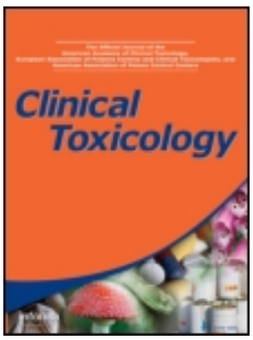

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REVIEW

How toxic is ibogaine?

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ABSTRACT

Context: Ibogaine is a psychoactive indole alkaloid found in the African rainforest shrub *Tabernanthe Iboga*. It is unlicensed but used in the treatment of drug and alcohol addiction. However, reports of ibogaine's toxicity are cause for concern. **Objectives**: To review ibogaine's pharmacokinetics and pharmacodynamics, mechanisms of action and reported toxicity. **Methods**: A search of the literature available on PubMed was done, using the keywords "ibogaine" and "noribogaine". The search criteria were "mechanism of action", "pharmacokinetics", "pharmacodynamics", "neurotransmitters", "toxicology", "toxicity", "cardiac", "neurotoxic", "human data", "animal data", "addiction", "anti-addictive", "withdrawal", "death" and "fatalities". The searches identified 382 unique references, of which 156 involved human data. Further research revealed 14 detailed toxicological case reports. **Pharmacokinetics and pharmacodynamics**: Ibogaine is metabolized mainly by CYP2D6 to the primary metabolite noribogaine (10-hydroxyibogamine). Noribogaine is present in clinically relevant concentrations for days, long after ibogaine has been cleared. **Mechanisms of action**: Ibogaine and noribogaine interact with multiple neurotransmitter systems. They show micromolar affinity for *N*-methyl-D-aspartate (NMDA), κ- and μ-opioid receptors and sigma-2 receptor sites. Furthermore, ibogaine has been shown to interact with the acetylcholine, serotonin and dopamine systems; it alters the expression of several proteins including substance P, brain-derived neurotrophic factor (BDNF), c-*fos* and *egr*-1. **Neurotoxicity**: Neurodegeneration was shown in rats, probably mediated by stimulation of the inferior olive, which has excitotoxic effects on Purkinje cells in the cerebellum. Neurotoxic effects of ibogaine may not be directly relevant to its anti-addictive properties, as no signs of neurotoxicity were found following doses lower than 25 mg/kg intra-peritoneal in rats. Noribogaine might be less neurotoxic than ibogaine. **Cardiotoxicity**: Ether-a-go-go-related gene (hERG) potassium channels in the heart might play a crucial role in ibogaine's cardiotoxicity, as hERG channels are vital in the repolarization phase of cardiac action potentials and blockade by ibogaine delays this repolarization, resulting in QT (time interval between the start of the Q wave and the end of the T wave in the electrical cycle of the heart) interval prolongation and, subsequently, in arrhythmias and sudden cardiac arrest. Twenty-seven fatalities have been reported following the ingestion of ibogaine, and pre-existing cardiovascular conditions have been implicated in the death of individuals for which post-mortem data were available. However, in this review, 8 case reports are presented which suggest that ibogaine caused ventricular tachyarrhythmias and prolongation of the QT interval in individuals without any pre-existing cardiovascular condition or family history. Noribogaine appears at least as harmful to cardiac functioning as ibogaine. **Toxicity from drug–drug interaction**: Polymorphism in the CYP2D6 enzyme can influence blood concentrations of both ibogaine and its primary metabolite, which may have implications when a patient is taking other medication that is subject to significant CYP2D6 metabolism. **Conclusions**: Alternative therapists and drug users are still using iboga extract, root scrapings, and ibogaine hydrochloride to treat drug addiction. With limited medical supervision, these are risky experiments and more ibogaine-related deaths are likely to occur, particularly in those with pre-existing cardiac conditions and those taking concurrent medications.

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Introduction

Ibogaine is a psychoactive indole alkaloid derived from the root bark of the African rainforest shrub *Tabernanthe Iboga* that is native to Central-West Africa (Figure 1). Ibogaine was first isolated from the iboga root in 1901.[1] Although ibogaine was recommended for a number of indications such as the treatment of convalescence, neurasthenia and trypanosomiasis, it was never widely used in a clinical setting and did not receive much attention from the scientific community for several decades.[1–3] However, an extract of the relative plant *Tabernanthe Manii* was sold in France during the 1930s under the name Lambarène and remained on the market until 1970. During that year, ibogaine became a Schedule I controlled substance in the USA and later in other countries. The Lambarène extract contained 8 mg of ibogaine per tablet and was recommended for combating fatigue,

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depression, asthenia and the recovery from infectious diseases.[1–4]

In the 1940s, several articles were published about the pharmacological properties of ibogaine on the cardiovascular system and isolated tissues.[4] The anti-addictive properties of ibogaine were first reported in 1963 when a group of drug experimenters, of whom nine were addicted to opioids, engaged in an ibogaine experiment in a non-clinical setting.[3] None of the group members had any knowledge about its effects. The opioid-dependent group members noted an apparent effect on withdrawal symptoms.[3,4]

This led subsequently to patents being filed for the use of ibogaine in abuse due to opioids (1985), stimulants and cocaine (1986), alcohol (1989), nicotine (1991) and polysubstances (1992). In these patents, it was claimed that a single oral or rectal dose of ibogaine 4–25 mg interrupted addictive behaviour for 6–36 months.[5]

In 2006, it was estimated that 3414 individuals had taken ibogaine, this was a 4-fold increase compared to five years earlier.[6] A large percentage of the users had taken ibogaine for treatment of a substance-related disorder (68%) and more than half specifically for opioid withdrawal (53%). The ibogaine employed is often the purified ibogaine hydrochloride (up to 98% purity) from extracts of the root bark.[1]

Since the alleged anti-addictive properties of ibogaine were discovered, there have been a vast number of animal studies, but little research in humans. More recently, after some serious incidents have been described in the media, there has been increasing concern about the toxicity of ibogaine for humans.

This review will focus on the pharmacokinetic and pharmacodynamic profiles of ibogaine, its possible mechanisms of action as well as the reported toxicity in humans.

Figure 1. The *Tabernanthe Iboga* shrub.

Methods

A search of the literature available on PubMed was done, using the keywords "ibogaine" and "noribogaine". The search criteria were "mechanism of action", "pharmacokinetics", "pharmacodynamics", "neurotransmitters", "toxicology", "toxicity", "cardiac", "neurotoxic", "human data", "animal data", "addiction", "anti-addictive", "withdrawal", "death" and "fatalities". These searches identified 382 unique references, and 38 were related to toxicology (animal and human). 156 of the 382 references were related to human data and further research revealed 14 original clinical and toxicological case reports. Four case reports were excluded because they were forensic reports about fatalities and contained no reliable information on clinical course or cause of death.

Pharmacokinetics

Ibogaine (10-methoxyibogamine) is metabolized mainly by CYP2D6 (Figure 2) to the primary metabolite noribogaine (10-hydroxyibogamine), which also has psychoactive properties and its own pharmacological profile (Table 1).[7,8] CYP2C9 and CYP3A4 also contribute to the conversion of ibogaine to noribogaine. Noribogaine was found in the blood 15 min after

Table 1. Affinity of ibogaine and noribogaine for receptor sites (k_i values).

	Ibogaine	Noribogaine
κ opioid	2–4 μM	0.6–1 μM
μ opioid	10–100 μM	3 μM
Δ opioid	>100 μM	25 μM
NDMA	1–3 μM	6 μM
Sigma 1	9 μM	15 μM
Sigma 2	0.09–0.2 μM	5 μM
Dopamine transporter	2 μM	2 μM
Serotonin transporter	0.5 μM	0.04 μM
Nicotinic	0.02 μM	1.5 μM

Adapted from Mash et al.[2]

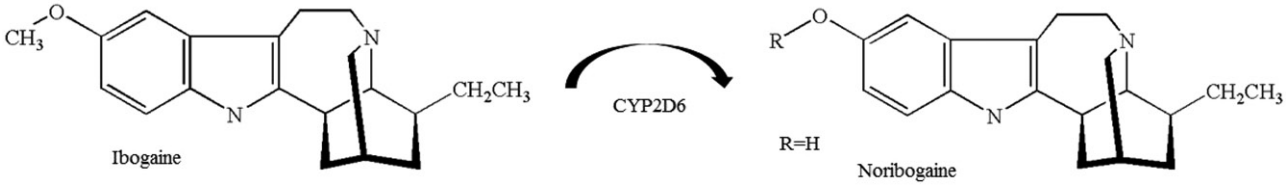

Figure 2. Structure of ibogaine and its metabolite noribogaine, R = H.

administration of ibogaine.[8] From the limited pharmacokinetic studies in humans, it has become clear that a polymorphism in the CYP2D6 enzyme can influence blood concentrations of both ibogaine and its primary metabolite,[8] which may have implications when a patient is taking other medication that is subject to significant CYP2D6 metabolism (see later).

A half-life value in humans for ibogaine of 7.45 h was determined in CYP2D6 extensive metabolizers.[8] In a study in human volunteers, noribogaine was administered in various doses (3, 10, 30 and 60 mg), and the mean plasma elimination was 28–49 h across dose groups,[9] thereby confirming that noribogaine has a much longer half-life. Thus, noribogaine is present in relevant concentrations, long after ibogaine has been cleared.

Both Ibogaine and noribogaine are highly lipophilic which leads to high concentrations of these compounds in brain and fat tissue. A post-mortem analysis of a person who died from iboga poisoning revealed particularly high concentrations of ibogaine and noribogaine in liver, spleen, lung and brain.[10] In this particular individual an exceptionally high ratio of ibogaine to noribogaine was found and the time of death was estimated to be 53 h after last intake. Normally, noribogaine concentrations are expected to exceed ibogaine blood concentrations, because of the slower clearance rate of noribogaine. This may indicate that this particular case involved a slow metabolizer CYP2D6 type that may have played a role.

Mechanisms of action

Ibogaine's effects result from a complex interaction with multiple neurotransmitter systems rather than predominant activity within a single neurotransmitter system. Ibogaine shows micromolar affinity for *N*-methyl-D-aspartate (NMDA), κ- and μ-opioid receptors and sigma-2 receptor sites.[11] Furthermore, ibogaine has been shown to interact with the acetylcholine, serotonin and dopamine systems and alters the expression of several proteins including substance P, brain-derived neurotrophic factor (BDNF), c-*fos* and *egr*-1.[4,12] Additionally, its primary metabolite noribogaine has its own unique pharmacological profile.[13]

Ibogaine is a competitive antagonist of NMDA receptor-coupled ion channels at micromolar concentrations,[4] and there is evidence to suggest that the NMDA receptor system also has a modulatory effect on the actions of addictive drugs. Antagonists acting at the NMDA receptor suppress symptoms of morphine withdrawal in animal experiments.[14] In addition, binding of ibogaine-to-κ-opioid receptors, located on the presynaptic dopamine terminals of the striatum, may also be involved its anti-addictive effects.[15] Pretreatment with ibogaine was shown to double the rise of dynorphin A concentrations in striatum, substantia nigra and nucleus accumbens in response to cocaine.[16] Dynorphin A concentrations are thought to be associated with dysphoric effects caused by excessive cocaine use via stimulation of κ-opioid sites and high concentrations may therefore cause aversion to cocaine.[16,17]

He et al. [18] have ascribed ibogaine's long-term effects on alcohol consumption to an increase in glial cell line-derived neurotrophic factor (GDNF) transcription. In studies with rats it was found that ibogaine increases GDNF concentrations in midbrain regions, including the ventral tegmental area (VTA).[19] GDNF is known to promote regrowth and survival of dopaminergic neurons following injury, and is essential for the survival and maintenance of adult dopaminergic neurons. These findings raise the possibility that ibogaine (partly) restores pre-addiction dopaminergic functioning through increased GDNF transcription. GDNF may have a regulatory role in substance-use disorders, including alcohol, psychostimulants and opioids.[19]

Neurotoxicity

Experimental studies

In 1993, O'Hearn et al. [20] reported that they had observed degeneration of Purkinje cells following the administration of ibogaine 100 mg/kg or three doses of 100 mg/kg to rats. Neurodegeneration from ibogaine is probably mediated by stimulation of the inferior olive which has excitotoxic effects on Purkinje cells in the cerebellum.[21] In a study [22] involving rats that were given ibogaine 100–300 mg/kg (as in O'Hearn et al. [20]) and a 40-mg/kg dose (that attenuated withdrawal signs), the neurotoxic effects of ibogaine (degeneration in the intermediate and lateral cerebellum and the vermi) were observed at the 100-mg/kg dose, but no signs of neurotoxicity were found following the 40-mg/kg single dose (using a Fink–Heimer II stain to assess for Purkinje cell degeneration).

In a dose-response study by Xu et al. [23] ibogaine was found to cause neurodegeneration at a 50-, 75- and 100-mg/kg dose intra-peritoneal in rats, but no signs of neurotoxicity were present at 25 mg/kg. Chronic administration of ibogaine 10 mg/kg did not induce Purkinje cell loss.[24]

Ibogaine caused tremors for several hours following administration in rats.[25] Ibogaine-induced tremors show much similarity with harmaline-induced tremors, a plant-derived compound that is chemically related to ibogaine. Both harmaline- and ibogaine-induced tremors appear to be the result of stimulation of olivo-cerebellar pathways.[21,26] This indicates that tremors may be an early indicator of inferior olive-mediated neurotoxicity in the cerebellum. However, mice also displayed tremors after ibogaine administration,[27] without neurodegeneration.

The finding that these tremors are only briefly present indicate that the tremorigenic activity is more likely to be ibogaine rather than noribogaine mediated. It has been suggested that noribogaine may be less neurotoxic than its parent compound ibogaine. This hypothesis is supported by the finding that the LD_{50} value for noribogaine is 2.4 times lower than the LD_{50} value for ibogaine in mice.[28]

Human studies

As tremors in rats are associated with stimulation of the inferior olive,[21,26] it could be that ibogaine may also be neurotoxic in humans at therapeutic dosages. It is unclear whether the olivo-cerebellar organization in humans is similar to that of mice or rats. Some evidence of ibogaine being less neurotoxic

in humans comes from a pathological evaluation of a fatality and some studies with primates reported later.

An autopsy was performed on a woman who had received four doses of ibogaine (10–30 mg/kg) over a period of 15 months, the last administration being approximately 25 d prior to her death of natural causes.[2] There were no signs of damage to the cerebellum and her Purkinje cells were normal.

Following ibogaine administration under open-label conditions in 30 drug-dependent subjects using three fixed-dose regiments of 500 , 600 and 800 mg, early nausea and mild tremors were reported frequently.[2] Many neurological symptoms have also been reported in case reports;[29–34] the most prevalent were ataxia, muscle spasms, tonic–clonic seizures and severe nausea (Table 2). In one case, permanent cognitive deficits and loss of vision remained for weeks after hospitalization.[34] Another case demonstrated encephalopathy of unknown origin.[33] In both cases, it was concluded that neurological deficits might have been due to hypoxia during ibogaine-induced respiratory depression and coma.

One study described three different patients suffering from grandiose delusions, sleeplessness, hallucinations and prominent manic disorder for days to weeks following ingestion of ibogaine.[35] Two of these patients used ibogaine as treatment for their opiate addiction, but otherwise none of them had any previous history of psychotic disorders or relevant medical family history. It remains unclear if any long-term neurological damage occurred in these patients.

Cardiotoxicity

Human studies

A rise in blood pressure and a decline in pulse rate have been recorded 1–5 h after ibogaine administration in several patients following doses of 10–25 mg/kg.[3]

A fatality resulting from acute heart failure has been described.[1] The deceased was reported to have suffered prior infarction of the left ventricle, had severe atherosclerotic changes and 70–80% stenosis of all major coronary artery branches. The autopsy report suggested the possibility of an interaction between ibogaine and pre-existing conditions.

In a recent review of ibogaine fatalities, it was concluded that pre-existing medical conditions, mainly cardiovascular, were an important factor contributing to the death of individuals for which adequate post-mortem data were available.[36] Some 27 fatalities have been reported associated with ingestion of ibogaine or iboga.[10,29,36–40] In a recent forensic case series report,[36] 19 fatalities were described in detail, of which at least 9 could be attributed to cardiotoxicity. Features included cardiomyopathy, myocardial infarct, arrhythmias and cardiac hypertrophy. In several cases patients had pre-existing cardiac problems. An interesting finding was the fact that some fatalities occurred many hours to even days after the ingestion of ibogaine,[36] which could imply that noribogaine is at least as cardiotoxic as ibogaine, or that the deaths were not due to ibogaine/iboga-induced cardiotoxicity.

Maas and Strubelt [37] have suggested that during a phase of the "ibogaine experience", where participants experience "visions", there is a parasympathetic dominance which

Table 2. Clinical case reports of cardiac abnormalities after ibogaine ingestion.[29–34,41,42]

Age (years)	Gender (m/f)	Time after intake	Dose taken	Cardiac symptoms	Other clinical symptoms	Toxicological analysis	Medical history/family history	Duration and clinical course	Publication date; reference
33	M	7.5 h	3.8 g	VT, prolonged QT interval (527 ms)	Ataxia, vomiting, tremors	Ibogaine	None	Patient discharged 24 h after admission	2015; 32
26	M	5 h	2.4 g	Cardiac arrest, VT, prolonged QT interval (663 ms)	Coma (GCS score 3), seizures	Ibogaine	None, previously normal ECG	Prolonged QT 32 h after defibrillation, patient awoke from coma weeks later with cognitive deficits	2014; 34
39	M	5 h	7 g	Bradycardia (55 b/m), polymorphic VT, prolonged QT interval (640 ms on day one, 730 ms on day 2)	GCS score 14, multiple seizures, electrolytes normal range	Absence other substances	None	3 h after admission episodes of pulseless polymorphic VT, isoproterenol treatment didn't resolve bradycardia, no more VT after 72 h, patient discharged at day 7	2015; 42
31	F	unknown	3.8 g	VT, prolonged QT interval (616 ms)	Electrolyte imbalance, nausea	Unknown	None	QT normalized after 42 h, patient discharged	2009; 31
49	M	1–2 d	unknown	VT, prolonged QT interval (>700 ms)	Electrolyte imbalance, nausea	Opioids	None	No more VT after 10 d, prolonged QT remained, patient discharged	2012; 33
unknown	M	unknown	7 g	Cardiac arrest, VT, prolonged QT interval (600 ms)	Tonic-clonic seizures	N.A.	None	Several defibrillations eventually resolved QT and cardiac symptoms, patient discharged	2013; 30
33	M	unknown	0.6 g	VT during micturition, prolonged QT interval (460 ms, after amiodarone treatment up to 593 ms)		Ibogaine, methadone	None	VTs occurred during the first 2 d, prolonged QT interval until 9th day of admission, patient discharged	2012; 41
25	M	3 h	2.5 g	Cardiopulmonary arrest	Ataxia, muscle spasms, fever, decorticate posturing	Ibogaine	Supraventricular tachycardia	Patient expired after 2 d of intensive care	2013; 29

protects the cardiac system. The risk is thought to be highest in the period afterwards. In Gabon, where iboga is taken in a religious context, a period of at least 3 d following ingestion of iboga is considered a critical period. During this period, a person undergoing iboga therapy should remain under observation and protected from sudden stress to avoid sympathetic overstimulation. This is done by taking the person under the influence of iboga out of daily life and creating a hypnotic trance state which prevents sudden sympathetic reactions that could endanger the heart.[37]

The hypothesis that cardiac arrhythmias are responsible for a number of ibogaine deaths finds further support in a well-described case report from 2009.[31] It was found that ibogaine produced a severely prolonged QT interval (616 msec corrected for heart rate) and ventricular tachyarrhythmias in a woman who had ingested 3.5 grams of 15% iboga extract for the treatment of her alcohol addiction. This individual did not have any further pre-existing medical problems or family history of cardiac-rhythm abnormalities. During admission to the intensive care unit, the QT interval normalized at 42 h, and the patient was subsequently discharged fully recovered. The authors concluded that sudden deaths after ibogaine intake can be ascribed to these cardiac-rhythm abnormalities and they recommended continuous electrocardiographic monitoring while undergoing ibogaine therapy. In recent years, many case reports have been published describing similar cardiotoxicity in patients who ingested ibogaine (Table 2).[29–34,41,42] Except for one,[29] none of these cases had any pre-existing medical problems or family history of cardiac-rhythm abnormalities.

Although evidence for ibogaine's cardiotoxic effects has been accumulating, ibogaine and noribogaine appear to have been well-tolerated in open-label trials.[8,9,43] This discrepancy could be explained by the fact that doses of ibogaine used in the case reports of cardiotoxicity are higher than those described in the open-label trials. For instance, Mash et al. [44] used fixed doses of ibogaine hydrochloride 500, 600 or 800 mg in their trial. In other studies, ibogaine/noribogaine was administered in even much lower doses (3, 10, 30 and 60 mg).[9,43,45] In most case reports about cardiotoxicity, ibogaine doses exceeded 2 g. Second, it was not always clear in which form these doses were taken and whether it was purified ibogaine. These are all likely factors to have played a role in toxicity occurring or not.

Koenig and colleagues [46,47] have suggested a mechanism by which ibogaine may cause cardiac arrhythmias. They found that ibogaine inhibits ether-a-go-go-related gene (hERG) potassium channels in the heart. These hERG channels are vital in the repolarization phase of cardiac action potentials and the blockade by ibogaine delays this repolarization, resulting in QT interval prolongation and, subsequently, in arrhythmias and sudden cardiac death. The doses by which ibogaine exerts this inhibition of hERG channels are equivalent to the doses used to treat drug addicts. They demonstrated that ibogaine also inhibited human sodium and calcium currents in ventricular cardiomyocytes and stated that the inhibitory effects on human ion channels would also result in a prolongation of the QT interval.

Toxicity from drug–drug interactions

Another factor which cannot be excluded is the use of other substances at the time of ibogaine treatment or shortly after.[36] For instance, benzodiazepines or methadones have also been detected in the blood of deceased victims.[36,38] It is possible that there is an interaction between ibogaine and other drugs or medications used.

Ibogaine reportedly enhances morphine's analgesic effects in morphine-tolerant mice.[48,49] If this lowering of tolerance also occurs in humans, there is a higher probability of overdosing when drug addicts return to using their drug of abuse. As previously mentioned, the CYP2D6 metabolizer status of subjects participating in ibogaine treatment may also influence blood concentrations of ibogaine and noribogaine.[7,8]

In fact, a recent study confirmed an interaction between other drugs that undergo breakdown by CYP2D6 and ibogaine. A total of 21 healthy subjects who had been pretreated for 6 d with placebo or the CYP2D6 inhibitor paroxetine showed a ~2-fold higher active moiety (ibogaine plus noribogaine) in paroxetine-pretreated subjects.[43] Polymorphisms in the CYP2D6 gene can significantly affect blood concentrations of ibogaine and noribogaine. This led to the conclusion that CYP2D6 poor metabolizers should decrease their dose of ibogaine (which was 20 mg in this study) to at least half. Another example pointing towards a possibility of interaction was a person who expired after the use of ibogaine and buprenorphine, which is metabolized by CYP3A4, an enzyme that also contributes to ibogaine's degradation.[10,50] Buprenorphine may have caused slower clearance of ibogaine.

Conclusions

Alternative therapists and drug users are still using iboga extract, root scrapings and ibogaine hydrochloride to treat drug addiction. With the poorly understood effects of the extract and ibogaine alone, the limited medical supervision, these are risky experiments and more ibogaine-related deaths are likely to occur, particularly in those with pre-existing cardiac conditions and those taking concurrent medications.

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Disclosure statement

The authors have no conflicts of interest to report.

References

[1] Alper KR. Ibogaine: a review. Alkaloids Chem Biol. 2001;56:1–38.
[2] Mash DC, Kovera CA, Buck BE, et al. Medication development of ibogaine as a pharmacotherapy for drug dependence. N Y Acad Sci. 1998;844:274–292.
[3] Lotsof HS, Alexander NE. Case studies of ibogaine treatment: implications for patient management strategies. Alkaloids Chem Biol. 2001;56:293–313.

[4] Popik P, Layer RT, Skolnick P. 100 years of ibogaine: neurochemical and pharmacological actions of a putative anti-addictive drug. Pharmacol Rev. 1995;47:235–253.

[5] Maciulaitis R, Kontrimaviciute V, Bressolle FM, et al. Ibogaine, an anti-addictive drug: pharmacology and time to go further in development. A narrative review. Hum Exp Toxicol. 2008;27:181–194.

[6] Alper KR, Lotsof HS, Kaplan CD. The ibogaine medical subculture. J Ethnopharmacol. 2008;115:9–24.

[7] Hough LB, Pearl SM, Glick SD. Tissue distribution of ibogaine after intraperitoneal and subcutaneous administration. Life Sci. 1996;58:119–122.

[8] Mash DC, Kovera CA, Pablo J, et al. Ibogaine in the treatment of heroin withdrawal. Alkaloids Chem Biol. 2001;56:155–171.

[9] Glue P, Lockhart M, Lam F, et al. Ascending-dose study of noribogaine in healthy volunteers: pharmacokinetics, pharmacodynamics, safety, and tolerability. J Clin Pharmacol. 2015;55:189–194.

[10] Kontrimaviciūte V, Mathieu O, Mathieu-Daudé JC, et al. Distribution of ibogaine and noribogaine in a man following a poisoning involving root bark of the *Tabernanthe iboga* shrub. J Anal Toxicol. 2006;30:434–440.

[11] Bowen WD. Sigma receptors: recent advances and new clinical potentials. Pharm Acta Helv. 2000;74:211–218.

[12] He DY, Ron D. Autoregulation of glial cell line-derived neurotrophic factor expression: implications for the long-lasting actions of the anti-addiction drug, Ibogaine. FASEB J. 2006;20:2420–2422.

[13] Glick SD, Maisonneuve IS. Mechanisms of antiaddictive actions of ibogaine. Ann N Y Acad Sci. 1998;844:214–226.

[14] Trujillo KA, Akil H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science. 1991;251:85–87.

[15] Sershen H, Hashim A, Lajtha A. The effect of ibogaine on kappa-opioid- and 5-HT3-induced changes in stimulation-evoked dopamine release in vitro from striatum of C57BL/6By mice. Brain Res Bull. 1995;36:587–591.

[16] Alburges ME, Hanson GR. Ibogaine pretreatment dramatically enhances the dynorphin response to cocaine. Brain Res. 1999;847:139–142.

[17] Broderick PA, Phelan FT, Eng F, et al. Ibogaine modulates cocaine responses which are altered due to environmental habituation: in vivo microvoltammetric and behavioral studies. Pharmacol Biochem Behav. 1994;49:711–728.

[18] He DY, McGough NN, Ravindranathan A, et al. Glial cell line-derived neurotrophic factor mediates the desirable actions of the anti-addiction drug ibogaine against alcohol consumption. J Neurosci. 2005;25:619–628.

[19] Carnicella S, Ron D. GDNF–a potential target to treat addiction. Pharmacol Ther. 2009;122:9–18.

[20] O'Hearn E, Molliver ME. Degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis after treatment with ibogaine or harmaline. Neuroscience. 1993;55:303–310.

[21] O'Hearn E, Molliver ME. The olivocerebellar projection mediates ibogaine-induced degeneration of Purkinje cells: a model of indirect, trans-synaptic excitotoxicity. J Neurosci. 1997;17:8828–8841.

[22] Molinari HH, Maisonneuve IM, Glick SD. Ibogaine neurotoxicity: a re-evaluation. Brain Res. 1996;737:255–262.

[23] Xu Z, Chang LW, Slikker Jr. W, et al. A dose-response study of ibogaine-induced neuropathology in the rat cerebellum. Toxicol Sci. 2000;57:95–101.

[24] Helsley S, Dlugos CA, Pentney RJ, et al. Effects of chronic ibogaine treatment on cerebellar Purkinje cells in the rat. Brain Res. 1997;759:306–308.

[25] Glick SD, Kuehne ME, Raucci J, et al. Effects of iboga alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum. Brain Res. 1994;657:14–22.

[26] Miwa H. Rodent models of tremor. Cerebellum. 2007;6:66–72.

[27] Scallet AC, Ye X, Rountree R, et al. Ibogaine produces neurodegeneration in rat, but not mouse, cerebellum. Neurohistological biomarkers of Purkinje cell loss. Ann N Y Acad Sci. 1996;801:217–222.

[28] Kubiliene A, Marksiene R, Kazlauskas S, et al. Acute toxicity of ibogaine and noribogaine. Medicina (Kaunas). 2008;44:984–988.

[29] Jalal S, Daher E, Hilu R. A case of death due to ibogaine use for heroin addiction: case report. Am J Addict. 2013;22:302

[30] Asua I. Growing menace of ibogaine toxicity. Br J Anaesth. 2013;111:1029–1030.

[31] Hoelen DW, Spiering W, Valk GD. Long-QT syndrome induced by the antiaddiction drug ibogaine. N Engl J Med. 2009;360:308–309.

[32] O'Connell CW, Gerona RR, Friesen MW, et al. Internet-purchased ibogaine toxicity confirmed with serum, urine, and product content levels. Am J Emerg Med. 2015;33:e5–e6.

[33] Paling FP, Andrews LM, Valk GD, et al. Life-threatening complications of ibogaine: three case reports. Neth J Med. 2012;70:422–424.

[34] Vlaanderen L, Martial LC, Franssen EJ, et al. Cardiac arrest after ibogaine ingestion. Clin Toxicol (Phila). 2014;52:642–643.

[35] Marta CJ, Ryan WC, Kopelowicz A, et al. Mania following use of ibogaine: a case series. Am J Addict. 2015;24:203–205.

[36] Alper KR, Stajić M, Gill JR. Fatalities temporally associated with the ingestion of ibogaine. J Forensic Sci. 2012;57:398–412.

[37] Maas U, Strubelt S. Fatalities after taking ibogaine in addiction treatment could be related to sudden cardiac death caused by autonomic dysfunction. Med Hypotheses. 2006;76:960–964.

[38] Mazoyer C, Carlier J, Boucher A, et al. Fatal case of a 27-year-old male after taking iboga in withdrawal treatment: GC-MS/MS determination of ibogaine and ibogamine in iboga roots and postmortem biological material. J Forensic Sci. 2013;58:1666–1672.

[39] Papadodima SA, Dona A, Evaggelakos CI, et al. Ibogaine related sudden death: a case report. J Forensic Leg Med. 2013;20:809–811.

[40] Chèze M, Lenoan A, Deveaux M, et al. Determination of ibogaine and noribogaine in biological fluids and hair by LC-MS/MS after *Tabernanthe iboga* abuse Iboga alkaloids distribution in a drowning death case. Forensic Sci Int. 2008;176:58–66.

[41] Pleskovic A, Gorjup V, Brvar M, et al. Ibogaine-associated ventricular tachyarrhythmias. Clin Toxicol (Phila). 2012;50:157

[42] Hildyard C, Macklin P, Prendergast B, et al. A case of QT prolongation and Torsades de Pointes caused by Ibogaine toxicity. J Emerg Med. 2015; doi: 10.1016/j.jemermed.2015.06.051.

[43] Glue P, Winter H, Garbe K, et al. Influence of CYP2D6 activity on the pharmacokinetics and pharmacodynamics of a single 20 mg dose of ibogaine in healthy volunteers. J Clin Pharmacol. 2015; 55:680–687.

[44] Mash DC, Kovera CA, Pablo J, et al. Ibogaine: complex pharmacokinetics, concerns for safety, and preliminary efficacy measures. Ann N Y Acad Sci. 2000;914:394–401.

[45] Baumann MH, Pablo J, Ali SF, et al. Comparative neuropharmacology of ibogaine and its O-desmethyl metabolite, noribogaine. Alkaloids Chem Biol. 2001;56:79–113.

[46] Koenig X, Kovar M, Rubi L, et al. Anti-addiction drug ibogaine inhibits voltage-gated ionic currents: a study to assess the drug's cardiac ion channel profile. Toxicol Appl Pharmacol. 2013;273:259–268.

[47] Koenig X, Kovar M, Boehm S, et al. Anti-addiction drug ibogaine inhibits hERG channels: a cardiac arrhythmia risk. Addict Biol. 2014;19:237–239.

[48] Bhargava HN, Cao YJ. Effects of noribogaine on the development of tolerance to antinociceptive action of morphine in mice. Brain Res. 1997;771:343–346.

[49] Sunder Sharma S, Bhargava HN. Enhancement of morphine antinociception by ibogaine and noribogaine in morphine-tolerant mice. Pharmacology. 1998;57:229–232.

[50] Kobayashi K, Yamamoto T, Chiba K, Tani M, Shimada N, Ishizaki T, Kuroiwa Y. Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. Drug Metab Dispos. 1998;26:818–821.