2013).

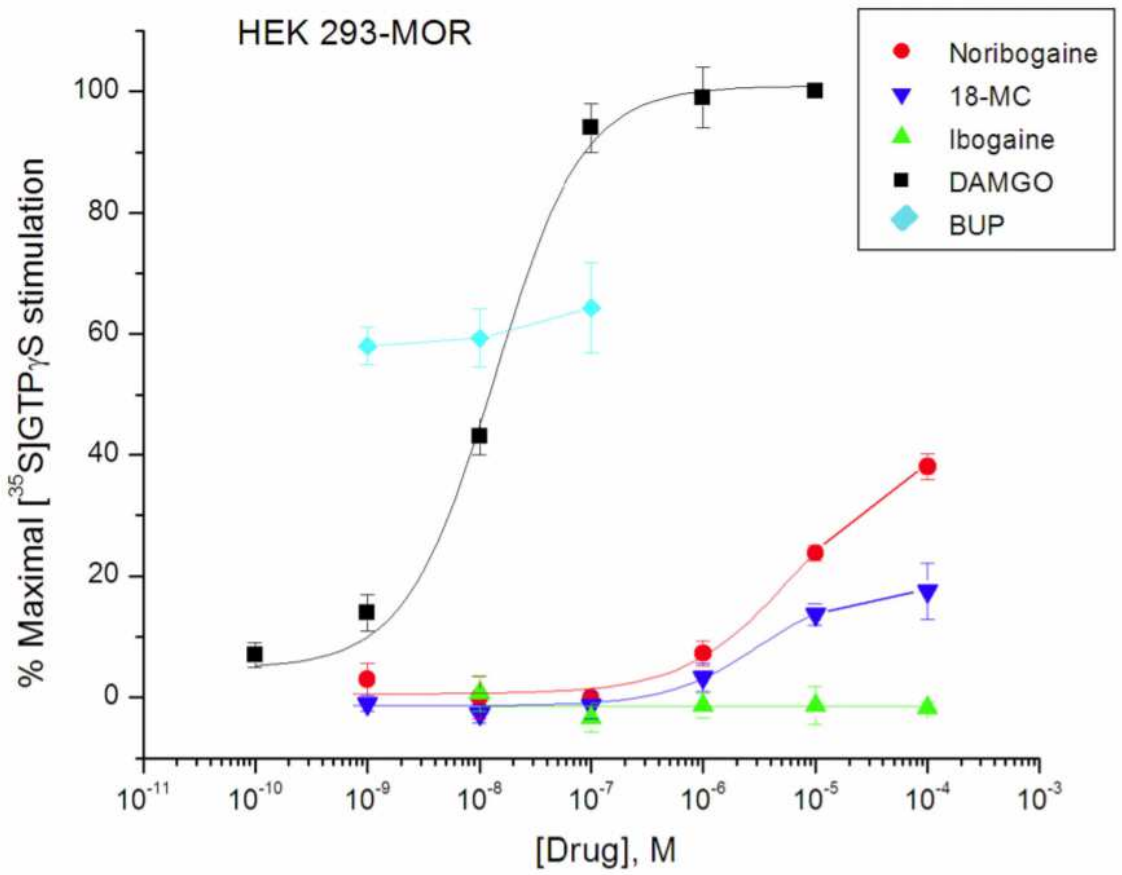


Figure 2. Effect of ibogaine, noribogaine, and 18-MC on [^{35}S]GTPγS binding in HEK 293-mMOR cells compared with full agonist DAMGO and partial agonist buprenorphine (BUP). Cell suspension aliquots were incubated with indicated drug for 15 min and subsequently with an additional concentration of 0.08 nM of [^{35}S]GTPγS at 30°C. Data are expressed as % of maximal stimulation by 10 μM DAMGO and presented as mean ± SEM (vertical bar) for 3 - 4 independent experiments assayed in triplicate. Figure and description adapted from (Antonio et al. 2013).

Serotonin

An indole ring is found in the ibogaine and serotonin chemical structure, which allows ibogaine to increase serotonin levels in the nucleus accumbens by binding to the

serotonin transporter [28]. Ibogaine is attracted to the serotonin transporter at a concentration of 0.55 to 10 μM (Piotr Popik and Wróbel 2001)·(D C Mash, Staley, Baumann, et al. 1995)·(Wells, Lopez, and Tanaka 1999)·(Staley et al. 1996). Noribogaine has an attraction that is approximately 10-fold stronger (Piotr Popik and Wróbel 2001)·(D C Mash, Staley, Baumann, et al. 1995)·(Wells, Lopez, and Tanaka 1999)·(Staley et al. 1996). Ibogaine's action on the serotonin transporter (SERT) is allosteric, noncompetitive and inhibitory, dissimilar to other inhibitors which compete with serotonin (Bulling et al. 2012). Ibogaine inhibits serotonin reuptake the 5-HT2 and 5-HT3 receptors by binding to the serotonin transporter (Schep et al. 2016). Despite the structural similarity between ibogaine and serotonin, ibogaine binds to a distinct substrate site on SERT (Bulling et al. 2012). The site is accessible from the cell exterior and has been shown to block both serotonin transportation and ionic currents induced by serotonin (Bulling et al. 2012). When ibogaine binds to SERT, it increases a pathway between the substrate-binding site and the cytoplasm, resulting in a rise of 5-HT outside the cell (Schep et al. 2016)·(Bulling et al. 2012). The kinetics of ibogaine's binding and dissociation with SERT indicate that ibogaine does not form a long-term association, but has its inhibitory effect by directly binding and stabilizing an inward-open conformation of the transporter (Bulling et al. 2012).

The increase in serotonin levels modulate ibogaine's dampening action on dopamine release in the NAC (Sershen, Hashim, and Lajtha 1997). Modified serotonin neurotransmission is also likely to mediate ibogaine's psychedelic actions by specifically binding to the 5-HT2A receptor (S D Glick and Maisonneuve 1998)·(Glennon n.d.).

Indolealkylamine and phenethylamine hallucinogens have also been found to exert their effects through this receptor (S D Glick and Maisonneuve 1998)·(Glennon n.d.).

Dopamine

There is no measurable binding to D1, D2, D3, or D4 receptors by ibogaine, however, dopamine uptake is blocked competitively at the dopamine transporter at a concentration between 1.5 to 20 μM (Sweetnam et al. 1995)·(Wells, Lopez, and Tanaka 1999). Ibogaine has a 10 to 50 times stronger association to the SERT than dopamine transporter (DAT) (Wells, Lopez, and Tanaka 1999)·(Staley et al. 1996). Reabsorption of norepinephrine is not apparently affected by ibogaine (Wells, Lopez, and Tanaka 1999)·(Staley et al. 1996). Acute morphine administration is known to increase the action of ventral tegmental area (VTA) dopamine (DA) neurons in animal models (Maisonneuve, Keller, and Glick 1991). Oddly, ibogaine appears to diminish dopamine action in the rat and mouse brain, lowering the concentration of dopamine and increasing the level of its metabolites (Baumann, Rothman, and Ali 1998). An in vivo microdialysis study determined that ibogaine pretreatment of (40 mg/kg i.p.) when injected 19 h prior to a morphine test (5 mg/kg i.p.) caused DA levels outside the cell to decrease in the striatum, increase in the prefrontal cortex, but not affect the nucleus accumbens levels (Maisonneuve, Keller, and Glick 1991) (Table 2. and Figure 3). Decreased DA levels were observed in the striatum even 19 hours after ibogaine injection (S.D. Glick et al. 1994)·(Maisonneuve, Keller, and Glick 1991). A day after administration, pharmacologically active ibogaine was detected in the rat plasma and brain (Gallagher et al. 1995)·(S D Glick et al. 1993). Administration of a high dose of morphine (30 mg/kg i.p.) did not result in increased DA levels outside

the cell; it is not clear how a low dose would affect dopamine level (Maisonneuve, Keller, and Glick 1991). Nonetheless, ibogaine evidently affects the brain's DA system in response to morphine after its physiologic removal (Maisonneuve, Keller, and Glick 1991). Ibogaine's dopamine transporter action may block the movement of dopamine into synaptic vesicles, altering dopamine's location of storage from vesicular to cytoplasmic (Ibogaine Scientific Literature Overview 2012). This decreased dopamine release could be a reason for excessive prolactin levels after ibogaine administration (Staley et al. 1996)[,](Baumann, Rothman, and Ali 1998). Continuous dopamine metabolism while dopamine levels remain depressed means monoamine oxidase will decrease tissue dopamine content as the levels of its metabolites increase (Ibogaine Scientific Literature Overview 2012). Morphine has been observed to lessen dopamine release in the NAC in animal models given ibogaine, noribogaine or 18-MC beforehand (Figure 4.) (Pearl, Maisonneuve, and Glick 1996)[,](Maisonneuve, Keller, and Glick 1991)[,](S D Glick, Kuehne, et al. 1996)[,](S D Glick, Pearl, et al. 1996)[,](Maisonneuve and Glick 1992)[,](Maisonneuve and Glick 1999). The acute effects on DA levels were not the same, however, similar delayed effects were observed in the studied regions (S D Glick et al. 1991).

Table 2. Estimated extracellular basal values of DA, DOPAC and homovanillic acid (HVA) in prefrontal cortex, nucleus accumbens and striatum in naive and ibogaine-pretreated rats. PFC, prefrontal cortex; NAC, nucleus accumbens; STR, striatum. Data includes (means_+ S.E.). Ibogaine-pretreated rats were given 40 mg/kg, 19 h beforehand. Table and description adapted from (Maisonneuve, Keller, and Glick 1991)**.**

	DA (nM)	DOPAC (μM)	HVA (μM)
In naive rats			
PFC	2.55 ± 0.2	0.19 ± 0.02	0.38 ± 0.03
NAC	14.27 ± 1.1	4.91 ± 0.60	2.10 ± 0.22
STR	24.00 ± 1.6	6.96 ± 0.44	4.40 ± 0.31
In ibogaine-pretreated rats			
PFC	2.49 ± 0.4	0.04 ± 0.01 [a]	0.12 ± 0.03 [a]
NAC	14.10 ± 2.1	1.94 ± 0.77 [a]	0.81 ± 0.15 [a]
STR	14.38 ± 2.9 [a]	2.73 ± 1.09 [a]	2.04 ± 0.58 [a]

[a] Significantly different from correspondent levels found in naive rats ($P < 0.05$).

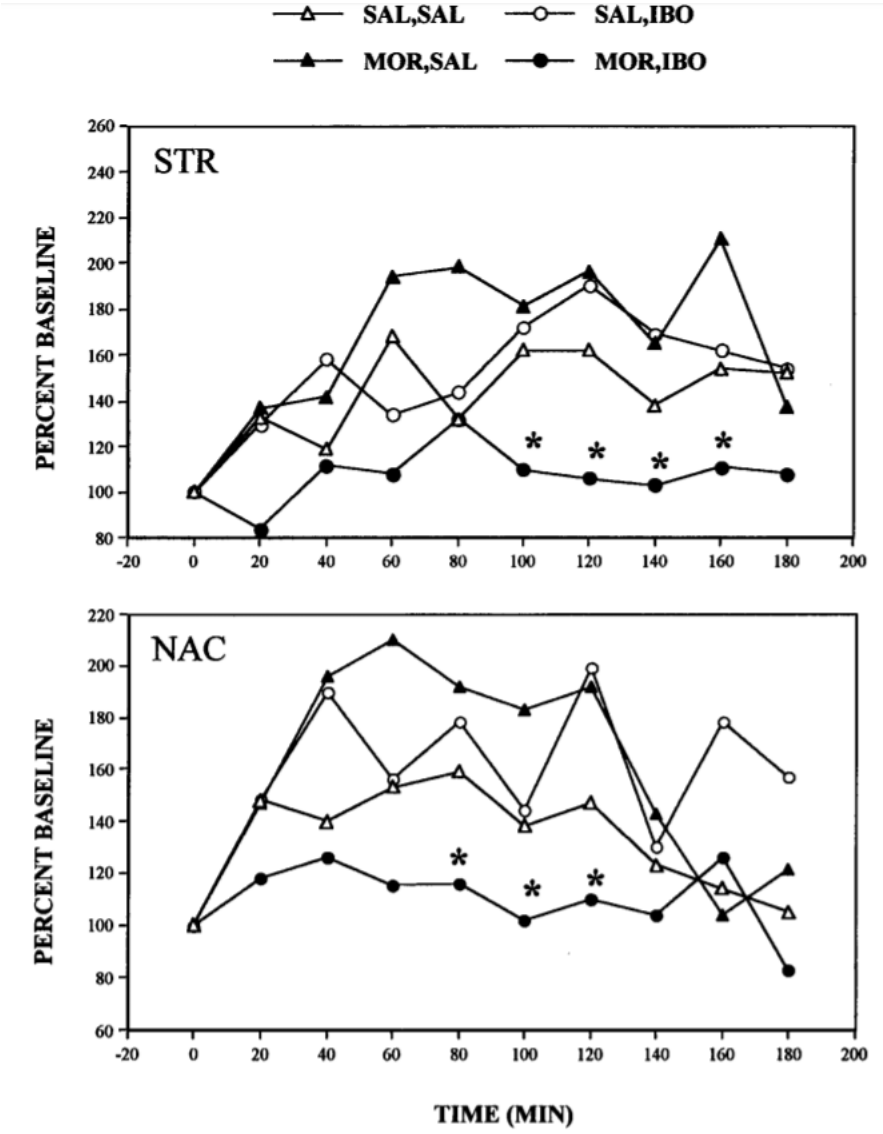


Figure 3. Changes in dopamine in the striatum and nucleus accumbens following a morphine challenge. Morphine challenge (5 mg/kg, i.p.), (STR, top panel), (NAC, bottom panel). Rats received either morphine (20 mg/kg, i.p.) or saline pretreatment once a day for 2 days followed by ibogaine (10m @ kg, i.p.) or saline 5 hr after the last pretreatment. All rats were challenged 19 hr after ibogaine or saline with morphine. N = 4-8 rats per group. Figure and description adapted from (Pearl, Maisonneuve, and Glick 1996).

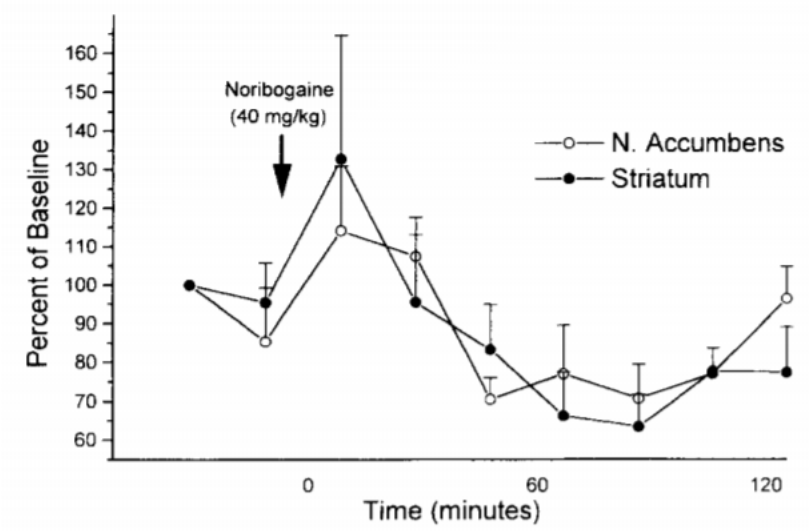


Figure 4. Time course of extracellular dopamine in the nucleus accumbens and striatum after administration of noribogaine (40 mg/kg, n = 6). Samples were collected at 20-min intervals. Data are expressed as a percent (±S.E.) of baseline dialysate values. There were significant decreases in dopamine in both regions (ANOVA, $P < 0.02$-0.05). Figure and description adapted from (S D Glick, Pearl, et al. 1996).

Acetylcholine

Ibogaine acts as a noncompetitive allosteric antagonist of the α3β4 nicotinic acetylcholine receptor (nAChR) by open channel blockade, and is responsible for reduced acetylcholine-stimulated nicotinic receptor catecholamine release in in-vitro cells (Stanley D Glick et al. 2002)·(Antonio et al. 2013)·(Benwell et al. 1996)·(Badio, Padgett, and Daly 1997)·(Mah et al. 1998)·(Fryer and Lukas 1999). A 10 mg/kg dose of ibogaine resulted in complete central antinociceptive nicotinic receptor-mediated response blockage to epibatidine in mice (Ibogaine Scientific Literature Overview 2012). It and noribogaine are also nonselective and weak inhibitors of muscarinic receptors (Sweetnam et al. 1995)·(Staley et al. 1996). Ibogaine has an affinity between the ranges of 7.6 and 16 μM and 5.9 and 31 μM, respectively, for the M1 and M2 type of muscarinic receptor

(Ibogaine Scientific Literature Overview 2012),(Sweetnam et al. 1995). A different study reported that ibogaine did not interact at a statistically measurable level with muscarinic receptors (Deecher et al. 1992). Ibogaine interacts with muscarinic cholinergic receptors in the following ways: elimination of ibogaine-induced EEG dyssynchrony by atropine in cats, decreased heart rate following ibogaine administration in rats, and cholinesterase inhibition (Ibogaine Scientific Literature Overview 2012),(SCHNEIDER and SIGG 1957),(Binienda et al. 1998).

Sigma Receptors

Ibogaine has an affinity for the sigma2 receptor in the range between 0.09 to 1.8 μM which is relatively strong compared to other known CNS receptors (Itzhak and Ali 1998),(Bowen et al. 1995). Ibogaine's affinity for the sigma1 receptor is reportedly between 2 to 100 times less strong than its attraction for the sigma2 receptor (Itzhak and Ali 1998),(Bowen et al. 1995). NMDA's neurological response is increased by the sigma2 receptor, and may be associated with the neurotoxic effects of ibogaine (Couture and Debonnel 1998). Conversely, noribogaine does not have affinity for the sigma2 receptors (Deborah C Mash et al. 2016).

Sodium Channels

Ibogaine is attracted to sodium channel ranging between 3.6 to 9 μM (Sweetnam et al. 1995),(Deecher et al. 1992). The functional significance or evidence of ibogaine's action at sodium channels is unsupported by experimental data (Ibogaine Scientific Literature Overview 2012).

Effects on Neuropeptides

Ibogaine treatment may act in the brain by resetting or normalizing neuroadaptation related to drug sensitization or tolerance (Szumlinski, Maisonneuve, and Glick 2001). Increases in glial-derived neurotrophic factor (GDNF) prevalence in vivo and in cultured cells has been observed and hypothesized to be responsible for ibogaine's prolonged action of reducing opioid self-administration (He et al. 2005). Evidence of ibogaine's neuroadaptive properties are observed by the reduced voluntary movement and dopamine release in the NAc after morphine administration among morphine tolerant animals after ibogaine treatment (Pearl, Maisonneuve, and Glick 1996),(Pearl, Johnson, and Glick 1995). Additionally, ibogaine inhibits morphine tolerance in mice, but does not affect morphine nociception in morphine-naïve mice (Ibogaine Scientific Literature Overview 2012). The persistent effects of ibogaine may be a result of preventative neurologic changes related to opioid sensitivity or tolerance (S D Glick et al. 1991),(Maisonneuve, Keller, and Glick 1991). Sensitization to opiates is thought to involve persistent effects on second messengers and increased activation of cyclic AMP (Rabin and Winter 1996b),(Rabin and Winter 1996a),(White and Kalivas n.d.). Ibogaine was observed to increase the inhibitory effects of adenylyl cyclase by serotonin (Rabin and Winter 1996b),(White and Kalivas n.d.). This action may reverse the stimulation of cyclic AMP related to sensitization (Rabin and Winter 1996b),(White and Kalivas n.d.).

PHARMACOKINETICS

Absorption

Administration of 5 mg/kg and 50 mg/kg of ibogaine as an oral single dose to rats has a 16 and 71% bioavailability, respectively, when dosed at the aforementioned levels in

females, and 7 and 43% in males (Ibogaine Scientific Literature Overview 2012). A dose of 40 mg/kg i.p. was reported to have entire brain concentrations at 1, 5, and 19 hours after administration of 10, 1, and 0.7 μM among rats of female gender, and 6, 0.9, and 0.2 μM among rats of male gender (Pearl et al. 1997). Similarly, brain levels of noribogaine at 1, 5, and 19 hours after administration were 20, 10, and 0.8 μM in rats of female gender, and 13, 7, and 0.1 μM in rats of male gender (Pearl et al. 1997). The greater peak concentration and bioavailability in females is apparently due to gender-related differences in absorption kinetics (Ibogaine Scientific Literature Overview 2012). The dose-dependent bioavailability suggests a nonlinear elimination and/or uptake of ibogiane (Ibogaine Scientific Literature Overview 2012).

Distribution

After subcutaneous administration the amount of ibogaine was greater when compared to intraperitoneal administration, which implies a significant hepatic extraction during the "first pass" (Ibogaine Scientific Literature Overview 2012)(Hough, Pearl, and Glick 1996). Ibogaine appears to have a highly lipophilic nature supported a 100x increase in fat, and 30x increase in brain compared to plasma concentration 1 hour after adminstration (Hough, Pearl, and Glick 1996). Adipose tissue may serve as a metabolizing and releasing reservoir prolonging the action of ibogaine (Hough, Pearl, and Glick 1996). Ibogaine was found at increased amounts in natural blood compared to plasma suggesting that platelets may also serve as a depot for ibogaine (S D Glick and Maisonneuve 1998). Prolonged effects of ibogaine are also observed in the central nervous system (CNS) after conversion of ibogaine to noribogaine in the brain (S D Glick

and Maisonneuve 1998). Since ibogaine's primary metabolite, noribogaine has greater polarity and excellent brain penetration it is suggested to have more of a central than peripheral nervous system effect (Figure 5.) (Deborah C Mash et al. 2016). Research reports that the CNS effects of noribogaine are most marked following oral doses (Deborah C Mash et al. 2016). Ibogaine's effects are most observed when given via the systemic route, not intracerebroventricularly (Deborah C Mash et al. 2016).

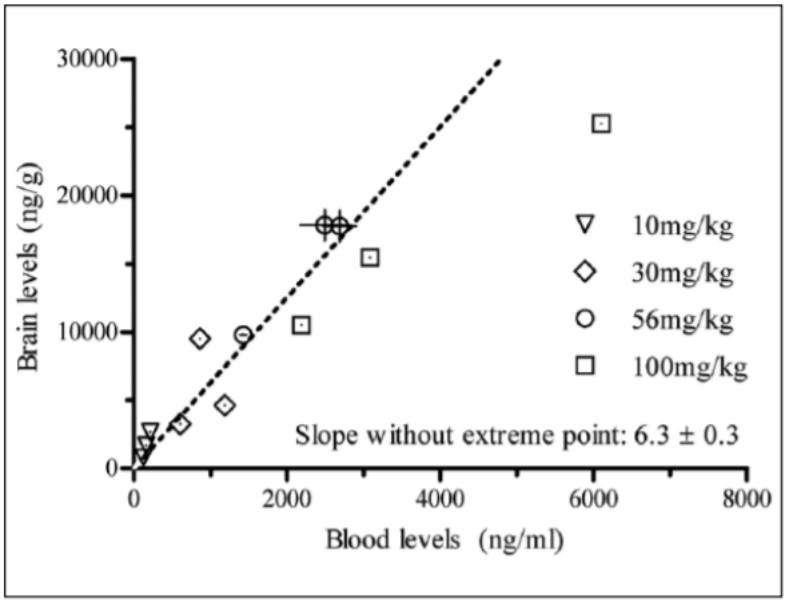


Figure 5. Noribogaine blood levels versus brain levels. A single point from three animals is shown for the three noribogaine dosing groups at 10, 30, and 100 mg/kg. The animals in the noribogaine dose group at 56 mg/kg were assayed twice, and mean±SEM are shown. Blood and brain samples were collected two hours after oral dosing of noribogaine. Figure and description adapted from (Deborah C Mash et al. 2016).

Metabolism

Ibogaine undergoes demethylation when acted upon by the cytochrome P-450 2D6 (CYP2D6) isoform producing noribogaine (O-desmethylibogaine or 10-hydroxyibogamine), the most common metabolic product (Ibogaine Scientific Literature Overview 2012)·(Antonio et al. 2013)·(K. Alper et al. 2016)·(Obach, Pablo, and Mash

1998). After 15 minutes elapsed from the time of a 50 mg/kg oral administration of ibogaine, a first-pass metabolic step, noribogaine was detectable in brain tissue (Staley et al. 1996). The half-life of ibogaine in homo sapiens is approximately 4–7 h, and the half-life of noribogaine is 24-72 hours (K. Alper et al. 2016). The longer half-life of noribogaine supports the claim that both ibogaine and noribogaine are critical for the effectiveness of ibogaine therapy (K. Alper et al. 2016)·(Antonio et al. 2013).

Studies of human liver microsomes provide evidence of upper and lower limits for Michaelis constant (Km_{app}) ibogaine O-demethylase (Obach, Pablo, and Mash 1998). The lesser limit of Km_{app} CYP2D6 O-demethylase accounts for 95% of all the clearance in liver microsomes (Obach, Pablo, and Mash 1998). Pharmacogenetic differences in human CYP2D6 suggest metabolic differences and may be the reason for difficulty in creating standard dosing regimens (Wolf and Smith 1999). Genetic polymorphism of CYP2D6 resulted in differing levels of ibogaine and noribogaine in human subjects, implying three groups of ibogaine metabolizers: rapid, intermediate, and poor. (Ibogaine Scientific Literature Overview 2012)·(Wolf and Smith 1999).

Excretion

The estimated half-life of ibogaine is approximately 1 hour in small mammals, and 7.5 hours in humans (Zubaran 2006). Ibogaine and its main metabolic product, noribogaine, exit the body through the kidney and intestinal system (Ibogaine Scientific Literature Overview 2012). In rodents, 60 to 70% leaves the body during urination and defecation within 24 hours (Hough, Pearl, and Glick 1996). One hour after administration plasma and tissue concentrations were reported to be 10 to 20-times greater than at 12 hours

post-administration (Hough, Pearl, and Glick 1996). Ibogaine metabolism and clearance rates differ between species (D C Mash et al. 1998). For example, primate eliminate ibogaine much quicker than rats or humans (D C Mash et al. 1998). In human subjects, ibogaine takes 24 hours to reach 90% elimination of a 20 mg/kg p.o. treatment (D C Mash et al. 1998). The majority of ibogaine's effects are likely due to noribogaine since it stays in the blood significantly longer (D C Mash et al. 1998), (Hearn et al. 1995). The long-term actions of ibogaine could be due to tissues withholding and delaying the release of ibogaine or noribogaine from tissues (D C Mash et al. 1998).

EVIDENCE OF EFFICACY IN ANIMAL MODELS

Among rodents, a dose-dependent administration of ibogaine of at least (2.5 mg/kg) lessened opioid seeking behavior within 60 minutes of ibogaine administration, and over 24 hours later (S D Glick et al. 1991). Long-term effects of ibogaine were observed when ibogaine was expected to be physiologically removed (S D Glick et al. 1991). It has been difficult to predict the length of time that ibogaine will have an effect due to variation in ibogaine metabolism within the same animal species (S D Glick et al. 1991). For example, when long-term effects from ibogaine treatment were not observed, ibogaine treatments given at weekly or biweekly intervals began to report long-lived effects (S D Glick et al. 1991). This implies that developing a standard dosing regimen may be difficult in humans due to individual differences in drug metabolism and sensitivity (S.D. Glick et al. 1994), (O'Hearn and Molliver 1993). With regards to addiction, animal studies have found that ibogaine is not addictive and desire to take ibogaine after repetitive treatments is not been observed (Kenneth R. Alper, Lotsof, and Kaplan 2008).

Opioid Self-Administration

Support for ibogaine's effectiveness at reducing self-administration of morphine or heroin is offered by animal studies (S D Glick et al. 1991)[9](S.D. Glick et al. 1994)[7](Dworkin et al. 1995)[7](S D Glick, Kuehne, et al. 1996). Ibogaine's effect on opioid use lasted for at least 2 days in a dose dependent manner when given at the levels of 2.5 to 80 mg/kg (S D Glick et al. 1991)[9](S.D. Glick et al. 1994). A 40 mg/kg i.p. administration of ibogaine abruptly lessened opioid seeking behavior, although the effect did not persist beyond 24 hours (Dworkin et al. 1995). Noribogaine was observed to persistently lessen opioid seeking behavior for up to two days (see Figure 4.) (S D Glick, Pearl, et al. 1996). Other iboga alkaloids such as the iboga congener, 18-methoxycoronaridine (18-MC) have been observed to lessen opioid seeking behavior in rodents for durations over 24 hours (S.D. Glick et al. 1994).

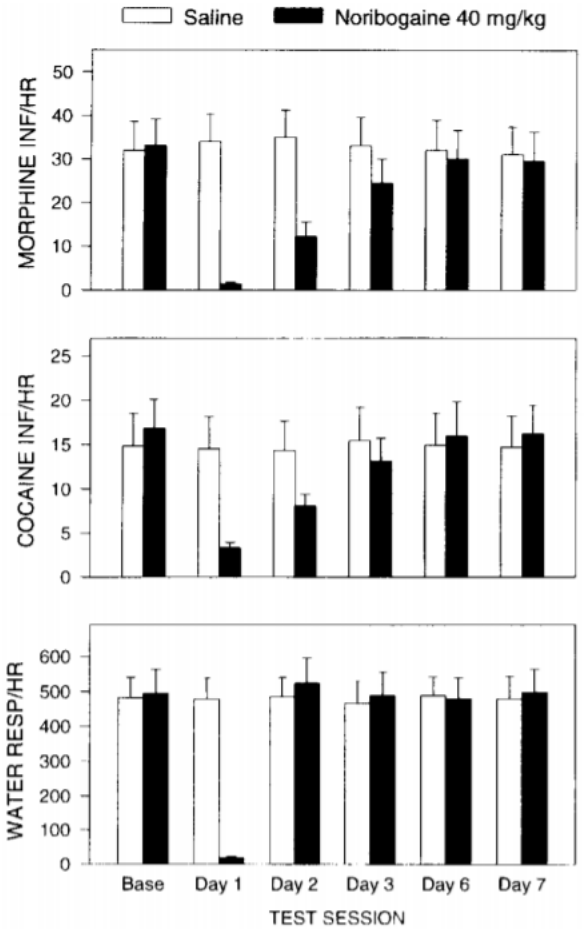


Figure 6. Effects of noribogaine on morphine and cocaine self-administration and on bar-press response for water. Each data point is the mean (+S.E.) from 5 to 6 rats. 'Base' refers to the baseline rate of responding, calculated as the average for the three sessions preceding drug (noribogaine (40 mg/kg)) or saline treatment. There were significant effects on Day 1 in all cases and on both Days 1 and 2 in rats self-administering morphine or cocaine (ANOVA and t-tests, $P < 0.05$-0.01). Figure and description adapted from (S D Glick, Pearl, et al. 1996).

Acute Opioid Withdrawal

Ibogaine administered at a concentration between 4 to 16 µg intra-cerebroventricularly has been reported to dose-dependently reduce naloxone-precipitated withdrawal signs in rats (Dzoljic, Kaplan, and Dzoljic n.d.). 40 mg/kg ibogaine given i.p. has been shown to attenuate opioid seeking signs in rodents (Dzoljic, Kaplan, and Dzoljic n.d.). Ibogaine

given at amounts of 20, 40, or 80 mg/kg i.p or 18-MC at amounts of 20 and 40 mg/kg i.p. dose-dependently reduced observations of naltrexone-precipitated opioid withdrawal in rats (S D Glick, Rossman, et al. 1992)·(Rho and Glick 1998). Reduction of opioid seeking behavior was reported in opioid-addicted primates administered 2 or 8 mg/kg ibogaine subcutaneously. 40 mg/kg ibogaine given i.p has been shown to attenuate naloxone-produced opioid craving and place aversion in rodents (Ibogaine Scientific Literature Overview 2012).

Locomotor Activity

Ibogaine and NMDA antagonists reportedly reduce opioid-induced locomotor stimulation (Ibogaine Scientific Literature Overview 2012). Ibogaine induced motor impairment has been observed within the first 24 hours after administration (Belgers et al. 2016b). Weakened locomotor activation in response to morphine was reported after treatment with ibogaine and noribogaine (Pearl et al. 1997)·(Pearl, Maisonneuve, and Glick 1996)·(Maisonneuve, Keller, and Glick 1991)· (Pearl, Johnson, and Glick 1995)·(S D Glick, Pearl, et al. 1996)·(S D Glick, Maisonneuve, and Pearl 1997)·(Maisonneuve et al. 1992). Reduced morphine induced locomotor activity after ibogaine administration is apparently more pronounced in female than in male rodents, demonstrating the increased effects of ibogaine in females (Ibogaine Scientific Literature Overview 2012)·(Pearl et al. 1997).

UTILITY AND DESCRIPTIVE EFFECTS IN HUMANS

Evidence of Utility

After a single dose of ibogaine, reduced opioid desire and relief from opiate withdrawal signs and symptoms were reported to occur within 1 to 2 hours by opiate addicts (D C Mash et al. 1998),(Luciano 1998). One study summarized 33 cases (Table 3.) treated under open label conditions for opioid detoxification in a nonmedical setting (Ibogaine Scientific Literature Overview 2012),(Brown and Alper 2017). The patients reported average daily heroin use of 0.64 ± 0.50 g, usually through injection (Ibogaine Scientific Literature Overview 2012),(Brown and Alper 2017). The patients received dosages of approximately 19.3 ± 6.9 mg/kg p.o. of ibogaine on average (Ibogaine Scientific Literature Overview 2012),(Brown and Alper 2017). 25 patients were relieved of opioid withdrawal and no longer in pursuit of opioids (Ibogaine Scientific Literature Overview 2012),(Brown and Alper 2017). Four patients experienced a lack of desire to take opioids and did not show clinical signs of withdrawal, a complete lack of opioid use and withdrawal was observed in two patients, one patient continued to seek opiates and felt withdrawal signs, and one patient died attributed to clandestine opiate use (Ibogaine Scientific Literature Overview 2012),(Brown and Alper 2017). Although the half-life of ibogaine in humans is on the order of 4 to 7 hours, after a period of one month since treatment, decreased levels of depression and desire to use opiates was reported (Ibogaine Scientific Literature Overview 2012),(Brown and Alper 2017). Since ibogaine treatment typically consists of a single dose, it does not need to be slowly reduced over time to lessen withdrawal signs common among opioid agonists.

Table 3. Demographic and Drug Use Characteristics of an Ibogaine Study Sample. Table adapted from (K R Alper et al. 1999)**.**

Gender	22 (67%) male, 11 (33%) female
Mean Age	27.3 ± 4.7 years
Ethnicity	32 Caucasian, 1 Surinamese
Mean daily heroin use	.64 ± .50 grams/day
Predominant route of heroin self administration	26 intravenous, 4 intranasal, 3 smoking
Mean duration of heroin use	6.2 ± 5.8 years
Number of subjects with concurrent methadone maintenance	8 (24%)
Mean methadone dose (N = 8)	48 ± 30 milligrams
Number of subjects additional seeking treatment for concurrent cocaine use	8 (24%)
Mean daily cocaine use (N = 8)	1.4 ± 2.3 grams

Activist/Self-help Clinics

Opiate users struggling with addiction who want to try ibogaine therapy has led to a demand for "informal" therapy networks in Europe and the United States (Sheppard n.d.). Travel to addiction clinics that cater to foreigners is also becoming more common (Kenneth R. Alper, Lotsof, and Kaplan 2008). St. Kitts and Mexico are destinations with well-regarded addiction clinics that have medically trained staff on-site (Kenneth R. Alper, Lotsof, and Kaplan 2008). Before these clinics begin treatment, their patients are transitioned to an orally administered short acting opioid (Kenneth R. Alper, Lotsof, and Kaplan 2008). This opioid is then slowly discontinued for at least three serum half-lives before ibogaine treatment (Kenneth R. Alper, Lotsof, and Kaplan 2008). Standard patient procedure requires a pre-treatment Holter monitor and 12 lead EKG, vital sign and pulse oximetry monitoring (Kenneth R. Alper, Lotsof, and Kaplan 2008). During treatment intravenous access is maintained, and a physician trained in emergency medicine and knowledgeable about cardiac life support remains on site (Kenneth R. Alper, Lotsof, and

Kaplan 2008). A certified nurse also continuously monitors the patient (Kenneth R. Alper, Lotsof, and Kaplan 2008).

The following quote from a post to an ibogaine list server provides insight of the personal struggle of opiate addiction and the potential benefit of therapeutic ibogaine treatment:

"...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." Quote taken from (Kenneth R. Alper, Lotsof, and Kaplan 2008).

An introspective experience of meaning and insight was also common among users of ibogaine, likely a result of ibogaine's psychoactive properties (Brown and Alper 2017).

One subject wrote:

"I saw my family from young to older and how everything has been and how I affected them."…"When I closed my eyes most of the time I had visions from my past. . . A profound sense of love for my family and their love for me and an intense, almost piercing agony as I was overwhelmed with the remorse and the waste and loss, feeling empathy with my family over all their hopes for me dashed by my relentless pursuit of drugs. . . I kept seeing clips – real memories, of high-school girlfriends and playing music with friends – but then also clips of the present day in an alternate reality where I hadn't squandered so much love or compassion that had been offered to me." Quote taken from [1].

Post-treatment opiate users also commonly felt that the absence of cravings provided them with the freedom to change personal behaviors, as displayed in comments such as:

"...you could safely say that iboga will give an opiate addict several months to a half a year of freedom from cravings and an expanded awareness. This gives the user a period

of time in which to get his/her life together and learn to face things straightforwardly, directly and honestly. Iboga will not do the work for you. However, it will help you do your own work." Quote taken from (Brown and Alper 2017).

Long-Term Outcomes

Reports from ibogaine therapy over an extended period of time consists of primarily self-reports obtained retrospectively (Table 4.) (Ibogaine Scientific Literature Overview 2012). A single oral dose of 6-19 mg/kg of ibogaine is claimed to have a therapeutic effect lasting six months (S D Glick et al. 1991). When four therapeutic treatment sessions are given to a patient the complexities of drug use are interrupted for approximately three years (S D Glick et al. 1991). Ibogaine's successfulness at reducing desire for continued opioid use is reportedly statistically similar to that of methadone (Brown and Alper 2017).

Table 4. ASIC scores at pretreatment baseline and 1, 3, 6, 9, and 12 months, and opioid free days (Kenneth R Alper, Beal, and Kaplan 2001)**.**

	Pretreatment	One month	3 months	6 months	9 months	12 months
n	30	20	19	14	17	14
ASIC Scores						
Drug Use	0.40 ± 0.08	0.11 ± 0.09†††	0.15 ± 0.13†††	0.12 ± 0.09†††	0.13 ± 0.13†††	0.17 ± 0.10†††
Alcohol Use	0.08 ± 0.18	0.09 ± 0.13	0.07 ± 0.11***	0.16 ± 0.16*	0.12 ± 0.13*	0.16 ± 0.24
Family/Social Status	0.24 ± 0.16	0.07 ± 0.13†††	0.06 ± 0.13†††**	0.08 ± 0.15††*	0.03 ± 0.09†††*	0.04 ± 0.07†††
Employment Status	0.34 ± 0.26	0.44 ± 0.28††	0.33 ± 0.27**	0.26 ± 0.22***	0.37 ± 0.29***	0.25 ± 0.19***
Legal Status	0.22 ± 0.24	0.10 ± 0.18††	0.04 ± 0.09††**	0.14 ± 0.14†*	0.05 ± 0.10†**	0.10 ± 0.17††*
Medical Status	0.19 ± 0.31	0.26 ± 0.28	0.27 ± 0.34*	0.25 ± 0.28**	0.15 ± 0.31**	0.26 ± 0.35**
Psychiatric Status	0.27 ± 0.18	0.18 ± 0.22	0.17 ± 0.20†*	0.16 ± 0.23††*	0.14 ± 0.20	0.23 ± 0.20
Opioid-free days in the previous 30 days						
Among subjects available for follow up	1.0 ± 3.3	27.7 ± 5.7	22.5 ± 11.2	20.2 ± 13.5	20.6 ± 13.4	17.3 ± 14.0
Among all subjects (N=30), missing values set to pretreatment baseline	1.0 ± 3.3	18.9 ± 13.6	14.9 ± 13.7	9.9 ± 13.6	11.7 ± 14.4	8.8 ± 12.7
Number of subjects reporting no opioid use in previous 30 days (%N)	0	15 (50%)	10 (33%)	6 (20%)	11 (37%)	7 (23%)

Paired *t*-tests (†): $^{\dagger}p < .05$; $^{\dagger\dagger}p < .01$; $^{\dagger\dagger\dagger}p < .001$.
Noninferiority tests (*): $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Paired t-tests were used to compare ASIC scores at 1, 3, 6, 9, and 12 months post-treatment to their baseline pretreatment values (N = 30; significance level of p-values indicated by †). Noninferiority tests were used to compare ASIC scores at 3, 6, 9, and 12 months post-treatment to their 1- month post-treatment values (n = 20; significance level of p-values indicated by *). The means and standard deviations are unadjusted and computed on the subjects (n) available at the respective time point. The p-values are adjusted for missing follow-up data by performing the respective statistical tests with missing values set equal to their baseline pretreatment value. Opioid-free days in the previous 30 days are shown in the lower part of the table. Table and description adapted from (Brown and Alper 2017).

THE IBOGAINE EXPERIENCE

Within hours of ibogaine treatment, patients are typically relieved of withdrawal symptoms and opioid cravings (K R Alper et al. 1999). The “stages” of the ibogaine detoxification experience consist of an acute, an evaluative and a residual stimulation phase. Generally, a clinic is the most common place where ibogaine treatment is given, usually as one dose by mouth in the morning (Ibogaine Scientific Literature Overview 2012). Several hours after treatment, a single episode of vomiting is commonly reported (Ibogaine Scientific Literature Overview 2012). The vomiting is often induced by

movement, so most patients do not move and stay in a peaceful, dark room during their treatment (Ibogaine Scientific Literature Overview 2012). The dark, quiet room probably also helps induce the retrospective cerebellar effects of ibogaine (Ibogaine Scientific Literature Overview 2012). Patients often experience muscle soreness later in treatment, but this resolves with motion, stretching, or massage (Ibogaine Scientific Literature Overview 2012).

Acute

Approximately one to three hours after taking the ibogaine dose, extreme states of recall remain for about four to eight hours (K R Alper et al. 1999). Typically patients experience large amounts of visual material related to previous experiences rooted in old memories (K R Alper et al. 1999) (Roberts and Owen 1988). This stage is considered to contain "visions" or "waking dreams" rather than hallucinations, and patients often report interaction with spirits, walking along an imaginary path, or flying (Ibogaine Scientific Literature Overview 2012). Patients emphasize that the experience is not an intrusion of visual or auditory input, but one instantaneous appearance in, or entrance/exit from visual phenomena (Ibogaine Scientific Literature Overview 2012). Visual phenomena are apparently more profound while the eyes are closed and not as common when the eyes are open (Ibogaine Scientific Literature Overview 2012). However, not all subjects experience visual phenomena, evidencing the inter-individual variation to dose and bioavailability (Ibogaine Scientific Literature Overview 2012).

Evaluative

Approximately 4 to 8 hours after ingestion, an evaluative state occurs which lasts approximately 8 to 20 hours (K R Alper et al. 1999)·(Ibogaine Scientific Literature Overview 2012). Patients experience less recall of visual images, while their focus is oriented at thoughts and experiences from the acute phase (K R Alper et al. 1999). This second state offers patients a general sense that is calm and introspective (K R Alper et al. 1999)·(Ibogaine Scientific Literature Overview 2012). Patients direct their thoughts toward their previous acute phase experience, and they may be easily distracted or annoyed by their ambient environment (Ibogaine Scientific Literature Overview 2012).

Residual Stimulation

After twelve to twenty-four hours have elapsed after taking a dose of ibogaine, patients may feel the effects of insomnia for a duration of 24 to 72 hours or longer (Ibogaine Scientific Literature Overview 2012). Patients begin to allocate a normal amount of focus to their surroundings, and the hallucinogenic aspect of the drug is reduced (Ibogaine Scientific Literature Overview 2012).

SAFETY

Despite the therapeutic benefits of ibogaine, reluctance to its use by medical professionals is primarily due to safety concerns (Lavaud and Massiot 2017). There are reports of several patients dying after ibogaine treatment, most likely due to neurotoxicity or cardiotoxicity (Lavaud and Massiot 2017). Abnormal activity has been observed neurologically in Purkinje cells and in the cardiovascular system as polymorphic ventricular tachycardia (PVT) including torsade de pointes (TdP) (Lavaud and Massiot

2017),(K. Alper et al. 2016),(Alburges, Foltz, and Moody 1995). A pattern among ibogaine patient fatalities is not present, and those who develop adverse effects often survive (Lavaud and Massiot 2017).

Neurotoxicity in Animal Models

Cerebellar Purkinje cells have been reported to degenerate in rodents that were administered an ibogaine dose of 100 mg/kg i.p. (O'Hearn and Molliver 1993),(O'Hearn and Molliver 1997). Alternatively, a different study reported no degeneration of cerebellar Purkinje cells with a 40 mg/kg i.p. dose, which is a strong enough administration to lessen the tendency of opioid self-administration/withdrawal in rodents (S D Glick et al. 1991),(S D Glick, Rossman, et al. 1992),(Molinari, Maisonneuve, and Glick 1996),(Cappendijk, Fekkes, and Dzoljic 1994). A 25 mg/kg dose was reported to have no-observable-adverse-effects (Xu et al. 2000). A study in which 10 mg/kg of ibogaine was given at an interval of two days for sixty days to rats did not report findings of neurologic injury (Helsley, Dlugos, et al. 1997). Biomarkers of cerebellar neurotoxicity specifically label neurologic injury with Ag, and Purkinje brain cells with antisera to calbindin (Xu et al. 2000). Most research reports that the cerebellum is highly vulnerable part of the brain to neurotoxic effects of ibogaine, but especially high doses may be neurotoxic to other brain regions (Ibogaine Scientific Literature Overview 2012). One study exposed rodents of both genders to either an "acute" schedule of giving ibogaine at 50, 100, or 150 mg/kg i.p. each day for three days or a "chronic" schedule of orally giving 25, 75, or 150 mg/kg administrations for 14 days (O'Callaghan et al. 1996). These rats were then monitored for signs of glial fibrillary acidic protein (GFAP), which

marks neuronal injury (Xu et al. 2000)·(O'Callaghan et al. 1996). The findings suggest that male and female rodents on the acute i.p. dosage schedule demonstrated an elevated GFAP (Ibogaine Scientific Literature Overview 2012)·(O'Callaghan et al. 1996). Cerebellar and hippocampal neurological changes were reported when a 50 mg/kg dose was administered, and in the cortex, hippocampus, olfactory bulb, brain stem, and striatum after a 100 mg/kg administration (Ibogaine Scientific Literature Overview 2012)·(O'Callaghan et al. 1996). The schedule of acute ibogaine administration no longer showed evidence of an effect after fourteen days with the two ibogaine dosage levels in rodents of male gender, and was only observed in the cerebellum with the 100 mg/kg dose in rodents of the female gender (O'Callaghan et al. 1996). No elevations of GFAP were found after seventeen days had elapsed since the end of any of the chronic dose administrations in all the parts of the brain that were investigated of male rodents (O'Callaghan et al. 1996). However, a different study found GFAP elevation, silver, or Fluoro-Jade markers of neurodegeneration in the cerebellum of male rodents given 100 mg/kg doses i.p (O'Hearn and Molliver 1993)·(Schmued, Albertson, and Slikker 1997; Schmued and Hopkins 2000)·(Scallet et al. 1996). A rise in GFAP was observed among rodents of female gender only in the hippocampus after a 25 mg/kg dose (O'Callaghan et al. 1996). At the 150 mg/kg dosage regimen elevations of GFAP were found in the hippocampus, olfactory bulb, striatum, and brain stem (O'Callaghan et al. 1996). The severity of neurologic damage after ibogaine treatment seems to depend greatly on the species of the animal (Ibogaine Scientific Literature Overview 2012). No observable signs of neurologic injury were found in primates over a period of repetitive 5 to 25

mg/kg oral or 100 mg/kg subcutaneous ibogaine administrations over a five day duration (D C Mash et al. 1998). The mouse also appears to be less sensitive, and shows no signs of cerebellar damage at a 100 mg/kg i.p. administration of ibogaine (Scallet et al. 1996).

Tremor in Animal Models

When ibogaine is given at doses of 10 mg/kg i.p. and 12 mg/kg s.c. tremor has been observed in rats and mice, respectively (Helsley, Fiorella, et al. 1997)·(Zetler, Singbartl, and Schlosser 1972). In rats, whole body tremors were observed within an hour after ibogaine treatment (S D Glick et al. 1991).The tendency of iboga alkaloids to be effective against opioid self-administration and produce tremor is not necessarily related (S.D. Glick et al. 1994). Enhancement of tremor is caused when a methoxy group is at position 10 or 11, and is reduced or non-existent when a carbomethoxy group is at position 16 (Ibogaine Scientific Literature Overview 2012)·(Zetler, Singbartl, and Schlosser 1972)·(Singbartl, Zetler, and Schlosser 1973). Ibogaine's main metabolite, noribogaine which does not have a methoxy group at position 10, did not produce tremors at a dose of 40 mg/kg i.p. (S D Glick, Pearl, et al. 1996). Similarly, 18-MC did not induce tremors when administered to rats at a dosage as high as 100 mg/kg (Ibogaine Scientific Literature Overview 2012). 18-MC also lacks a methoxy group at position 10, and has a carbomethoxy group at position 16 (S D Glick, Kuehne, et al. 1996).

Mechanisms of Neurotoxicity

Tremors and the potential for neurotoxicity accompany ibogaine's stimulant, ataxic, and hallucinogenic properties (S.D. Glick et al. 1994)·(O'Hearn and Molliver 1997). Ibogaine's potential toxicity appears to be caused by excessive glutaminergic input to

cerebellar Purkinje cells by sigma2 receptors in the olivocerebellar projection (O'Hearn and Molliver 1997)·(Belgers et al. 2016a). Simultaneous and excessive input leads to a continuous flow of glutamate at climbing fiber synapses on Purkinje cells, and their subsequent excitotoxic degeneration (S.D. Glick et al. 1994)·(O'Hearn and Molliver 1993)·(O'Hearn and Molliver 1997)·(O'Hearn, Zhang, and Molliver 1995). The synaptic redundancy of cerebellar Purkinje cells makes for a chance for excitotoxic damage (O'Hearn and Molliver 1997).

Sigma2 agonists such as ibogaine have also been shown to induce specific neurologic damage through the stimulation of apoptosis in cell cultures (O'Hearn and Molliver 1997). Therefore, ibogaine may have a combined direct neurotoxic and indirect excitotoxic effect, both effects being mediated by sigma2 receptors (O'Hearn and Molliver 1997).

Glial cell activation by ibogaine was previously found to cause death of Purkinje cells in narrow parasagittal bands (Figure. 7) (O'Hearn and Molliver 1993)·(O'Hearn and Molliver 1997). A neurotoxicity mechanism that is indirect to Purkinje cells and dependent on the olivocerebellar projection is supported by an experiment in which pharmacologic ablation of the inferior olive in rodents by the administration of a neurologically toxic administration of 3-acetylpyridine, almost completely prevented Purkinje cell death or glial stimulation (O'Hearn and Molliver 1993). Reduced cerebellar cell counts have been observed when high doses of ibogaine are administered, sometimes even weeks later (Belgers et al. 2016b)·(Belgers et al. 2016a). This finding is supported by experimental evidence of disappearance of Nissl-stained Purkinje cell bodies, loss of

neuronal microtubule-associated protein 2, and calbindin (O'Hearn and Molliver 1993). Interestingly, 18-MC, the synthetically produced compound that mimics ibogaine is not nearly as attracted to the sigma2 receptor, does not cause neurologic damage at increased dose levels, and offers comparative outcomes to ibogaine regarding opioid self-administration among rodents (S D Glick and Maisonneuve 1998)·(S D Glick, Kuehne, et al. 1996)·(S D Glick et al. 1998). Sigma2 receptors are apparently not related to the reduction in opioid self-administration (S D Glick and Maisonneuve 1998)·(S D Glick, Kuehne, et al. 1996)·(S D Glick et al. 1998). It seems that the neurologically damaging action of ibogaine can be separated from its therapeutic anti-addiction potential (S D Glick and Maisonneuve 1998)·(S D Glick, Kuehne, et al. 1996)·(S D Glick et al. 1998).

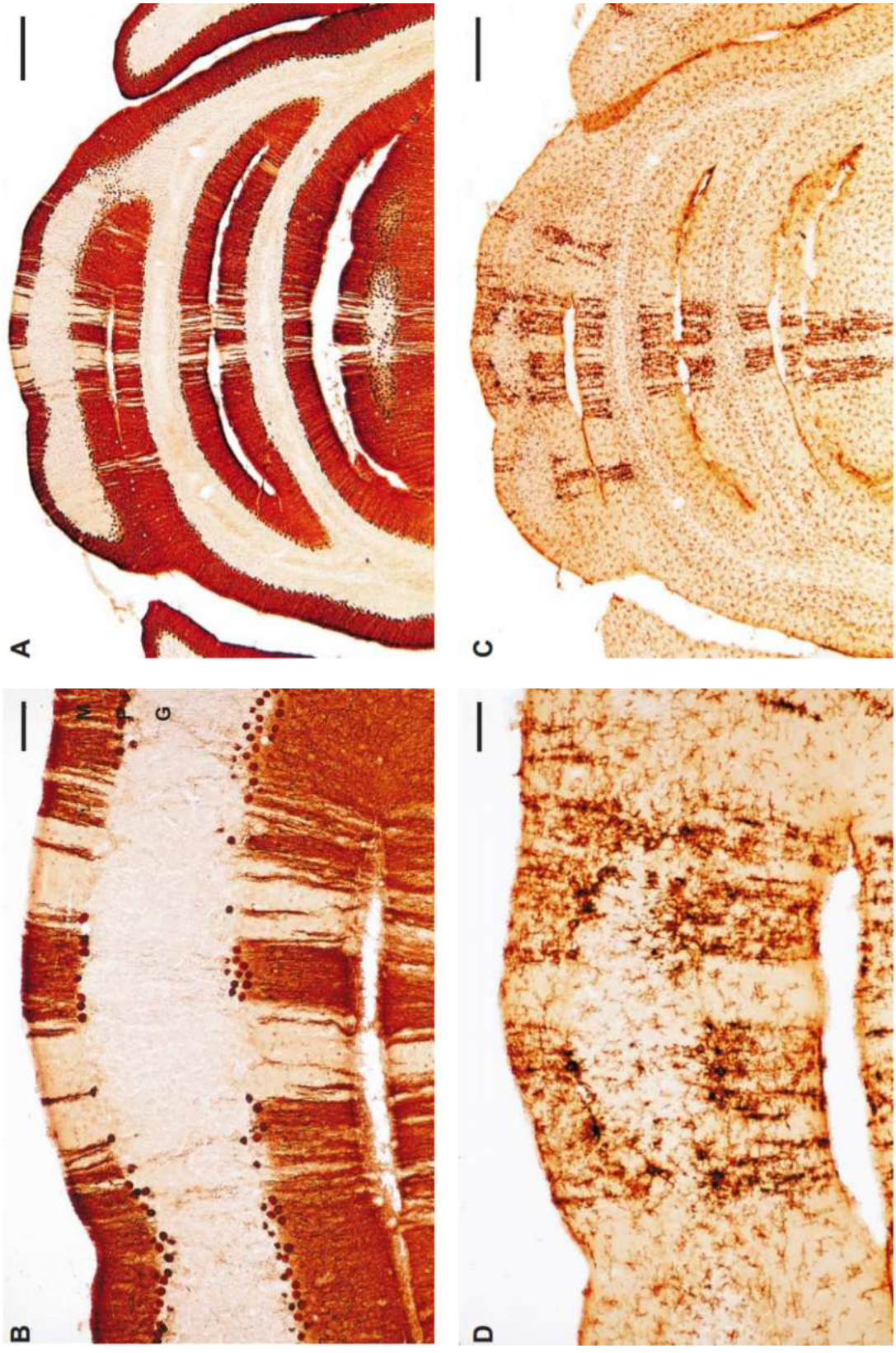

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Figure 7. Ibogaine causes degeneration of Purkinje cells and activation of microglia in discrete radial bands of cerebellar cortex. A, B, Purkinje cells of cerebellar vermis at low (A) and high (B) magnification seven days after receiving ibogaine (100 mg/kg once). Unstained gaps in the Purkinje cell and molecular layers indicate regions in which Purkinje cells have degenerated (Cam-kin II immunoreactivity, coronal sections). C, D, Clusters of activated microglial cells form darkly stained radial stripes within the cerebellar vermis, in sections adjacent to those showing Purkinje cells. The stripes containing activated microglia are approximately coextensive with regions of Purkinje cell loss (compare densely stained stripes in C with pale zones in A). The largest and most activated microglia are located in the Purkinje cell layer, where they are presumably phagocytizing a Purkinje cell body (D). Resting microglia are the small, lightly stained cells with fine processes in C and D that are widely distributed throughout all layers of cerebellar cortex and white matter. Microglia are immunoreactive with OX42, which recognizes the complement receptor 3B. Activated microglia are more intensely immunoreactive and have larger processes and cell bodies (D). M, Molecular layer; P, Purkinje cell layer; G, granule cell layer. Scale bars: A, C, 500 mm; B, D, 100 mm.(O'Hearn and Molliver 1997). Figure and description adapted from (O'Hearn and Molliver 1997).

Cardiovascular Toxicity

The most common cause of ibogaine related fatalities is due to adverse cardiovascular events, primarily cardiac arrhythmia (Brown and Alper 2017),(K. Alper et al. 2016). Clinical reports reveal that this arrhythmia is a result of ibogaine's increase of the QT interval and/or of PVT including TdP, in addition to bradycardia, which increases the risk of PVT (K. Alper et al. 2016),(Szumlinski, Maisonneuve, and Glick 2000). Both ibogaine and noribogaine cause blockages to the voltage-gated cardiac potassium channel of the human ether-a-go-go-related gene (hERG) which is probably responsible for drug-induced TdP (K. Alper et al. 2016),(Kannankeril, Roden, and Darbar 2010),(Sanguinetti and Tristani-Firouzi 2006). At the repolarization phase of the cardiac action potential, the rapid delayed rectifier current (IKr) is based on the potassium efflux through the hERG channel of the cardiac myocyte (K. Alper et al. 2016). If the hERG channel is blocked cardiac repolarization is blocked, and increased duration of the QT interval and PVTs, as

well as TdP will occur (K. Alper et al. 2016). QT prolongation and arrhythmia resulting from ibogaine treatment has reportedly persisted for days (K. Alper et al. 2016). Since the inhibition of hERG by ibogaine occurs at concentrations similar to that needed to produce the drug's intended effects, there is a risk of adverse cardiovascular events (K. Alper et al. 2016).

An ibogaine administration of 40 mg/kg i.p. reported no alteration in base level heart rate or blood pressure among animal models (Ibogaine Scientific Literature Overview 2012). When a larger sized administration of ibogaine (100 and 200 mg/kg) was given, the heart rate was reduced, but blood pressure remained unaffected (Ibogaine Scientific Literature Overview 2012). 18-MC did not result in any change in heart rate or blood pressure during administration of the experimental doses (Ibogaine Scientific Literature Overview 2012). Significant decreases in the heart rate of rodents administered ibogaine 50 mg/kg i.p. has been observed (Binienda et al. 1998).

In a 39 human subject study, participants that were either dependent on cocaine or heroin were monitored for cardiac function after receiving fixed p.o. doses of ibogaine of 500, 600, 800, or 1000 mg (Koenig and Hilber 2015). Six patients were found to have significantly decreased resting pulse rates with respect to baseline (Koenig and Hilber 2015). One patient was reported to have a major reduction in blood pressure due to a short-acting vasovagal reflex (Koenig and Hilber 2015). Careful evaluation for EKG abnormalities reported no appearance or intensification among subjects while ibogaine was administered (Koenig and Hilber 2015). No obvious life-threatening cases were observed through the conclusion of this study, and it was settled that ibogaine was

relatively safe when given as a single dose (Ibogaine Scientific Literature Overview 2012).

DISCUSSION

Ibogaine's action on Learning and Memory

Ibogaine's anti-addiction properties could be due to its potential alteration of the learning and memory aspects of addiction. Ibogaine's interaction with the NMDA receptor apparently greatly modifies addiction related neurology (Ibogaine Scientific Literature Overview 2012). The NMDA receptor is activated during learning which is critical for long-term potentiation (LTP), which plays a significant role in neural plasticity and memory (P Popik et al. 1995)·(P Popik, Layer, and Skolnick 1995)·(Wickelgren 1998)·(Di Chiara 1999)·(Noguès 1997). Neurological change induced by ibogaine is supported by a reduced place preference for morphine administration among rodents (Ibogaine Scientific Literature Overview 2012). Consistent with the specific actions of ibogaine for neuroadaptation after drug use is the reduced locomotor activity and dopamine efflux in animals with prior exposure to morphine (Pearl, Maisonneuve, and Glick 1996)·(Pearl, Johnson, and Glick 1995). In general, ibogaine appears to interfere with learning, but some studies actually show an enhancement by ibogaine (Helsley, Dlugos, et al. 1997)·(Kesner et al. 1995)·(P Popik 1996). Many ibogaine patients report experiences involving their memories, such as panoramic recall culminating in new perspectives about themselves and their behaviors (Ibogaine Scientific Literature Overview 2012). Human case studies report that a single treatment has been reported to have significant

changes for six months, and a set of four treatments could benefit patients for approximately three years (Szumlinski, Maisonneuve, and Glick 2000).

Safety Trials

In accordance with United States FDA safety trials, nine subjects given 1-2 mg/kg of ibogaine were studied for postural stability, body tremor, and appendicular tremor and were found to have only a statistically insignificant increase in body sway six hours since the administration of ibogaine (Ibogaine Scientific Literature Overview 2012),(D C Mash et al. 1998). After five to seven days had passed since the administration of ibogaine at a dosage between 10 to 30 mg/kg, ten patients demonstrated no abnormal findings on quantitative measures of static or dynamic posturography or hand accelometry, or on clinical neurologic exam (Ibogaine Scientific Literature Overview 2012),(D C Mash et al. 1998). However, preclinical ibogaine studies have shown evidence of neurotoxicity in animal models.

Potential for Abuse

Ibogaine has not been shown to have a great chance of recreational or other forms of abuse (Ibogaine Scientific Literature Overview 2012). Ibogaine does not appear to stimulate the 5-HT2A receptor, which is the main pathway for "hallucinogenic" or "psychedelic" drugs such as LSD (Helsley et al. 1998b),(Helsley et al. 1998a). Rodents administered either 10 or 40 mg/kg ibogaine each day for six consecutive days showed no evidence of withdrawal, reward or aversive behavior (Beardsley et al. 2004). During the

1995 Ibogaine Review Meeting, none of the consultants to NIDA made note of a safety concern regarding the chance for recreational abuse of ibogaine (Ibogaine Scientific Literature Overview 2012). This is not a surprising conclusion since ibogaine is rarely reported to be used recreationally.

Case Reports of Toxicity and Fatalities in Humans

Case reports and case series from human studies have reported instances of ataxia, gastrointestinal distress, ventricular arrhythmias and sudden and unexplained deaths of patients undergoing ibogaine therapy for opiate addiction (Schep et al. 2016). Ibogaine's complex actions on numerous neurological receptors and transporters makes it difficult to establish a well-defined toxicology profile (Schep et al. 2016). It is therefore difficult to identify appropriate and safe doses for humans (Schep et al. 2016). Experimental evidence implies that ibogaine induced death in rodents occurs when about 263 mg/kg body weight is administered orally (Schep et al. 2016). After accounting for interspecies variability, a conservative starting dosage given to patients was approximated at 0.87 mg/kg body weight (Schep et al. 2016).

A comprehensive study of all available autopsy, toxicological, and investigative ibogaine records for deaths outside of West Central Africa associated with ibogaine use during the 1990 - 2008 timeframe found that: nineteen individuals (15 men, four women between 24 and 54 years old) were reported to have died within 1.5–76 h of taking ibogaine (Kenneth R Alper, Stajić, and Gill 2012). A common characteristic of neurotoxicity or otherwise was not found after clinical and postmortem evaluation (Kenneth R Alper, Stajić, and Gill 2012). Preexisting medical comorbidities among the deceased were primarily

cardiovascular, and/or related to the presence of an abused substances in 12 of the 14 cases when enough postmortem data was provided (Kenneth R Alper, Stajić, and Gill 2012). An additional risk of seizure may be activated by the withdrawal from alcohol, benzodiazepines, or an unreported recent or concurrent use of ibogaine (Kenneth R Alper, Stajić, and Gill 2012). This highlights the need for better regulation of ibogaine rather than its criminalization. Opiate users who are unaware of the serious and potentially fatal aspects of ibogaine therapy may ignorantly use ibogaine in an unsafe or nonmedical setting. Ibogaine's unique set of side effects must be carefully considered on a case-by-case basis. Similar to a pre-operative exam before surgery, potential ibogaine patients should be evaluated before ibogaine therapy. Since most ibogaine related mortalities are related to cardiovascular failure, patient's cardiovascular health should be carefully evaluated. For these reasons, it is recommended that ibogaine be used in a medically competent setting with staff that is familiar with its effects. Morbidities and mortalities are likely to remain unless standardized dosage guidelines and evaluative procedures are established.

CONCLUSION

Substance use disorder such as opioid addiction is responsible for a major part of the global burden of disease (Belgers et al. 2016b). Nearly 5% of all disability-adjusted life years and 4% of overall mortality can be traced to SUDs (Belgers et al. 2016b). Opioid use, an SUD is commonly classified by its addictiveness and multiple relapses among those who attempt quitting (Belgers et al. 2016b). Despite traditional methods of treatment, 5-year relapse rates are as high as 97% for opioid addiction (Belgers et al.

2016b). Alternative or better forms of treating opioid addiction should be investigated and possibly adopted. Ibogaine shows evidence of numerous beneficial effects in preclinical studies of opioid addiction, such as the dampening of addiction responses evidenced by reduced dopamine release in the NAc (Ibogaine Scientific Literature Overview 2012). Animal models also offer evidence of reduced opiate withdrawal signs and reduced self-administration of many drug types including morphine, cocaine, alcohol, and nicotine (Ibogaine Scientific Literature Overview 2012). Ibogaine's therapeutic use is supported by consistency between both recent and old case report evidence for ibogaine's effectiveness at helping patients overcome opioid addiction and withdrawal (Luciano 1998),(Sheppard n.d.),(K R Alper et al. 1999)(D C Mash et al. 1998).

Ibogaine's complex pharmacological mechanism of action is due to its association with many neurotransmitter systems including NMDA, nicotinic, mu- and kappa-opioid, and serotonergic systems, all of which are potentially related to addiction (Ibogaine Scientific Literature Overview 2012). No single neurotransmitter system appears to explain the reported efficacy of ibogaine, and its persistent effects have been suggested to involve its principle metabolite noribogaine (Ibogaine Scientific Literature Overview 2012). There is also evidence for ibogaine's activation of a second messenger signal transduction cascade involving multiple neurotransmitter systems to produce persistent effects outlasting ibogaine or its metabolites (Ibogaine Scientific Literature Overview 2012). Despite this potential for successful anti-addiction therapy, ibogaine does possess evidence of neurotoxic properties. Careful consideration of patients should be conducted before they

are given ibogaine therapeutically. Patients should be given a through physiologic exam focused on determining whether there are any pre-existing conditions that may be aggravated by an ibogaine dose. Continued ibogaine research should emphasize the invention of ibogaine congeners that retain the apparent efficacy against drug dependence, but minimize unwanted toxic or psychological effects.

Ibogaine's use is often thought of as informal or related to a subculture, sometimes even retaining a sacramental context similar to its original use by the Bwiti of West Central Africa (Ibogaine Scientific Literature Overview 2012). This subculture is not explicitly preferred by ibogaine users and prescribers, but exists mainly due to a lack of official approval. The often informal treatment setting of ibogaine and the marginalizing social circumstance of addiction has diverted focus away from ibogaine's therapeutic benefits, instead focusing on criticism (Blatt et al. 1984), (Acker 1993). The United States currently faces an epidemic of opioid use and dependence, urging the development of novel and effective therapeutic options. Currently, ibogaine is not approved for use in the United States. Despite not being used to treat addiction and classified as a schedule I drug in the United States, patients seeking opiate addiction treatment may find legal and approved ibogaine therapy in countries such as Norway, Canada, and the U.K. Further investigation of ibogaine's ability to reduce opioid use, attenuate withdrawal symptoms and cease drug cravings is warranted.

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