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Article *in* Journal of Forensic Sciences · March 2012

DOI: 10.1111/j.1556-4029.2011.02008.x · Source: PubMed

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J Forensic Sci, March 2012, Vol. 57, No. 2
doi: 10.1111/j.1556-4029.2011.02008.x
Available online at: onlinelibrary.wiley.com

PAPER

TOXICOLOGY

Kenneth R. Alper,[1] *M.D.; Marina Stajić,*[2] *Ph.D.; and James R. Gill,*[3] *M.D.*

Fatalities Temporally Associated with the Ingestion of Ibogaine

ABSTRACT: Ibogaine is a naturally occurring psychoactive plant alkaloid that is used globally in medical and nonmedical settings for opioid detoxification and other substance use indications. All available autopsy, toxicological, and investigative reports were systematically reviewed for the consecutive series of all known fatalities outside of West Central Africa temporally related to the use of ibogaine from 1990 through 2008. Nineteen individuals (15 men, four women between 24 and 54 years old) are known to have died within 1.5–76 h of taking ibogaine. The clinical and postmortem evidence did not suggest a characteristic syndrome of neurotoxicity. Advanced preexisting medical comorbidities, which were mainly cardiovascular, and/or one or more commonly abused substances explained or contributed to the death in 12 of the 14 cases for which adequate postmortem data were available. Other apparent risk factors include seizures associated with withdrawal from alcohol and benzodiazepines and the uninformed use of ethnopharmacological forms of ibogaine.

KEYWORDS: forensic science, toxicology, ibogaine, iboga alkaloid, substance abuse, human, fatality, opioid, opioid detoxification, ethnopharmacology

The iboga alkaloids are a group of monoterpene indole alkaloids, some of which reportedly reduce the self-administration of drugs of abuse and opiate withdrawal symptoms in animal models and humans (1,2). Ibogaine (Fig. 1), the most extensively studied iboga alkaloid, occurs in the root bark of the West African Apocynaceous shrub *Tabernanthe iboga* Baill. In Gabon, eboga, the scrapings of the root bark, has been used as a psychopharmacological sacrament in the Bwiti religion for several centuries (3,4). Elsewhere, including North America, Europe, and South Africa, ibogaine is used for the purpose of acute opioid detoxification, and to reduce craving and maintain abstinence from opioids and other abused substances including stimulants and alcohol, as well as for psychological or spiritual purposes (5).

Ibogaine is used most frequently as a single oral dose in the range of 10–25 mg/kg of body weight for the specific indication of detoxification from opioids (5,6). It is most commonly used in the form of the hydrochloride (HCl), which certificates of analysis typically indicate is 95–98% pure, with present retail prices in the range of *c.* $125–$250 USD per gram. Ibogaine is also used in the form of alkaloid extracts or dried root bark (Fig. 2).

Ibogaine is a schedule I substance in the United States, and similarly is illegal in France, Denmark, Sweden, Belgium, Switzerland, and Australia. However, it is unregulated in most countries, where it is neither illegal nor officially approved. Lay providers administer ibogaine in nonmedical settings and have accounted for the majority of treatments (5). Ibogaine is administered in medical settings in countries such as Mexico and South Africa, where physicians have the legal prerogative to prescribe unapproved medications.

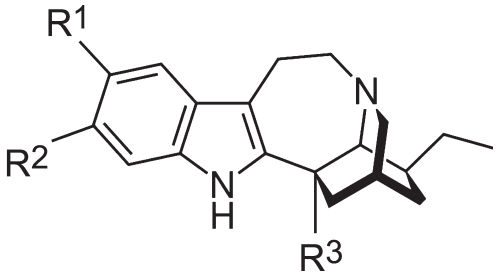
Published case series and individual accounts regarding ibogaine for opioid detoxification tend to be consistent with regard to rapid remission of acute withdrawal symptoms following a single administration that is subsequently sustained without further ibogaine treatment or the use of opioids (1,6,7). This effect of ibogaine appears to be pharmacologically mediated and not accounted for by placebo, which has clinically negligible effects in opioid detoxification (8–10). In the naloxone-precipitated withdrawal model of opioid detoxification, iboga alkaloids have attenuated opioid withdrawal signs in 13 of 14 independent replications in two rodent and two primate species (11–24). Ibogaine administered to rats or mice as a single dose reduces the self-administration of morphine (25–28), cocaine (26,29,30), and alcohol (31,32), with sustained treatment effects for 48–72 h averaged for an entire sample, and an even longer duration in individual animals (25,26,28,30). The serum half-life of ibogaine in the rat is *c.* 1–2 h (33,34), indicating that the prolonged effect on self-administration outlasts the presence of ibogaine itself, without compelling evidence that it is mediated by a long-lived metabolite (35).

Ibogaine does not appear to be an abused substance. The National Institute on Drug Abuse (NIDA) did not identify potential abuse as an issue in the context of its research program on ibogaine, which included preclinical testing and the development of a clinical trial protocol (1). Animals do not self-administer 18-methoxycoronaridine (18-MC), a closely structurally related ibogaine congener with the same effects as ibogaine on self-administration and withdrawal in preclinical models (36). Aversive side effects such as nausea and ataxia limit ibogaine's potential for abuse.

Ibogaine potentiates the lethality of opioids (33,37–39). This is apparently because of an enhancement of opioid signaling (1,40), and not because of binding at opioid receptors as an agonist (such

[1]Departments of Psychiatry and Neurology, New York University School of Medicine, 550 First Avenue, New York, NY 10016.
[2]Department of Forensic Toxicology, New York City Office of Chief Medical Examiner and Department of Forensic Medicine, New York University School of Medicine, 520 First Avenue, New York, NY 10016.
[3]New York City Office of Chief Medical Examiner and Department of Forensic Medicine, New York University School of Medicine, 520 First Avenue, New York, NY 10016.

Received 28 July 2010; and in revised form 17 Nov. 2010; accepted 20 Nov. 2010.



Iboga alkaloid	R^1	R^2	R^3
Ibogaine	OCH_3	H	H
Noribogaine	OH	H	H
Ibogamine	H	H	H
Ibogaline	OCH_3	OCH_3	H
Tabernanthine	H	OCH_3	H
Voacangine	OCH_3	H	CO_2CH_3

FIG. 1—*Chemical structures of ibogaine and its major metabolite noribogaine, and the alkaloids ibogamine, ibogaline, tabernanthine, and voacangine that co-occur with ibogaine in* T. iboga. *In the Chemical Abstracts system the positions of R^1, R^2, and R^3 on the ibogamine parent structural skeleton are respectively numbered 12, 13 and 18, whereas in the Le Men and Taylor system these same positions are numbered 10, 11 and 16.*

as methadone) or antagonist. Doses of ibogaine used in opioid detoxification do not produce signs of overdose in individuals who lack tolerance to opioids, such as African Bwiti adepts, or individuals in non-African contexts who take ibogaine for psychological or spiritual purposes or the treatment of addiction to substances other than opioids. If ibogaine was acting as an opioid agonist, it would not be tolerated by opioid-naïve individuals because the methadone dosage of 60–100 mg/day that is used to stabilize withdrawal symptoms in the maintenance treatment of opioid-dependent patients (41) substantially exceeds the estimated LD_{50} of 40–50 mg in humans who are not pharmacologically tolerant to opioids (42). Other evidence that ibogaine alters signaling through opioid receptors but is not itself an orthosteric agonist includes its potentiation of morphine analgesia in the absence of a direct analgesic effect (22,38,39,43–47). Ciba Pharmaceutical patented the use of ibogaine to reduce tolerance to opioid analgesics in 1957 (47).

Although ibogaine contains an indole ring and is designated as a "hallucinogen," it is pharmacologically distinct from the "classical" hallucinogens such as LSD, mescaline, or psilocybin, which are thought to act by binding as agonists to the serotonin type 2A ($5\text{-}HT_{2A}$) receptor (48). Serotonin agonist or releasing activity does not appear to explain ibogaine's effects in opioid withdrawal (2,49). There is no anecdotal or preclinical evidence for a significant effect of classical hallucinogens in acute opioid withdrawal, and in the animal model ablation of 90% of the raphe, the major serotonergic nucleus of the brain does not significantly affect the expression of opioid withdrawal (50). Descriptions of subjective experiences associated with ibogaine differ from those associated with the classical hallucinogens (5,48,51). The visual effects of classical hallucinogens are typically most strongly experienced with the eyes open and limited to alterations of colors, textures, and patterns. In contrast, the psychoactive state associated with ibogaine is experienced most intensely with the eyes closed and has been described as "oneiric" and likened to a "waking dream," with

FIG. 2—*Forms of availability of ibogaine: Ibogaine is available in form of the hydrochloride (HCl) dried root bark, or alkaloid extract. The upper left photo shows 96% pure ibogaine HCl in the form of powder in the upper left quadrant of the photo. In the lower left quadrant of the photo are five capsules. The four lighter colored capsules contain 96% pure ibogaine HCl; the smaller two contain 120 mg and the larger two contain 250 mg respectively. The largest capsule is darker and contains 330 mg of 85% ibogaine HCl. In the lower right quadrant of the photo is ground dried root bark. The upper right photo shows alkaloid extract with an estimated total iboga alkaloid content of about 40–50%. The lower photo shows a partially scraped dried* Tabernanthe iboga *root, with external bark layer, an inner bark layer, and wood. The alkaloid content is mainly concentrated in the inner root bark layer, which is exposed along the lower border of the bare wood in left middle portion of the photo (photos courtesy of Robert Bovenga Payne and Rocky Caravelli).*

interrogatory verbal exchanges involving ancestral and archetypal beings, and movement and navigation within visual landscapes. Another frequently described experience is panoramic memory, the recall of a rapid, dense succession of vivid autobiographical visual memories. Mechanistically, these subjective experiences associated with ibogaine might possibly suggest functional muscarinic cholinergic effects, which are prominent in the mechanisms of dreaming and memory (52). In animals, ibogaine is reported to enhance spatial memory retrieval (53,54), and to produce an atropine-sensitive EEG rhythm (55,56), commonly regarded as a model of REM sleep (57).

Ibogaine's highest affinity receptor interactions are as an agonist at the σ_2 receptor, and an antagonist at the *N*-methyl-D-aspartate-type (NMDA) glutamate and $\alpha 3\beta 4$ nicotinic acetylcholine receptors (1,2,58). Initially, ibogaine's mechanism of action in drug self-administration and withdrawal was hypothesized to involve NMDA receptor antagonism (59); however, this hypothesis is now viewed as unlikely because the synthetic ibogaine congener 18-MC has negligible NMDA receptor affinity but is equally effective as ibogaine in reducing withdrawal and self-administration in the animal model (2). Studies of iboga alkaloids and nicotinic agents (60–64) provide some support for antagonism of the $\alpha 3\beta 4$ nicotinic receptor as a possible mechanism of action with regard to drug craving and self-administration but do not appear to explain detoxification in the setting of extensive physical dependence on opioids. Likewise, the increased expression of glial cell-derived neurotrophic factor may mediate reduction in drug craving and self-administration (32) but does not explain ibogaine's effect in opioid detoxification.

Ibogaine was administered to human subjects in a clinical Phase I dose escalation study under a physician-initiated Investigational New Drug Application approved by the FDA in 1993 (65). The study was eventually discontinued because of disputes related to contractual and intellectual property issues (66); however, the available safety data indicated no adverse events (65). Most of the available preclinical pharmacological, toxicological, and pharmacokinetic data on ibogaine are derived from research supported by NIDA between 1991 and 1995. NIDA eventually ended its ibogaine project without having initiated a clinical trial apparently because of its high cost and complexity relative to NIDA's existing resources (1). Ibogaine's underlying structure cannot be patented because it is naturally occurring, which limits the financial incentive for its development. Ibogaine continues to be used in unregulated contexts with associated risks because of a lack of clinical and pharmaceutical standards (5).

Deaths have occurred temporally related to the use of ibogaine. This article presents a systematic review of all available autopsy, toxicological, and investigative reports on the consecutive series consisting of all known fatalities temporally related to the use of ibogaine that have occurred outside of West Central Africa from 1990 through 2008.

Materials and Methods

The Institutional Review Board of the New York University School of Medicine and the General Counsel of the New York City Office of Chief Medical Examiner (OCME) approved this research.

Identification of Cases

This series spans the time interval beginning with the first reported fatality in 1990 (1) until December 2008. Eighteen of the 19 fatalities in this series were found through contact with ibogaine treatment providers since the mid-1990s (5,6,67,68). One of these fatalities was also investigated by the OCME (69) as are all unexpected, violent, and suspicious deaths in New York City. One fatality was found by literature search (70). The ethnographic methodology and access to the network of the providers of ibogaine treatment and other participants in the ibogaine subculture are described in detail elsewhere (5,67).

All fatalities were followed up by contact with appropriate medico-legal death investigation agencies to obtain all available autopsy and toxicology reports, inquest testimony, and other investigative reports. In addition to documentary evidence, in most instances, treatment providers and other first-hand observers of the death scene were interviewed. Systematic evaluation of the literature included Medline searches from 1966 to June 2010 utilizing PubMed and ISI Web of Knowledge with the search terms "ibogaine" combined with "death" or "fatality" in addition to searches of periodical and nonindexed "grey" literature as described elsewhere (5,67).

Analytical Toxicology

Various methodologies for toxicological analysis of ibogaine (molecular weight 310.44) have been previously described, including liquid chromatography with flourimetric detection (71), gas chromatography/mass spectrometry (GC/MS) (72–76) liquid chromatography/mass spectrometry (LC-MS) (70,75,77–80), and liquid chromatography-tandem mass spectrometry (LC-MS/MS) (81–83). There is a potential for confusion because of the use of two different schemes for numbering the iboga alkaloid parent ibogamine skeleton (84), the *Chemical Abstracts* system, which is common in the biological and medical literature, and the Le Men and Taylor system, which tends to be favored by natural products and synthetic chemists and is also frequently encountered in the biological literature (see Fig. 1).

Ibogaine screening usually is not included in most routine forensic toxicological laboratories and a suspicion of use is required for analysis, which is typically performed by a referral laboratory. For two fatalities in this series (cases #3 and #10 in Table 1), the Forensic Toxicology Laboratory at the OCME performed the analysis. The presence of ibogaine was confirmed by GC/MS and the concentration determined using GC with a nitrogen phosphorus detector (69).

Cause of Death

The certified cause of death is included in Table 1, entitled "Official cause of death." The certified cause of death is that which is indicated by the official documentation, that is, autopsy report or death certificate, by the local authority that investigated and recorded the death. The available documentation varied greatly with regard to investigative rigor, level of detail, and geographic location of the official entity that issued the report. As an approach to controlling for this variance, a coauthor (JRG, a board-certified forensic pathologist) made a determination regarding the cause of each death on the basis of all available data, which in addition to the official documentation, included any information that was provided by treatment providers and other first-hand observers of the death scene, or friends and acquaintances of the decedent. Table 1 provides the conclusions of this systematic, critical evaluation of all available evidence in the far right-hand column entitled "Proximate cause of death."

The cause of death is defined as the original, etiologically specific, underlying medical condition that initiates the lethal sequence

TABLE 1—*Worldwide known fatalities outside of West Central Africa temporally associated with the ingestion of ibogaine, 1990–2008.*

	Age/Gender, Reason for Ibogaine Use	Country	Year	Circumstance	Time Interval from Most Recent Ingestion of Ibogaine Until Death	Ibogaine Form, Dose	Ibogaine (Blood, mg/L or mg/kg)	Other Toxicology (mg/L)	Other Autopsy or Historical Findings	Official Cause of Death	Proximate Cause of Death
1	44 F Psychological/ spiritual (1)	France	1990	Witnessed to become unresponsive during treatment	4 h	Ibogaine HCl 300 mg (*c.* 4.5 mg/kg)	0.24 Liver: 0.17 Kidney: 0.3	Negative	Hypertension; prior left ventricular myocardial infarct, marked 3-vessel coronary artery atherosclerosis, inverted T waves noted on EKG 3 months prior to death	Acute heart failure (autopsy)	Acute ibogaine intoxication. Contributing conditions: atherosclerotic and hypertensive cardiovascular disease
2	24 F Opioid detoxification (6)	Netherlands	1993	Died during ibogaine treatment; gurgling sounds	19 h	Ibogaine HCl 29 mg/kg	Cardiac: 0.74 Femoral vein: 0.75	Morphine: ''trace'' <0.01 Noribogaine: Cardiac: 11.28 Femoral vein: 3.96	Charred tin foil found in room	Undetermined; role of ibogaine unknown due to lack of information relating levels to toxic effects (autopsy)	Acute intoxication due to the combined effects of ibogaine and morphine
3	36 M Opioid detoxification, cocaine dependence (69)	USA	1999	Found dead at home. A syringe found near body	8–9 h	Ibogaine HCl; believed to be 16–20 mg/kg	Subclavian vein: 9.3 Brain: 18.6 Liver: 18.1	Benzoylecgonine: 0.6 Opiates: 0.1 (Morphine: <0.1)	Depression, adverse life events prior to treatment; decedent was aware of dangers of use of cocaine or heroin concurrently with ibogaine	Acute intoxication due to the combined effects of opiates, cocaine, and ibogaine (autopsy)	Acute intoxication due to the combined effects of opiates, cocaine, and ibogaine
4	40 M Opioid detoxification	United Kingdom	2000	Died in bathroom; vomited immediately prior to death	40 h	*Tabernanthe iboga* alkaloid extract 6 g administered over *c.* 6 h	0.36	Other toxicology: negative Noribogaine: detected Ibogamine: detected	Hepatitis C with liver fibrosis, pulmonary and cerebral edema	Fatal reaction to *Tabernanthe iboga* preparation. Contributing condition: Hepatitis C (autopsy)	Acute ibogaine intoxication
5.	35 F Psychological/ spiritual	Germany	2002	Found dead in bed (complained of not feeling well the day before)	1.5 h	Ibogaine HCl 500 mg (*c.* 8 mg/kg)	Unknown	Unknown	Childhood heart surgery congenital, moderate coronary artery atherosclerosis	Heart failure/ intoxication (autopsy)	Acute ibogaine intoxication (unknown if other drugs involved). Contributing conditions: atherosclerotic cardiovascular disease

Continued.

TABLE 1—*Continued.*

	Age/Gender, Reason for Ibogaine Use	Country	Year	Circumstance	Time Interval from Most Recent Ingestion of Ibogaine Until Death	Ibogaine Form, Dose	Ibogaine (Blood, mg/L or mg/kg)	Other Toxicology (mg/L)	Other Autopsy or Historical Findings	Official Cause of Death	Proximate Cause of Death
6.	32 M Opioid detoxification (self-administered by opiate abuser)	USA	2003	Found dead in bed at his residence	Unknown	Bag of brown powder at scene that tested positive for ibogaine (alkaloid extract vs powdered dried root bark)	Cardiac: 0.95 Femoral vein: 1.5 Liver: 8.0 Urine: 26 Vitreous: 0.54 Gastric: 2.9 Bile: 0.54	Benzoylecgonine 0.1 Methadone: <0.1 Nordiazepam: <0.1	Moderate coronary artery atherosclerotic stenosis. History of opiate abuse, and had been in methadone maintenance treatment at time of death	Ibogaine intoxication. Contributing conditions: atherosclerotic cardiovascular disease, cocaine use (autopsy)	Acute ibogaine intoxication. Contributing conditions: atherosclerotic cardiovascular disease, chronic cocaine abuse
7	54 M Opioid detoxification, alcohol dependence	Mexico	2003	Died at ibogaine treatment facility	60 h	Ibogaine HCl 13 mg/kg	Unknown	Unknown	Obesity, chronic alcoholism, smoker (unclear if autopsy was performed; report unavailable)	Pulmonary thromboembolism (death certificate)	Insufficient information
8	45 M Opioid detoxification, alcohol dependence	Mexico	2004	Died at ibogaine treatment facility	20 h	Ibogaine HCl 15 mg/kg	Unknown	Unknown	Chronic alcoholism, obesity, cardiac pacemaker	Acute hemorrhagic pancreatitis. Contributing conditions: Chronic alcoholism, obesity, opiate pain medication dependency (autopsy)	Acute hemorrhagic pancreatitis (during ibogaine treatment) complicating chronic alcoholism
9	48 F Opioid detoxification	Mexico (autopsied in the US)	2005	Died at ibogaine treatment facility	2 days	Ibogaine HCl 14 mg/kg	0.82 Liver: 0.72	Diazepam: 0.06 Oxazepam: 0.39 Temazepam (trace)	Prior gastric bypass surgery with 135 lb weight loss in 8 months preceding death. Fibromyalgia, benzodiazepine dependence that was not disclosed to treatment providers	Sudden cardiac death due to acute myocardial infarct due to acute coronary syndrome. Contributing conditions: Fibromyalgia, chronic pain medication dependency (autopsy)	Acute myocardial infarct due to coronary artery atherosclerosis during ibogaine therapy for opiate dependence complicating chronic fibromyalgia

Continued.

TABLE 1—*Continued.*

	Age/Gender, Reason for Ibogaine Use	Country	Year	Circumstance	Time Interval from Most Recent Ingestion of Ibogaine Until Death	Ibogaine Form, Dose	Ibogaine (Blood, mg/L or mg/kg)	Other Toxicology (mg/L)	Other Autopsy or Historical Findings	Official Cause of Death	Proximate Cause of Death
10	43 M Opioid detoxification, alcohol dependence	USA	2005	Witnessed cardiac arrest during self-administered ibogaine treatment. Witnessed apparent generalized tonic-clonic seizure 17 h after ibogaine ingestion	27 h	Ibogaine HCl, dose unknown	2.8	Diazepam: 0.03 Trimetho-benzamide: 0.85 Benzoylecgonine: detected Ibogamine, ibogaline: detected	Dilated cardiomyopathy, coronary artery atherosclerosis, pulmonary edema Hepatitis B	Valvular heart disease. Contributing conditions: Dilated cardiomyopathy (autopsy)	Acute ibogaine intoxication. Contributing conditions: Mitral insufficiency with dilated cardiomyopathy
11	51 M Opioid detoxification, methamphetamine and alcohol dependence	Mexico	2005	Died at ibogaine treatment facility	24 h	Ibogaine HCl 12 mg/kg	Unknown	Unknown	Autopsy not performed	Cardiorespiratory arrest due to acute myocardial infarction (death certificate, clinical diagnosis of attending physician)	Insufficient information
12	38 M Opioid detoxification	Mexico	2006	Died at ibogaine treatment facility. Found dead within 1 h of having last been seen alive	12 h	Ibogaine HCl 13 mg/kg	Unknown	Cocaine and morphine metabolites	Cutaneous abscesses, hepatitis. Autopsy was done, but inadequate for determination of a proximate cause of death	Pulmonary thromboembolism (death certificate)	Insufficient information
13	48 M Unknown (70)	France	2006	Ingested root bark of *Tabernanthe iboga* followed by vomiting and dyspnea	53 h	18 ''soup-spoons'' of a mixture of powdered *Tabernanthe iboga* root bark and sweetened condensed milk over 10 h	Vena cava: 6.6 Femoral vein: 5.4 Brain: 12.5 Liver: 40.5	Other toxicology: negative Noribogaine: Vena cava: 15.5 Femoral vein: 5.6 Brain: 18.7 Liver: 50.5 Ibogamine: detected	Pulmonary edema. Buprenorphine tablets and ''different objects and burned-out parts of plants found at the death scene suggested that some sort of esoteric ritual may have taken place.'' History of substance abuse	Acute ibogaine intoxication (autopsy)	Acute ibogaine intoxication (unknown if other drugs involved)

Continued.

TABLE 1—*Continued.*

	Age/Gender, Reason for Ibogaine Use	Country	Year	Circumstance	Time Interval from Most Recent Ingestion of Ibogaine Until Death	Ibogaine Form, Dose	Ibogaine (Blood, mg/L or mg/kg)	Other Toxicology (mg/L)	Other Autopsy or Historical Findings	Official Cause of Death	Proximate Cause of Death
14	28 M Opioid detoxification	The Netherlands	2006	Fluctuating level of consciousness following immersion in a warm bath for a 4-h period prior to death. Subject was observed and at no time was his head underwater, ruling out drowning	76 h	*Tabernanthe iboga* alkaloid extract, 7.5 grams over *c.* 18 h	Unknown	Quantitative toxicology results not available but ibogaine and cannabinoid concentrations reportedly "low." Negative for other drugs of abuse and ethanol	Choroid plexus papilloma involving hippocampus with hypoxic damage to hippocampus. Large duodenal ulcer with accumulation of blood in duodenum	Not conclusive regarding proximal cause of death. Possible causal and/or contributing factors were hemorrhagic complications of duodenal ulcer, increased intracranial pressure resulting from obstruction of third ventricle, and/or partial seizures originating from the temporal lobe "Toxicological cause not likely" (autopsy)	Hemorrhagic complications of duodenal ulcer
15	30 M Opioid detoxification	South Africa	2006	"Gurgling sounds" on expiration. Died en route to hospital after appearing to respond to resuscitative efforts	8 h	Ibogaine HCl 17 mg/kg (1.75 g) Single dose	Not tested	Not tested	Autopsy not performed	"Cardio-respiratory collapse secondary to drug related illness" (death certificate)	Insufficient information
16	27 M Unknown	France	2006	Discovered dead in meditation room at a center oriented toward psychological/spiritual use	≤20 h	Powdered root bark (7.2% ibogaine, 0.6% ibogamine). The actual amount ingested was not provided in the report. The medical examiner estimated 13 teaspoons at 1.5-g dried bark/teaspoon would have been required to achieve the measured ibogaine blood concentration	Peripheral blood immediately following death: 0.65 Peripheral blood at autopsy 8 days following death: 1.27	Peripheral blood immediately following death: Methadone: 0.077 Diazepam: 0.413 Oxazepam: 0.09 Temazepam: 0.04 Ibogamine: 0.05 Peripheral blood at autopsy 8 days following death: Ibogamine: 0.10	History of dependence on multiple substances including crack cocaine, benzodiazepines, and alcohol	Drug overdose due to ibogaine, methadone, diazepam, and temazepam (autopsy)	Acute intoxication due to the combined effects of ibogaine, methadone, and diazepam

Continued.

TABLE 1—*Continued.*

	Age/Gender, Reason for Ibogaine Use	Country	Year	Circumstance	Time Interval from Most Recent Ingestion of Ibogaine Until Death	Ibogaine Form, Dose	Ibogaine (Blood, mg/L or mg/kg)	Other Toxicology (mg/L)	Other Autopsy or Historical Findings	Official Cause of Death	Proximate Cause of Death
17	45 M Opioid detoxification	USA	2006	Found dead in bed following ibogaine treatment at a private residence	8–12 h	Ibogaine HCl 22 mg/kg	1.4	Diazepam: 77 ng/ml Fentanyl: 1.2 ng/ml Norfentanyl: 1.5 ng/ml Qualitative urine screen detected Oxycodone, Alpha-hydroxyalprazolam, Oxazepam, Temazepam, Ephedrine/ pseudo-ephedrine	Hepatic steatosis	Mixed drug intoxication (autopsy)	Acute intoxication due to the combined effects of ibogaine, fentanyl, and diazepam
18	33 M Opioid detoxification, crack cocaine dependence	Mexico	2007	Died at ibogaine treatment facility	6.5 h	Ibogaine HCl 11 mg/kg	Not tested	Not tested. History of having been caught using crack cocaine in the bathroom during a prior admission to the clinic	Family history of pulmonary thromboembolism in patient's father. Autopsy was done, but inadequate for determination of a proximate cause of death	Pulmonary thromboembolism (death certificate, clinical diagnosis of attending physician present at time of death)	Insufficient information
19	41 M Opioid detoxification, cocaine dependence	Mexico (autopsied in the US)	2007	Died at ibogaine treatment facility. Developed shortness of breath and became unresponsive during ibogaine treatment	6 h	Ibogaine HCl 13 mg/kg (1080 mg)	Not tested	Not tested	Cardiac hypertrophy Triglycerides: 397 mg/dL	Fatal arrhythmia during drug addiction treatment with cardiac hypertrophy (autopsy)	Acute ibogaine intoxication (unknown if other drugs involved). Contributing conditions: Cardiac hypertrophy

of events (85). A competent cause of death includes the proximate (underlying) cause, defined as that which in a natural and continuous sequence, unbroken by any efficient intervening cause, produces the fatality and without which the end result would not have occurred. Contributing conditions were additional disorders contributory to death but unrelated to the underlying cause of death.

The conclusion that death was caused by an acute intoxication requires that three conditions be met: the toxicological results are within the range typically encountered in such fatalities, the history and circumstances are consistent with a fatal intoxication, and the autopsy fails to disclose a disease or physical injury that has an extent or severity inconsistent with continued life (86). In deaths caused by drug intoxication with more than one drug in concentrations greater than trace amounts, it is customary to include all of the identified drugs in the cause of death.

Results

We report a summary of 19 ibogaine-associated deaths that have occurred worldwide between 1990 and 2008 including the probable causes of death based on the available clinical and pathologic information (see Table 1). There were 15 men and four women with a mean age of 39.1 ± 8.6 years ranging from 24 to 54 years. In 18 decedents, the estimated time intervals were available from the most recent ingestion of ibogaine in any form until death, and the mean interval was 24.6 ± 21.8 h and ranged from 1.5 to 76 h. In one other fatality (case #6) the time interval between death and the time when the decedent was last noted to be alive was 20 h, the decedent had been dead for at least several hours at the time the body was found. The time interval from the most recent ingestion of ibogaine until death in this instance was likely less than 76 h, but it was not included in the calculation of the mean interval.

Fifteen individuals took ibogaine for the indication of opioid detoxification, four of who were also dependent on alcohol, three on cocaine, and one on methamphetamine. Two individuals used it for a spiritual/psychological purpose and had no known substance abuse history, and two took it for unknown reasons but had a history of substance abuse. Ibogaine was given as the HCl form in 14 instances, as an alkaloid extract in two (cases #4 and #14), dried root bark in two (cases #13 and #16), and a brown powder that was probably either root bark or alkaloid extract in another (case #6). In the 12 fatalities where ibogaine was given as the HCl and a dose was reported, the mean dose was 14.3 ± 6.1 mg/kg (range 4.5–29 mg/kg). In the 10 fatalities in which ibogaine blood concentrations were determined, the mean was 2.38 ± 3.08 mg/L (range 0.24–9.3 mg/L), obtained at a mean of 25.5 ± 17.8 h following the ingestion of ibogaine (range 4–53 h). In addition, commonly abused drugs (including benzodiazepines, cocaine, opiates, and methadone) were detected in eight of 11 decedents on whom toxicological analysis for abused substances was performed.

Twelve of the decedents had medical comorbidities including liver disease, peptic ulcer disease, brain neoplasm, hypertensive and atherosclerotic cardiovascular disease, and obesity. Among the three decedents in which no other drugs of abuse were detected in postmortem toxicology analysis, one had advanced heart disease and another had liver fibrosis. Full toxicology and autopsy results were not available in eight and five decedents, respectively.

Discussion

In this series, 19 deaths occurred between 1990 and 2008, with an interval of 76 h or fewer between the most recent ingestion of ibogaine and death. In 14 instances, an autopsy was performed that allowed the determination of the proximate cause of death. The lack of clinical and pharmaceutical controls in settings in which ibogaine has been given, and the limited data regarding toxic concentrations of ibogaine in humans make the determination of the causes of these deaths difficult. Nonetheless, advanced comorbidities and contributing conditions appear to include preexisting medical, particularly cardiovascular disease, and drug use around the time of treatment.

This series of fatalities is consecutive in the sense that it represents a systematic application of an intensive methodology for identifying cases over the time interval spanned by this study. It is possible that additional fatalities may have occurred which were missed by death investigation agencies and this study. In the United States, this could relate to the surreptitiousness regarding the use of ibogaine because of its status as a schedule I substance, and individuals aware that ibogaine was used in temporal association with a fatal outcome might be reluctant to disclose that history. Without investigative information about the recent use of ibogaine, specialized analysis for ibogaine may not be performed. Under these circumstances, the cause of death of an individual treated with ibogaine for a substance use indication could be certified as a typical multidrug intoxication, particularly in view of the likelihood of detecting other drugs of abuse in these deaths. In most of the world, however, ibogaine is not illegal. In this series, outside of the United States, ibogaine was not illegal at the time of occurrence of the fatality in any country in which the fatality occurred.

In at least five instances, providers contacted the first author immediately regarding the death, and in a number of others, another individual close to the provider relayed the information, usually with the provider's consent. Their motivation to disclose this information included the wish to understand the causality of the death and prevent a future occurrence, abreaction regarding a traumatic event, and anxiety regarding legal liability. In a country in which ibogaine is not illegal, however, concealing its use is not necessarily perceived to be, or actually safer than disclosing it. Regardless of their distress regarding a death, experienced treatment providers such as those in Mexico or the Netherlands were aware that they did not face significant legal consequences. In a prior study by the first author of this article that surveyed the settings and extent of ibogaine use (5), it was estimated that 20–30% of the actual total number of ibogaine treatments had been missed by that study. Six of the series of 19 fatalities in this article occurred in settings and circumstances that are likely to have otherwise been hidden from the medical ethnographic study mentioned previously (5). While it is likely that some deaths temporally related to the use of ibogaine escaped inclusion in this series, it is also possible that treatments that are associated with a fatal outcome may come to attention relatively more frequently than those that are not.

For the purpose of this discussion, the terms "proximate cause" and "contributing condition" are used as they are defined previously in the methods section and appear in the extreme right-hand column of Table 1. A striking factor in this series of deaths is the identification of a comorbidity or intoxication (in addition to ibogaine) that could adequately explain or contribute to the death in 12 of 14 decedents that have adequate postmortem data. There are multiple possible pathways by which ibogaine may cause or contribute to death in these instances and include toxicological interactions with substances of abuse and direct cardiac effects.

Cardiac disease was a contributing condition or proximate cause in six deaths, suggesting cardiac mechanisms are an important mediator of fatal outcomes. Although preclinical toxicological testing by NIDA did not indicate prolongation of the QT interval (87),

it has been observed during ibogaine treatments with continuous EKG monitoring (88). Blockade of the potassium voltage-gated ion channel encoded by the human ether-a-go-go-related gene (hERG) is regarded as the most common cause of drug-related QT prolongation (89,90), which is associated with torsades de pointes (TdP), a morphologically distinctive polymorphic ventricular tachycardia. The effect of ibogaine differs from that of the hERG channel antagonist WAY-123.398 in studies of chromaffin cells (91–93); however, ibogaine is an hERG channel antagonist in the low micromolar range in human embryonic kidney tsA-201 cells (94). Ibogaine has low micromolar affinity for sodium channels (2,95,96), which might also possibly relate to cardiac risk in view of the possible association of sodium channel blockade with slowing of intraventricular conduction and the subsequent development of a re-entrant circuit resulting in ventricular tachyarrhythmia (89,97), and there is evidence for altered sodium channel functioning in some drug-induced forms of long QT syndrome (98–101).

QT prolongation is also regarded as a general correlate of cardiac instability that is associated with arrhythmias other than TdP (89,102,103), and with multiple risk factors relevant to the present study including bradycardia, coronary artery disease, dilated cardiomyopathy, recent myocardial infarction, ventricular hypertrophy, and liver disease (89,104). Bradycardia has been reported in humans in association with the ingestion of ibogaine in medical (88,105) and nonmedical (106) settings, and in some preclinical studies (33,36,107,108). The frequently altered nutritional status of substance abusers puts them at risk of hypomagnesemia and hypokalemia (90), which are associated with QT prolongation, as are bulimia and anorexia (109). Methadone is associated with QT prolongation, particularly in the presence of other drugs (110). Alcohol or cocaine use is associated with prolongation of the QT interval both acutely (111,112) and during withdrawal (113–115). In patients with alcohol dependence, QT prolongation has been observed to persist for 7 days after the last intake of alcohol (116), and withdrawal seizures contribute further independent and additive risk (114). Epileptic seizures, even in the absence of substance use or withdrawal, are an independent risk factor for QT prolongation (117).

A case report of QT prolongation and ventricular arrhythmia in association with the ingestion of *T. iboga* alkaloid extract (118) illustrates the variety of potential arrhythmogenic factors in the clinically uncontrolled settings in which ibogaine has been used. The patient survived in that case, which is not included in this present series. The patient had taken "Indra," an apocryphal brand of alkaloid extract that subsumes multiple sources of diverse origin, composition, and conditions of storage (67). Multiple confounding risk factors for QT prolongation and ventricular arrhythmia were present. The patient had presented with a witnessed generalized tonic-clonic seizure (GTCS) in the setting of acute alcohol withdrawal with hypomagnesemia and hypokalemia. Although the report made no mention of toxicological testing for illicit drugs, the patient had a prior history of cocaine abuse and a history of bulimia and had been purging prior to admission.

Bradycardia is a functional effect of potential medical significance that could possibly involve muscarinic cholinergic transmission. Ibogaine binds with reported affinities in the 10–30 μM range to M1 and M2 muscarinic cholinergic receptors and is generally assumed to act as an agonist (1,2); however, functional studies have not been performed. Although ibogaine is concentrated in brain tissue relative to serum in the animal model (119) and in the two cases reported here that reported on brain levels (cases #3 and #13), an older literature (120,121), as well as more recent data (122), indicates that the inhibition of acetylcholinesterase by ibogaine *in vitro* is negligible over the range of ibogaine concentrations observed in both blood and brain in this series. It is unclear whether the apparent association of ibogaine with bradycardia could possibly be related to orthosteric agonist actions at muscarinic cholinergic receptors, or to effects involving sodium channels (123) or other signal transduction pathways.

Pulmonary thromboembolism (PE) was the reported cause of death in three deaths (cases #7, #12, and #18) all of which occurred in Mexico. Two were not under direct observation at the time of the death. In all three of these cases, autopsy reports were inadequate as a basis for the determination of a proximate cause of death due the lack of evidence of systematic examination of the lungs and pulmonary vasculature. In Mexico, the death certificate provides the clinical conclusion reached by the physician who pronounced the death. In case #18, the attending physician patient observed the patient directly and based the clinical diagnostic impression of PE on acute dyspnea, tachypnea, and desaturation indicated by pulse oximetry. Although an adequate autopsy is lacking, the clinical picture mentioned previously is frequently seen with PE (124), and in instances where there is verification by a subsequent autopsy, the prospective clinical diagnosis of PE is less commonly falsely positive than falsely negative (125). The decedent had a family history of PE, and if he did indeed die from venous thrombotic disease, the family history suggests a possible etiological contribution because of genetic risk (126). Other possible risk factors for PE include travel to the treatment location (127) and/or inactivity and immobility during the treatment (128). Intravenous drug use is a risk factor for deep venous thrombosis (129–131), and hence for PE, and appears to be associated with injection per se, independent of the use of opioids versus other substances (132).

In this series, there appeared to be no clinical or postmortem evidence suggestive of a characteristic syndrome of neurotoxicity. Ibogaine's σ_2 agonist activity potentiates excitatory transmission in the olivocerebellar projection, where the redundancy of inputs to cerebellar Purkinje cells renders them vulnerable to excitotoxic injury (133,134). This is believed to be the mechanism of degeneration of cerebellar Purkinje cells observed in rats given substantially larger dosages of ibogaine than those used to study drug self-administration and withdrawal (135). Subsequent research found no evidence of neurotoxicity in the primate (65) or mouse (136) at dosages that produced cerebellar degeneration in the rat, or in the rat at dosages used in studies of drug self-administration and withdrawal (137). Neuropathological examination revealed no evidence of degenerative changes in a woman who had received four separate doses of ibogaine ranging between 10 and 30 mg/kg over a 15-month interval prior to her death due to a mesenteric artery thrombosis with small bowel infarction 25 days after her last ingestion of ibogaine (65).

In one fatality in this series, a GTCS occurred (case #10), which might have been due to alcohol or benzodiazepine withdrawal. In another death (case #14), a brain neoplasm might have explained the possibility of complex partial seizures mentioned in the autopsy report. The neurodegeneration observed in the rat following high dosages of ibogaine has mainly involved the cerebellum (134,135), which is an unlikely location for a seizure focus in humans. Seizures originating from the cerebellum in humans appear to be limited to rare instances in which a focus is located in a tumor mass distinct from normal cerebellar tissue, most commonly a gangliogliomа (138). Furthermore, cerebellar stimulation is viewed as a possible antiepileptic treatment (139), and ibogaine has been observed to protect against convulsions in animal models (140–142), which has been attributed to NMDA antagonist activity. Ibogaine causes

serotonin release in selected brain regions in the animal model (49), and seizures are sometimes seen in serotonin syndrome (143), but characteristic features of serotonin syndrome such as hyperthermia or rigidity were not present and a clinical picture suggestive of serotonin syndrome does not appear to have been evident in this series.

The apparent potentiation of both the analgesic (22,38,39,43–47) and toxic (33,37–39) effects of opioids by ibogaine may be mediated by enhanced transduction of signaling via opioid receptors (40), which might have been a factor in deaths involving the use of opioids in temporal proximity to the ingestion of ibogaine. In one fatality (case #2), it appeared that the decedent smoked heroin following ibogaine treatment and shortly before death (6). Toxicological analysis detected a low morphine concentration that nonetheless was in the range measured in human subjects within 30 min after inhalation of volatilized heroin (144), similar to the method of smoking heroin by heating tin foil known as ''chasing the dragon'' (145), and suggests possible potentiation of opioid toxicity by ibogaine in this death. Ibogaine increases cocaine-induced stereotypic motor behavior in the animal model (146), suggesting that ibogaine might also potentiate the toxicity of stimulants as well as opioids.

Postmortem toxicological analysis detected commonly abused drugs in eight of the 11 cases in which toxicological analysis was performed in this series. When considering a drug intoxication death because of multiple substances, it usually is not possible to differentiate the individual roles and complex interactions of these substances in causing the death. These deaths typically are certified as intoxications because of the combined effects of all substances detected. Therefore, it is not possible to determine whether the deaths in which drugs of abuse were detected were because of ibogaine alone, to one or more of the drugs of abuse, or a combination. There is also a general effect of the number of abused substances, with a larger number associated with a greater risk of death independent of the identity of specific substances involved (147). The unexplained variance of lethal outcome as a function of dose further adds to the difficulty of the determination of causality for ibogaine and drugs of abuse. For example, morphine concentrations associated with heroin overdose overlap substantially with concentrations obtained from living current heroin users (148), which may relate to the wide ranges of tolerance among opioid-dependent individuals, and within the same individual at different time points.

Systemic disease is a confounding factor that contributes to the mortality associated with substance use and further complicates the identification of the cause of death. The risk of death may represent a complex interaction involving a substance of abuse against a backdrop of systemic medical illness related to addiction. For example, the risk of death from opioid overdose is associated with cardiac hypertrophy and atherosclerotic disease (149), which were contributing conditions in this case series and which in turn are associated with a history of methamphetamine and cocaine use (150,151). The role of advanced preexisting medical comorbidities in this series of fatalities appears to be an instance of a more general association between systemic disease and risk of fatal overdose (149).

The reported elimination half-life of ibogaine in humans is on the order of 4–7 h (7,70), and that of noribogaine is apparently longer (7,35). Ibogaine is relatively lipophilic and accumulates preferentially in tissues containing a high density of lipids, such as brain or fat (119). Ibogaine undergoes demethylation to noribogaine via cytochrome P450 2D6 (CYP2D6) (152), which is expressed in the brain (153), where noribogaine may be ''trapped'' because it is more polar than ibogaine and may cross the blood–brain barrier more slowly. Postmortem redistribution of drugs and drug metabolites may occur due to passive drug release from drug reservoirs, cell autolysis, and putrefaction (154,155). In the three instances in which peripheral and cardiac concentrations of ibogaine were reported (cases #2, #6, and #13), the concentrations from the femoral and cardiac or vena cava sites were similar. However, the two that reported noribogaine concentrations (cases #2 and #13) demonstrated evidence for postmortem redistribution of noribogaine with ratios of *c*. 3:1 between cardiac and peripheral blood. The one instance that reported ibogaine concentrations at two time points (case #16) indicated 0.65 mg/L in blood at autopsy and 1.27 mg/L days following death.

The available data do not provide a basis for a reliable estimate of toxic concentrations of ibogaine. In humans administered fixed oral doses of ibogaine of 10 mg/kg, mean peak blood levels were 0.74 ± 0.08 and 0.90 ± 0.17 mg/L in extensive and poor CYP2D6 metabolizers, respectively (7). In series of cases reported here, the mean dosage was 14.3 ± 6.1 mg/kg (range 4.5–29 mg/kg), and the mean blood level was 2.38 ± 3.08 mg/L. The presence of cointoxicants and comorbidities, difference in dosages used, and the higher variance in dosages and blood levels in the present series does not provide for a meaningful comparison regarding a lethal dosage or level in humans.

In the rat, the animal model that is predominantly used in research on ibogaine, the dose that is usually used in models of drug self-administration and opioid withdrawal is 40 mg/kg administered intraperitoneally (i.p.) (1,2). This dose is approximately one-third of the LD_{50} of ibogaine administered i.p. (33), which in turn is approximately one-half to one-third of the LD_{50} by the intragastric route of administration (33,156). The animal data indicate a significant effect of abused substances on toxicity associated with ibogaine (33,37–39), and taken together with the clinical evidence for the effect systemic disease on fatal overdose (149) suggests that interactions involving cointoxicants and medical comorbidities preclude a reasonable estimate regarding a lethal dosage or level of ibogaine in humans.

Cointoxicants or contributing medical comorbidities were not reported in only two fatalities for which there were an adequate postmortem examination and toxicological analysis (cases #4 and #13). These two deaths involved the ingestion of crude alkaloid extract in one case, and root bark in the other. The overall composition, age, and origin of these sources of ibogaine are unknown. The iboga alkaloid content of *T. iboga* root bark extracts depends, among other factors, on the extraction method. The total alkaloid content of the root bark is *c*. 2–8% of the dry weight of the root bark, about half of which is iboga alkaloids, 80% of which is ibogaine (157,158). Utilization of water-soluble extractants yields an extract with an alkaloid fraction composed of *c*. 40% ibogaine, 10% related iboga alkaloids, and 50% other alkaloids, whereas utilization of an organic solvent such as acetone or methanol yields a total alkaloid fraction with relatively less non-iboga alkaloid content (157). Other iboga alkaloids that co-occur with ibogaine in *T. iboga* root bark include ibogamine, ibogaine, tabernanthine, and voacangine (157–159) (see Fig. 1). The overall iboga alkaloid composition of *T. iboga* alkaloid extracts may range from *c*. 15% to 50% (157) (C. Jenks, personal communication). Sources of ibogaine HCl are restricted and tend to be known to providers, and certificates of analysis have generally been available and corroborated when verified by independent laboratories, which up to the present time has distinguished ibogaine from the counterfeiting and adulteration seen with commonly abused ''street'' drugs (160).

Inexperience and lack of information regarding the use of ethnopharmacological forms of ibogaine may itself constitute a salient domain of risk, independent of the uncertain composition of alkaloid extracts and the undefined potential toxicity of the alkaloids that co-occur with ibogaine in *T. iboga* root bark. For example, one decedent (case #13) (70) may have ingested an amount of dried *T. iboga* root bark in excess of that which would typically be given in a full Bwiti initiation ceremony (5). The blood ibogaine concentration in this case was the second highest in the series, even though it was measured an estimated 53 h after ingestion, and does not take into account the likely presence of other alkaloids. This case additionally suggests that the bioavailability of the alkaloid content of dried root bark may be high.

The incidence of fatalities may have decreased in the recent past. As indicated in Table 1, in 2008, there were no known fatalities, and in 2007, there were 2. In contrast, there were a total of nine fatalities that occurred in 2005 and 2006. It is unlikely that this reflects a decline in the number of individuals treated, which appears to be continuing the trend of growth evident over the last decade (5). Greater recognition of medical risk on the part of treatment providers may have been a factor in the apparent reduction in the incidence of fatalities. Pretreatment screening including basic blood chemistries and EKG, the exclusion of patients with significant medical, particularly cardiac illness, and the recognition of the need to stabilize physical dependence on alcohol and benzodiazepines prior to ibogaine treatment has gradually become more widely accepted norms in the settings of ibogaine use (161). This might to a significant extent reflect the collective, cumulative experience of the fatal outcomes presented here.

In conclusion, in this series of 19 cases, advanced preexisting medical comorbidities, which were mainly cardiovascular, and/or one or more commonly abused substances explained or contributed to the death in 12 of the 14 cases for which adequate postmortem data were available. Significant factors in this series appear to include preexisting medical, particularly cardiovascular disease, possible PE, drug use during treatment, seizures associated with withdrawal from alcohol and benzodiazepines, and the uninformed use of ethnopharmacological forms of ibogaine.

Acknowledgment

We gratefully acknowledge the valuable assistance of Howard Lotsof in identifying cases and providing documents.

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Additional information and reprint requests:
Kenneth R. Alper, M.D.
Associate Professor of Psychiatry and Neurology
New York University School of Medicine
Brain Research Laboratories
8th Floor Old Bellevue Administration Building
462 First Avenue
New York, NY 10016
E-mail: kra1@nyu.edu