Ibogaine Investigator's Brochure

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List of Abbreviations

Abbreviation	Definition
2-BFI	2-(2-Benzofuranyl)-2-imidazoline
5-HIAA	5-Hydroxyindoleacetic acid
5-HT	5-Hydroxytryptamine (serotonin)
5-HT2A	Serotonin 2A receptor
5-HT2C	Serotonin 2C receptor
5-HT3	Serotonin type 3 receptor
5-MeO-DMT	5-Methoxy-N,N-dimethyltryptamine
AA	Alcoholics Anonymous
AChR	Acetylcholine receptor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APA	American Psychiatric Association
ASC	Altered state of consciousness
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BDNF	Brain-derived neurotrophic factor
bpm	Beats per minute
CA1	Cornu Ammonis 1 region of the hippocampus
CA3	Cornu Ammonis 3 region of the hippocampus
CCK-8	Cholecystokinin octapeptide
Cmax	Peak serum concentration
CPu	Caudate-putamen
CYP2C9	Cytochrome P450 isozyme 2C9
CYP2D6	Cytochrome P450 isozyme 2D6
CYP3A4	Cytochrome P450 isozyme 3A4
DA	Dopamine
DASH	Dutch Addict Self-Help
DAT	Dopamine transporter
DC	Direct current (as in DC shock)
DG	Dentate gyrus
DOM	2,5-Dimethoxy-4-methylamphetamine
DOPAC	3,4-Dihydroxyphenylacetic acid
DTDS	Dopamine transporter deficiency syndrome
ECG	Electrocardiogram
ED50	Effective dose for 50% of the animals in a study
EEG	Electroencephalogram
FCx	Frontal cortex

FDA	Food and Drug Administration
GDNF	Glial cell line-derived neurotrophic factor
GGT	Gamma-glutamyl transferase
GTCS	Generalized tonic-clonic seizure
HCl	Hydrochloride
hDAT	Human dopamine transporter
hERG	Human ether-à-go-go-related gene
HPPD	Hallucinogen-persisting perceptual disorder
HVA	Homovanillic acid
i.a.	Intra-arterial injection as a route of drug administration
ICASH	International Coalition of Addict Self-Help
i.c.v.	Intracerebroventricular administration as a route of drug administration
IEG	Immediate early genes
IFN	Interferon
i.g.	Intragastric injection as a route of drug administration
i.p.	Intraperitoneal injection as a route of drug administration
i.v.	Intravenous injection as a route of drug administration
LD50	Lethal dose for 50% of the animals in a study
LOAEL	Lowest observed adverse effects level
LSD	Lysergic acid diethylamide
LTP	Long-term potentiation
MAPS	Multidisciplinary Association for Psychedelic Studies
mg/kg	Milligrams of a drug per kilogram of body weight
mRNA	Messenger ribonucleic acid
MXR	Mitoxantrone
NA	Narcotics Anonymous
NAc	Nucleus accumbens
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NDA	New Drug Application (as in NDA International)
NGF	Nerve growth factor
NIDA	National Institute on Drug Abuse
NMDA	N-methyl-D-aspartate
nNOS	Neuronal nitric oxide synthase
NOAEL	No observed adverse effects level
NOS	Nitric oxide synthase
nRBC	Nucleated red blood cells
PCP	Phencyclidine
P-gp	P-glycoprotein
Ph-a	Pheophorbide-a
pKa	Acid dissociation constant (negative log)
p.o.	Per oral
QT	Time interval: start of Q wave to end of T wave in the cardiac electrical cycle
QTc	Corrected QT interval
REM	Rapid eye movement
Rh-123	Rhodamine-123
SAMHSA	Substance Abuse and Mental Health Services Administration
s.c.	Subcutaneous injection as a route of drug administration
SERT	Serotonin transporter
SLC6	Solute carrier family 6

SPECT	Single-photon emission computerized tomography
SRI	Serotonin reuptake inhibitor
t½	Half-life of a drug
TdP	Torsades de Pointes
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VTA	Ventral tegmental area

Summary

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a United States-based non-profit research and educational organization supporting research into the therapeutic potential of 12-methoxibogamine (ibogaine). MAPS has completed two observational studies of the long-term effects of ibogaine treatment on patients undergoing detoxification therapy for opioid use disorders at independent clinics in Mexico (T. K. Brown & Alper, 2017) and New Zealand (Noller et al., 2018). Thousands of people worldwide have used ibogaine to detoxify from addictive drugs. Although ibogaine has never been a common recreational drug, it became a Schedule I controlled substance in 1967 and thus is not used in mainstream substance-abuse treatment clinics in the United States. Nonetheless, American patients increasingly travel to ibogaine clinics in Mexico, Canada, and other jurisdictions for therapeutic purposes (Yockey, 2025).

The information presented in this Investigator's Brochure is summarized from published research studies about ibogaine, sponsor-collected data, and published studies of ibogaine use. For the purposes of this document, "ibogaine" refers to the chemical 12-methoxyibogamine and "iboga" to the plant *Tabernanthe iboga*, which is the botanical source of the drug.

Overview

Ibogaine is an indole alkaloid; a tryptamine with two chiral centers. It is commercially available as a hydrochloride salt with the appearance of a white or slightly off-white powder. In non-research settings, a brown powder made of pulverized *T. iboga* root bark or a whole-alkaloid extract of the root bark is sometimes used.

Ibogaine concentrations reach their peak approximately 2 hours after typical oral doses (500–1000 mg) in humans with maximum plasma concentrations (C_{max}) of approximately 1 µg/mL. The plasma half-life of ibogaine is approximately 7.5 hours, indicating that most of the drug (>97%) is eliminated after 38 hours. Ibogaine is lipophilic and accumulates in fat where its concentrations exceed that of plasma or brain by more than two orders of magnitude shortly after administration in animal models, establishing a peripheral pharmacological reservoir that permits slow redistribution into systemic circulation and sustains low-level parent-compound exposure well beyond the acute dosing phase (Esperança et al., 2026). The primary metabolite, noribogaine, is formed mainly by CYP2D6. Peak plasma concentrations (approximately 1 µg/mL) of noribogaine are reached approximately 6 hours after ibogaine ingestion and slowly decline, with an estimated terminal half-life of 28 to 49 hours. Controlled human pharmacokinetic data further demonstrate that reduced CYP2D6 activity substantially increases systemic exposure to the combined active moiety (ibogaine plus noribogaine), amplifying both the magnitude and duration of electrophysiological liability and contributing to clinically relevant interindividual variability in outcomes (Esperança et al., 2026; Glue, Winter, et al., 2015).

The pharmacology of ibogaine has been characterized in numerous animal studies. Recent mechanistic synthesis positions ibogaine within a distinctly polypharmacological framework, in which coordinated modulation of dopaminergic, serotonergic, opioid, glutamatergic, and nicotinic systems is conceptualized as a neurobiological "reset" of substance use disorder-related circuitry accompanied by a window of enhanced synaptic plasticity.

Neural mechanisms of ibogaine's effects are incompletely understood. It has been suggested that a "broad spectrum of activity may in part be responsible for ibogaine's putative anti-addictive activity" (Sweetnam et al., 1995). Ibogaine and its major metabolite noribogaine have low micromolar affinities for the serotonin transporter, sodium channels, sigma2 sites, NMDA receptors, 5HT3 receptors, mu and kappa opioid receptors (Glick et al., 2000), and α3β4 acetylcholine receptors (Arias, Feuerbach, et al., 2010). Interactions with NMDA receptors, sigma2, and serotonin binding sites may contribute to dream-like psychedelic states, while α3β4 interactions may be important for anti-addiction effects. More recent evidence further implicates the medial habenula–interpeduncular nucleus (MHb–IPN) axis, which integrates aversion-related signals and exerts inhibitory control over mesolimbic dopaminergic output; functional antagonism at α3β4-containing nicotinic receptors highly expressed in the medial habenula is now regarded as a core mechanistic substrate of ibogaine's reductions in self-administration across opioids, stimulants, nicotine, and alcohol (Esperança et al., 2026; Glick et al., 2002; Marton et al., 2019; Velasquez et al., 2014). A meta-analysis of 27 animal studies found that self-administration of opioids, cocaine, and ethanol were reduced within 24 hours following ibogaine administration (Belgers et al., 2016). Studies of ibogaine interactions with addictive drugs have shown that it blocks morphine and nicotine-induced DA release but enhances cocaine-induced increases in extracellular DA levels.

Ibogaine is distinguished among pharmacologic therapies for substance use disorder by a mechanism of action that does not rely on receptor substitution, as is the case with methadone or buprenorphine. Three therapeutic effects have been proposed: attenuation of tolerance, reduction of withdrawal symptomatology, and suppression of drug craving. Preclinical evidence further suggests that ibogaine may normalize neuroadaptations associated with sensitization and tolerance (K. R. Alper et al., 2006).

Ibogaine has psychological effects that have been categorized into three phases (K. R. Alper et al., 2001): An acute dream-like state, apparently reflective on long-term memories, that begins within 1 to 3 hours following ingestion and typically lasts 4 to 8 hours; a longer evaluative state typically lasting 8 to 20 hours in which the volume of recalled psychological material from the acute phase slows and the individual evaluates their inner subjective experience, often preferring an environment with minimal sensory stimulation to reduce distractions; and finally a period of waning residual stimulation that begins approximately 12 to 24 hours post-ingestion and endures for 24 to 72 hours "or longer". Some report additional symptoms such as "reduced need for sleep for several days to weeks following treatment." The visual and psychological effects of the first two phases have been likened to a "waking dream" (K. R. Alper et al., 2001), and clinicians harness these effects for psychotherapeutic purposes during detoxification (Dickinson, 2015).

Adverse Events, Risks, and Legality

The cardiovascular effects of ibogaine warrant particular attention. Ibogaine can prolong the QT interval and induce life-threatening torsades de pointes (TdP) arrhythmias. Both ibogaine and noribogaine inhibit hERG potassium channels at low micromolar concentrations, with IC_{50} values of 4 μM and 3 μM, respectively. hERG inhibition prolongs the repolarization phase of the cardiac action potential and the QT interval of the ECG, reducing repolarization reserve and facilitating early afterdepolarizations—a well-characterized substrate for torsades de pointes and malignant ventricular arrhythmias (Esperança et al., 2026).

Ibogaine-related deaths have been reported as late as 76 hours after ingestion, and QT prolongation typically persists for more than 24 hours, occasionally exceeding one week. The disparity between the elimination half-lives of ibogaine and noribogaine implicates the metabolite as a principal driver of delayed cardiotoxicity. A randomized, double-blind, placebo-controlled ascending-dose study has demonstrated a concentration-dependent increase in QTc with noribogaine exposure, directly linking circulating metabolite levels to delayed ventricular repolarization in humans. Toxicokinetic case reports

further document sustained QTc prolongation and ventricular arrhythmias persisting for several days following ingestion, despite near-complete clearance of the parent compound (Esperança et al., 2026; Henstra et al., 2017).

Collectively, hERG/IKr inhibition, CYP2D6-dependent noribogaine formation, slow metabolite elimination, and lipophilic tissue sequestration operate synergistically to extend the temporal window of cardiac vulnerability well beyond the acute dosing phase (Esperança et al., 2026).

Risks of ibogaine can be managed and reduced in clinical settings. Potential patients who have heart disease or seriously impaired liver function should be excluded. Dose can be adjusted based on gender and CYP2D6 status. Vital signs, including ECG, should be monitored at scheduled intervals and included as part of aftercare. Because ibogaine can produce sensitivity in the autonomic nervous system, the patient should be maintained in a low-stimulus environment for a few days after the ibogaine session in order to protect against heart problems.

To date, ibogaine has most frequently been administered outside of formal research settings for the treatment of opioid use disorder; however, the available literature supports its efficacy across multiple substance use disorders. A retrospective study evaluated outcomes in 75 patients with dependence on alcohol, cannabis, or cocaine, with a single patient presenting with concurrent opioid use (Schenberg et al., 2014). Across one to nine sessions at doses ranging from 7.5 to 20 mg/kg, ibogaine produced prolonged abstinence, with a median duration of 5.5 months following the initial session and 8.4 months when subsequent sessions were aggregated. No serious adverse events were observed or reported.

Other acute, self-reported effects include ataxia, dizziness, nausea, vomiting, diarrhea, tinnitus, discoordination, emotional distress, "difficulty trying to move", and the sensation of physical heaviness (Heink et al., 2017). In rats, ibogaine can produce whole-body tremors – possibly due to its effects on sodium channels (Deecher et al., 1992) – lasting 2 to 3 hours (Glick, Rossman, et al., 1992).

Animal studies have examined the potential for neurotoxic changes in the cerebellum. Investigations in rats have identified damage to cerebellar Purkinje cells, although comparable findings have not been observed in mice or non-human primates (vervet). Dose-response analyses in rats have established Purkinje cell degeneration at doses ≥50 mg/kg (i.p.), with a no-observed-adverse-effect level (NOAEL) of 25 mg/kg, quantitatively delineating the relationship between dose and cerebellar neurotoxic risk (Scallet et al., 1996; Xu et al., 2000).

Notably, neurotoxic changes were not identified on autopsy of an individual who died of natural causes approximately 25 days after the last of four ibogaine exposures. In rats, cerebellar damage was absent at 25 mg/kg but detectable at 50 mg/kg. The absence of comparable neuropathological findings in mice under similar experimental conditions underscores marked species-specific susceptibility and constrains direct extrapolation of cerebellar toxicity thresholds from rodent models to humans (Esperança et al., 2026). Studies in rats further suggest that females exhibit greater sensitivity to ibogaine than males, particularly during the preovulatory phase when estrogen levels are elevated, and may therefore require lower doses to achieve equivalent effects.

Ibogaine has been used by an estimated several thousand individuals outside of the traditional religious context of West Africa. A 2010 estimate placed the figure at fewer than 10,000, with substantial growth in use in the years since (Hamilton, 2010). While most administrations have not been associated with acute or persistent adverse outcomes, 34 fatalities have been documented, a subset of which occurred within substance use disorder treatment clinics. The majority of these cases involved cardiac complications, and several were attributable to adverse interactions with concomitant substances that had not been disclosed to providers. In response, ibogaine treatment facilities have implemented more rigorous screening protocols, and a corresponding reduction in morbidity and mortality has been observed despite a

concurrent expansion in the clinical use of ibogaine for substance use disorder. In parallel, the dissemination of harm-reduction information through online channels has provided individuals who self-administer with strategies for mitigating known risks, potentially decreasing the per-capita incidence of adverse events even as the absolute number of users has continued to rise.

The legal status of ibogaine varies by jurisdiction and remains subject to ongoing regulatory change; the current status across jurisdictions is summarized in Table 1. For certain countries, primary sources such as official government publications were unavailable, and secondary sources were consulted in their stead.

Table 1: Legal Status of Ibogaine by Country

Country	Legal Status	Summary	Source
Australia	Schedule 4 (Prescription Only)	Scheduled since 2010 under the Poisons Standard. Not approved under the Australian Register of Therapeutic Goods; clinical access is limited. Ibogaine-containing plants are not separately scheduled.	Therapeutic Goods Administration. (2025). Therapeutic Goods (Therapeutic Goods Administration, 2025) Instrument 2025. Commonwealth of Australia. https://www.tga.gov.au/resources/legislation/poisons-standard
Belgium	Controlled / Prohibited	Ibogaine and its isomers are listed among psychotropic substances whose import, manufacture, possession, and sale are prohibited without ministerial authorization.	Federal Agency for Medicines and Health Products. (2017). Royal Decree of 6 September 2017 regulating narcotic, psychotropic and soporific substances. https://www.famhp.be/
Brazil	Not scheduled; unregistered and commercially prohibited	ANVISA has stated officially that ibogaine does not appear on the controlled substances lists of Portaria SVS/MS 344/1998. However, the substance is not approved as a medicine and commercial sale is prohibited. A 2016 São Paulo state-level recommendation for hospital prescription exists but does not constitute federal approval.	Agência Nacional de Vigilância Sanitária. (2022, November 3). Tratamentos com ibogaína não estão regulamentados. Ministério da Saúde. https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2018/tratamentos-com-ibogaina-nao-estao-regulamentados
Canada	Prescription Drug List (unauthorized for use)	Added to the Prescription Drug List in 2017. No ibogaine-containing products are authorized for sale. Access may be sought via Health Canada's	Health Canada. (2017, May 19). Notice — Prescription Drug List (PDL): Multiple additions. Government of Canada. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/notice-prescription-drug-list-multiple-additions-2.html

		Special Access Program but is rarely granted. Health Canada has issued public safety warnings.	
New Zealand	Non-approved Prescription Medicine	Gazetted by Medsafe's Medicines Classification Committee in 2009–2010. Remains unapproved under the Medicines Act 1981, but may be prescribed by authorized practitioners under Section 25 with informed consent protocols.	Medsafe. (2009). Minutes of the 42nd meeting of the Medicines Classification Committee. Ministry of Health. https://www.medsafe.govt.nz/profs/class/Minutes/2006-2010/mccMin03Nov2009.htm
Portugal	Decriminalized (personal use)	Under Law 30/2000, personal use, acquisition, and possession of controlled substances are administrative offences within a 10-day supply threshold. Trafficking and commercial supply remain criminal.	Assembleia da República. (2000). Lei n.º 30/2000, de 29 de novembro. Diário da República, I Série-A, N.º 276.
South Africa	Schedule 6	Classified as a Schedule 6 substance under the Medicines and Related Substances Act 101 of 1965 by the Medicines Control Council (now SAHPRA). Supply requires a prescription.	South African Government. (n.d.). Medicines and Related Substances Act 101 of 1965. https://www.gov.za/documents/drugs-control-act-7-jul-1965-0000
United Kingdom	Prohibited supply (Psychoactive Substances Act 2016, 2016)	Production, supply, importation and exportation prohibited (with exceptions for approved medicines and research). Personal possession generally not criminalized outside custodial settings. Maximum supply penalty is 7 years.	Parliament of the United Kingdom. (2016). Psychoactive Substances Act 2016. The National Archives. https://www.legislation.gov.uk/ukpga/2016/2
United States	Schedule I (Federal Controlled Substance)	Listed as Schedule I under the Controlled Substances Act. Federally prohibited to manufacture, distribute, or possess. Some US states have introduced limited research or	Drug Enforcement Administration. (2025)

		program legislation, but no FDA approval exists.	
NOTE: THE BELOW COUNTRIES HAVE NOT BEEN VALIDATED BY A PRIMARY GOVERNMENT SOURCE			
The Bahamas	Reportedly unregulated	Reportedly not listed as a controlled substance; private clinics operate legally. Requires verification against current Bahamas Dangerous Drugs Act or equivalent.	No primary government source located. Verify against Bahamas National Drug Council or Ministry of Health publications.
Costa Rica	Reportedly unregulated	Reportedly not listed as a controlled substance under Costa Rican drug law (Ley 8204); private retreat centres operate openly. Requires verification against Ministerio de Salud and IAFA publications.	No primary government source located. Verify against Instituto sobre Alcoholismo y Farmacodependencia (IAFA) or Ministerio de Salud.
Denmark	Controlled substance (euphoriant)	Reportedly listed under List B of the Executive Order on Euphoriant Substances (Bekendtgørelse om euforiserende stoffer). Possession and distribution illegal without authorization.	Secondary source references: Ministry of Health and the Elderly executive order on euphoriant substances. Primary confirmation required via Lægemiddelstyrelsen (Danish Medicines Agency).
France	Controlled substance (stupéfiant)	Reportedly listed on the French list of narcotic substances (Liste des stupéfiants) alongside Tabernanthe iboga, Tabernanthe manii, and ibogaine's isomers, esters, ethers and salts. Possession, manufacture, and sale prohibited.	Secondary source references: Arrêté of the Agence nationale de sécurité du médicament (ANSM). Primary confirmation required via Journal officiel de la République française.
Gabon	Protected cultural heritage	Iboga (Tabernanthe iboga) reportedly designated a "national treasure" and its export regulated under a 1994 cultural protection law administered by the Ministry of Culture. Ibogaine as an isolated compound is not formally scheduled;	Secondary source references: 1994 Gabonese cultural protection law. Primary confirmation required via Ministère de la Culture du Gabon.

		traditional Bwiti use is permitted.	
Germany	Unregulated / Prescription (AMG)	Ibogaine reportedly not listed under the Narcotics Act (Betäubungsmittelgesetz, BtMG), but medical use is regulated under the Medicines Act (Arzneimittelgesetz, AMG). Clinical supply requires pharmacy dispensation.	Secondary source references: Arzneimittelgesetz (AMG). Primary confirmation required via Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM).
Ireland	Controlled substance	Reportedly covered under the Criminal Justice (Psychoactive Substances) Act 2010, which prohibits sale and supply of psychoactive substances not otherwise specifically scheduled. Personal possession generally not an offence.	Secondary source references: Criminal Justice (Psychoactive Substances) Act 2010. Primary confirmation required via Irish Statute Book (irishstatutebook.ie).
Mexico	Unregulated	Ibogaine reportedly not listed under the Ley General de Salud or the Reglamento de la Ley General de Salud en Materia de Control Sanitario. Clinics operate openly, particularly for substance use disorder treatment.	Secondary source references: Ley General de Salud. Primary confirmation required via COFEPRIS (Comisión Federal para la Protección contra Riesgos Sanitarios).
Netherlands	Not explicitly scheduled	Ibogaine reportedly not listed under the Opium Act (Opiumwet). Not a recognized medicine; the Health and Youth Care Inspectorate (IGJ) has previously closed clinics on safety grounds.	Secondary source references: Opiumwet. Primary confirmation required via Inspectie Gezondheidszorg en Jeugd (IGJ) or College ter Beoordeling van Geneesmiddelen (CBG).
Norway	Controlled substance	Reportedly covered under Norwegian drug legislation as a tryptamine derivative or listed in the Narcotics List (Narkotikalisten). Possession and distribution prohibited.	Secondary source references: Narkotikaforskriften. Primary confirmation required via Statens legemiddelverk (Norwegian Medicines Agency).
Sweden	Narcotic (Schedule I equivalent)	Reportedly classified as a narcotic substance under Swedish drug	Secondary source references: Läkemedelsverkets föreskrifter (LVFS) narkotikaförteckning. Primary

		legislation. Possession, sale, and distribution illegal.	confirmation required via Läkemedelsverket (Swedish Medical Products Agency).
Switzerland	Controlled substance	Reportedly listed on the Swiss narcotics schedule (Verzeichnis der kontrollierten Substanzen) under the Narcotics Act (Betäubungsmittelgesetz, BetmG). Prohibited for non-medical use.	Secondary source references: Betäubungsmittelgesetz (BetmG). Primary confirmation required via Swissmedic or Federal Office of Public Health (BAG).
Finland	Controlled substance (2014)	Reportedly listed since 2014 in the Government Regulation of Psychoactive Substances. Possession illegal; personal use may be decriminalized.	Secondary source references: Government Regulation on Psychoactive Substances (2014). Primary confirmation required via Fimea (Finnish Medicines Agency).
Hungary	Controlled (New Psychoactive Substance)	Reportedly listed under Section C (New Psychotropic Substances) of Government Regulation 66/2012 (IV. 2) on drugs and psychotropic substances.	Secondary source references: Government Regulation 66/2012. Primary confirmation required via Hungarian National Institute of Pharmacy (OGYEI).
Israel	Prohibited	Reportedly prohibited since 2015 under an Emergency Declaration on Dangerous Substances.	Secondary source references: Ministry of Health Emergency Declaration (2015). Primary confirmation required via Israeli Ministry of Health (health.gov.il).
Italy	Controlled substance	Reportedly added to the list of controlled substances by a 2016 Ministry of Health decree, covering both "iboga" and "ibogaine."	Secondary source references: Decreto Ministeriale 1 agosto 2016. Primary confirmation required via Ministero della Salute via gazzettaufficiale.it.

Table 1 note: Where conflicts between secondary sources were identified during cross-referencing, primary sources were used to resolve them. Notable clarifications: Australia is Schedule 4 (not Schedule 9, as occasionally misreported), per the Poisons Standard administered by the Therapeutic Goods Administration; Brazil is widely described in secondary sources as having "legalized" ibogaine for prescription use in 2016. ANVISA's official position is that ibogaine is neither on the controlled substances list nor approved as a medicine, and commercial sale is prohibited. The 2016 decision referenced in secondary sources was a São Paulo state-level recommendation that did not alter federal regulatory status.; Belgium's current controlling instrument is the Royal Decree of 6 September 2017, which supersedes the frequently cited Royal Decree of 22 January 1998.

This Investigator's Brochure will present the available nonclinical and clinical data on ibogaine, including studies using the drug in cell cultures, tissue cultures, animals, isolated animal tissues and organs, and in human beings.

Introduction

History & Background

Ibogaine is a naturally occurring psychoactive indole alkaloid found predominantly in the root bark of *Tabernanthe iboga* and in other plants of the Apocynaceae family (Krengel et al., 2016). Although ibogaine is usually described as the most prevalent alkaloid in the rootbark of *T. iboga*, the plant contains more than 30 other indole alkaloids, including ibogamine, ibogaline, voacangine, tabernanthine, and coronaridine, several of which may exert mutually supportive synergistic effects that contribute to the psychoactive and therapeutic potential of iboga preparations (Bading Taika et al., 2018; Michele & Sophie, 2023). It is a potent psychedelic (alternatively, hallucinogen) with dissociative properties. In Gabon, the Democratic Republic of the Congo, Republic of the Congo, and the Rio Muni region of Equatorial Guinea, members of the Bwiti and other West African religions ingest the root of *T. iboga* for ceremonial and medicinal purposes (Pope, 1969).

Table 2: Botanical sources of ibogaine and related iboga-type alkaloids, plant material used, and representative extraction approaches reported in the literature (Esperança et al., 2026)

Plant Source (Species)	Plant Material	Geographic Origin	Preparation/Extraction Method
Tabernanthe iboga	Root bark; minor amounts in leaves and seeds	Central Africa (Gabon, Congo, Cameron)	Classical maceration or percolation of powdered root bark with alcoholic or hydroalcoholic solvents, followed by successive acid–base extraction to obtain crude alkaloid fractions; isolation of ibogaine typically as hydrochloride salt ((Bruneton, 1999; Haller & Heckel, 1901; Jenks, 2002))
Tabernanthe iboga	Root bark	Central Africa	Modern analytical profiling using LC-MS/MS and LC-HRMS/MS applied to aqueous or hydroalcoholic root extracts, revealing complex alkaloid and phenolic profiles beyond ibogaine ((Bading Taika et al., 2018))
Voacanga africana	Seeds and stem bark	West and Central Africa	Acid–base extraction of total alkaloids from seeds or bark; isolation of voacangine as a major constituent, subsequently used as a semisynthetic precursor for ibogaine production (Jenks, 2002)
Peschiera affinis	Roots and stem	Brazil (Ceará)	Sequential cold extraction with hexane and ethanol, followed by conventional acid–base alkaloid extraction and chromatographic fractionation (silica gel, Sephadex LH-20) for isolation of individual iboga-type alkaloids (Santos et al., 2009)

In and around the Congo Basin, with its gravitational center in present-day Gabon, *T. iboga* has been used for generations by several ethnic groups, most notably the Babongo, Apindji, Mitsogho, Massango, Puna, and Fang peoples, for a variety of medical, invigorative, spiritual, and divinatory purposes (Bonhomme, 2005; Fernandez & Fernandez, 2001; Ona & Marie, 2026). Beyond its well-known ritual role in Bwiti initiation and healing ceremonies, iboga has been used locally to enhance the senses during hunting, as a stimulant to combat fatigue, as an aphrodisiac, as a mild anesthetic for stomach and tooth pain, and as a general remedy for promoting fertility and treating genitourinary infections, conjunctivitis, cough, and fever (Neuwinger, 2000). According to local narratives, the Babongo people, estimated to have inhabited the region for more than 5,000 years, are credited with discovering the psychoactive properties of the iboga root and sharing this knowledge with neighbouring Bantu peoples around the mid-19th century (Knight, 2003).

Written history of ibogaine in the West began when French navy surgeon Dr. Griffon du Bellay brought *T. iboga* from Gabon to Paris in 1864, describing it as being used by Gabonese as an inebriant, stimulant, and aphrodisiac. In 1885, French priest Father Henri Neu wrote *Le Gabon*, which contained an account of the Africans using the plant "to discover hidden things and to tell the future", thereby suggesting the French knew it to be psychoactive. In 1889, the French botanist Henri Ernest Baillon used this specimen to taxonomically describe the species. In 1901, two teams, Dybowski and Landrin and also Haller and Heckel, isolated ibogaine from the root bark of *T. iboga* (Dybowski & Landrin, 1901; Haller & Heckel, 1901). During the next few years, French scientists showed that ibogaine is pharmacologically active, and classified it as a stimulant (Lambert, 1901; Phisalix, 1901; Pouchet & Chevalier, 1905).

Contrary to the standard narrative that emphasizes only the well-known product *Lambarène* (marketed by Houdé Laboratoires from 1938 onward), recent archival research has documented that ibogaine was commercialized in numerous retail medicines throughout the early 20th century, including *Dragées Nyrdahl* (introduced by Landrin's laboratory by at least 1903), *Grains des Anémiques*, *Syséros*, *Viris Lucet*, *Ibobiose*, and *Iperton*. These products were used for neurasthenia, fatigue, convalescence, influenza, cardiac disorders, and as aphrodisiacs, with dosing typically ranging from 10 to 30 mg of ibogaine hydrochloride. *Syséros*, which combined ibogaine with strychnine and other botanicals, remained commercially available until as late as 1997, making ibogaine arguably the first commercialized psychedelic and the only one to have withstood international prohibition following the 1971 Convention on Psychotropic Substances (Ona & Marie, 2026).

Furthermore, archival evidence documents the sale and use of ibogaine-containing products in Mexico, Brazil, and Colombia during the early 20th century (Ona & Marie, 2026). Notably, a Mexican case report by Enrique O. Aragón published in 1913 describes the successful clinical administration of *Dragées Nyrdahl* (containing ibogaine) to a 25-year-old woman with severe alcoholism, in whom the treatment reportedly prevented delirium tremens and resolved withdrawal symptoms within 15 days. This finding complicates the widely accepted narrative attributing the discovery of ibogaine's anti-addictive properties exclusively to Howard Lotsof in 1962.

Following the commercialization of *Lambarène* in 1938, ibogaine gained popularity particularly among athletes, who reportedly used it to enhance performance, combat fatigue, and accelerate recovery. Consequently, ibogaine was subsequently included in the lists of doping agents banned by the International Olympic Committee, the International Union of Cyclists, and the French State Secretariat for Youth and Sports. Through the 1940s and 1950s, scientists at Ciba Pharmaceuticals and CIA-affiliated researchers, including Harris Isbell at the Substance use disorder Research Center in Lexington, Kentucky, conducted further experiments with ibogaine in both animals and humans, in some cases within the much-contested MK-ULTRA program, exploring its psychotomimetic properties and its capacity to potentiate the analgesic effects of morphine (Isbell, 1955; J. A. Schneider & McArthur, 1956; J. A. Schneider & Rinehart, 1957; J. A. Schneider & Sigg, 1957). The commercialization of *Lambarène* was ultimately forbidden in France in 1966, though the precise reasons, whether related to serious adverse events or the broader international prohibition of psychedelic drugs at the time, remain unclear (Ona & Marie, 2026).

The drug languished in relative obscurity for most of the 20th century until an American researcher, Howard Lotsof, began promoting ibogaine as a cure for heroin withdrawal symptoms (Lotsof & Alexander, 2001). Anecdotal reports indicated that ibogaine could also reduce craving and withdrawal symptoms for other addictive drugs, including alcohol, tobacco, cocaine, and amphetamines. Lotsof's efforts succeeded in stimulating both popular interest and scientific research (Popik, Layer, & Skolnick, 1995). In recent decades, a substantial amount of data has accumulated on the physiological and psychological effects of ibogaine and its primary metabolite noribogaine.

Available substance-abuse treatment has low efficacy and recovering individuals have notoriously high relapse rates. Established pharmacological strategies for the treatment of substance use disorder include substitution, blockade and extinction, and aversion. Citing the work of J.H. Jaffe, Popik et al. (Popik, Layer, & Skolnick, 1995) noted:

In substitution strategies, a less "dangerous" drug is substituted for the abused drug as in the treatment of heroin use disorder with methadone. Blockage and extinction involve the administration of an antagonist. In this strategy, it is hypothesized that blockade of the euphoric effects of an abused drug (such as heroin) by an antagonist (such as naltrexone) will lead to the extinction of the need to use the abused drug. In the strategy of aversion, a drug (such as disulfiram) produces severe discomfort whenever the subject uses the abused drug (alcohol). Although these strategies have been widely used to treat substance use disorder, they have not been proven very efficacious. Ibogaine presents a potential new strategy for treating substance use disorder to diverse drug classes (Popik, Layer, & Skolnick, 1995).

Ibogaine Governance in Gabon

Over the past decade, Gabon has developed an increasingly comprehensive governance framework around Tabernanthe iboga and its alkaloid ibogaine, integrating biodiversity law, cultural heritage protection, and emerging global pharmaceutical interest. Earlier regulatory approaches relied on the forestry code, export restrictions, and international commitments such as the Convention on Biological Diversity and the Nagoya Protocol, emphasizing state sovereignty, prior informed consent, and equitable benefit-sharing (ImNews Africa / Agence Gabonaise de Presse, 2026).

More recent initiatives culminated in a 2026 draft decree designating iboga and ibogaine as "strategic national heritage," establishing an interministerial authorization system, strengthening intellectual property protections, and embedding formal benefit-sharing mechanisms, which establishes a legal and political framework for governance and initiates an ongoing process of implementation for Indigenous and local knowledge holders (Ecofin Agency, 2026; Meridian News, 2026). Implementation of this decree is expected to require interministerial coordination, the development of administrative procedures, the establishment of oversight bodies and a sovereign fund, and consultation with traditional knowledge holders, local communities, civil society organizations, and relevant government institutions. Therefore, the decree is a significant milestone in an evolving governance process, and a fully operational governance system is still under development.

Parallel efforts by Gabonese institutions and non-governmental organizations such as Blessings of the Forest have focused on community engagement, domestication and conservation of iboga, as well as policy advocacy and the development of one of the only publicly documented access and benefit-sharing arrangements to date. Other organizations such as ICEERS have contributed to broader international discussions on sustainability and community engagement (Blessings of the Forest, 2024; ICEERS, 2021).

These developments build upon long-standing efforts by Gabonese traditional knowledge holders, local communities, civil society organizations, and public institutions, which have historically safeguarded iboga and laid the foundation for current governance, conservation, and sovereignty discussions. While significant policy discussions are underway, access and benefit-sharing (ABS) mechanisms should be understood as emerging and evolving, with a very limited number of publicly documented collaborations that are aligned with the principles of the Nagoya Protocol and equitable benefit-sharing (National Geographic, 2023).

These initiatives respond to calls for greater reciprocity in the clinical and commercial expansion of ibogaine-based therapies, as well as to mounting conservation concerns, including iboga's slow growth, overharvesting, and limited ecological data on wild populations (Ebando, n.d.; ICEERS, 2026). Concurrently, iboga remains a cultural keystone species within Bwiti spiritual traditions, underscoring the importance of safeguarding traditional knowledge systems and aligning future development with

principles of reciprocity, sustainability, and Indigenous rights (Chacruna Institute, 2021; Samorini, 2024). While these developments position Gabon as a central actor in evolving global governance discussions around ibogaine, international scientific and commercial expansion continues to outpace the implementation of equitable governance and benefit-sharing mechanisms in the country of origin.

Mechanism of Action

Molecular Targets of Ibogaine

Mechanistic investigations have demonstrated that ibogaine inhibits the serotonin transporter (SERT) through a noncompetitive mechanism, distinguishing it from all other known SERT inhibitors, which act competitively with substrate (Bulling et al., 2012). Consistent with this finding, ibogaine functions as a noncompetitive inhibitor of transport while exhibiting competitive binding with respect to selective serotonin reuptake inhibitors (Coleman et al., 2019). It has been proposed that ibogaine's preferential binding to the inward-facing conformation of SERT underlies this noncompetitive inhibition, given that serotonin does not compete for occupancy of this conformational state and that the SERT–ibogaine complex may exist in dynamic equilibrium with the occluded conformation in a manner dependent on ionic conditions (Mash, 2023).

Beyond its activity at SERT, ibogaine has been shown to be active in displacement assays at MK-801 binding sites on the N-methyl-D-aspartate (NMDA) receptor (K. Chen et al., 1996; Mash, Staley, Pablo, et al., 1995; Popik et al., 1994; Staley et al., 1996) and at kappa opioid receptors (Maillet et al., 2015; Pearl, Johnson, et al., 1995; Staley et al., 1996). Its rapid antidepressant effects are thought to be mediated, at least in part, through a ketamine-like antagonism of NMDA receptors (Mash, Staley, Pablo, et al., 1995; Popik et al., 1994). In addition to NMDA receptor blockade, ibogaine exerts modulatory effects on aminergic, opioid, and cholinergic systems, which may collectively contribute to the rapid behavioral changes observed following single-dose administration. Pharmacological activity has further been attributed to a noncompetitive inhibitory action at multiple nicotinic acetylcholine receptor subtypes, including the α3β4 subtype (Arias, Rosenberg, et al., 2010; Badio et al., 1997; Fryer & Lukas, 1999; Glick et al., 2000; Pace et al., 2004), which is highly expressed within the medial habenula–interpeduncular nucleus (MHb–IPN) axis and constitutes a mechanistically convergent substrate for ibogaine's reductions in self-administration across opioids, stimulants, nicotine, and alcohol (Esperança et al., 2026). Ibogaine also binds with high affinity to sigma-2 receptors (Bowen et al., 1995; Mach et al., 1995), although the physiological significance of this interaction has yet to be definitively established.

Contributions of Noribogaine

Noribogaine, the principal CYP2D6-mediated O-demethylated metabolite of ibogaine, contributes substantively to the overall pharmacodynamic profile through sustained modulation of endogenous opioid and monoaminergic systems. Through its activity at μ- and κ-opioid receptors, noribogaine attenuates withdrawal-related symptomatology without inducing the pronounced euphoria characteristic of full μ-opioid agonists (Damasceno de Lourdes, 2022). This pharmacological profile permits mitigation of both somatic and affective components of withdrawal, including dysphoria mediated by κ-opioid receptor signaling (Popik, Layer, & Skolnick, 1995), while minimizing the risk of substitution dependence. In parallel, noribogaine modulates serotonergic neurotransmission through reduced serotonin reuptake and enhanced serotonergic signaling within corticolimbic circuits originating in the raphe nuclei (Baumann, Rothman, et al., 2001; Damasceno de Lourdes, 2022). These serotonergic actions are believed to underlie the anxiolytic and antidepressant-like effects observed during the post-acute withdrawal phase.

This metabolic dependency reinforces a critical pharmacological principle: the pharmacodynamics of ibogaine cannot be dissociated from its pharmacokinetic variability. CYP2D6-mediated conversion to noribogaine governs both the persistence of therapeutic effects and the magnitude of interindividual cardiovascular risk, including QT interval prolongation (Esperança et al., 2026; Glue, Winter, et al.,

2015). Controlled human pharmacokinetic data demonstrate that reduced CYP2D6 activity substantially increases systemic exposure to the combined active moiety, amplifying both the magnitude and duration of electrophysiological liability (Glue, Winter, et al., 2015).

Glutamatergic Modulation and Neuroplasticity

Complementing these mechanisms, ibogaine exhibits noncompetitive antagonism at NMDA-type glutamate receptors with an IC50 in the range of 1–2 μM. While early hypotheses positioned NMDA antagonism as a central antiaddictive mechanism (Belgers et al., 2016), subsequent evidence indicates that this pathway is neither necessary nor sufficient to account for ibogaine's core effects, although it may contribute contextually to reduced excitotoxicity and to the attenuation of drug-associated memory reinstatement during withdrawal (Glick et al., 2002; Nestler, 2001).

Critically, these acute neurochemical effects occur within a broader framework of activity-dependent neuroplasticity. Ibogaine and noribogaine induce durable neuroadaptations through upregulation of neurotrophic factors, most consistently glial cell line–derived neurotrophic factor (GDNF) and, in a context-dependent manner, brain-derived neurotrophic factor (BDNF), within key reward-related regions including the ventral tegmental area (VTA) and nucleus accumbens (NAc) (Cameron et al., 2021; He & Ron, 2006). At the intracellular level, activation of mTOR-dependent signaling pathways supports synaptic remodeling and the corrective reorganization of maladaptive circuitry implicated in addictive behavior (Allen & Lyons, 2018; Ly et al., 2018).

Integrated Polypharmacological Framework

Taken together, these findings support a model in which ibogaine exerts its therapeutic effects not through acute substitution or single-receptor dominance, but through coordinated recalibration of reward, aversion, and plasticity networks. This polypharmacological profile distinguishes ibogaine from monotarget substance use disorder pharmacotherapies and underpins its distinctive, though still incompletely validated, therapeutic potential. From a pharmacodynamic standpoint, ibogaine represents one of the most comprehensive pharmacological approaches to addressing the system-level nature of substance use disorders, while simultaneously underscoring the imperative for rigorous translational evaluation in light of persistent safety and clinical-validation constraints.

Substance Use Disorder and Other Mental Health Conditions

The opioid use disorder crisis has reached pandemic proportions globally, accompanied by widespread misuse of additional classes of psychoactive substances. The compulsive consumption of these substances despite demonstrable adverse consequences imposes substantial societal and economic costs, generating an urgent need for novel therapeutic modalities and providing a strong rationale for continued investigation into the therapeutic properties of ibogaine. In parallel, post-traumatic stress disorder (PTSD) and trauma-related conditions represent a substantial and frequently treatment-resistant public health burden, particularly among military veteran populations, for which ibogaine has more recently emerged as a candidate therapeutic agent.

Ibogaine-assisted therapy has developed in parallel with other forms of psychedelic-assisted psychotherapy (Schenberg, 2018; Sessa & Johnson, 2015; Winkelman, 2014); however, ibogaine is distinguished by pharmacological properties that confer both unique risks and distinctive therapeutic potential. Unlike the classical psychedelics—including mescaline, psilocybin, and lysergic acid diethylamide (LSD)—ibogaine is associated with serious adverse physiological effects that must be carefully mitigated within clinical settings. Conversely, ibogaine possesses pharmacological properties that attenuate withdrawal symptomatology, reduce drug craving, and diminish tolerance to substances of misuse.

Opioid Use Disorder

Opioid use disorder represents a rapidly expanding and frequently fatal condition that imposes billions of dollars in annual costs upon the United States healthcare system (Florence et al., 2016). In 2019, an estimated 1.6 million individuals in the United States met diagnostic criteria for opioid use disorder, with more than ten million reporting opioid misuse within the preceding twelve months ("Key Substance Use and Mental Health Indicators in the United States: Results from the 2019 Survey on Drug Use and Health," 2020). The available treatment armamentarium remains limited in scope and efficacy. Although maintenance therapy with buprenorphine-containing medications constitutes the most prevalent treatment approach (Morgan et al., 2018), retention and outcome data are modest. One representative study reported that 55% of patients discontinued buprenorphine treatment within the first 180 days (Meinhofer et al., 2019). In light of these limitations, ibogaine-assisted detoxification represents a non-substitution therapeutic alternative with the potential to address a substantial unmet clinical need and to reduce the broader public health burden associated with opioid use disorder (Mash, 2018).

Preliminary evidence suggests that ibogaine reduces consumption not only of opioids but also of additional substances of misuse, including cocaine, ethanol, and nicotine (Glick & Maisonneuve, 2000). Ibogaine produces reductions in cocaine and heroin craving during inpatient detoxification, with parallel reductions in depressive symptomatology observed both during treatment and at 30 days following program discharge (Mash et al., 2000). Given the rapid systemic clearance of ibogaine, the durability of these therapeutic effects has been attributed to the central nervous system activity of the primary metabolite noribogaine.

Ibogaine exhibits a novel mechanism of action distinct from other non-opioid agents with clinical effects on opioid tolerance and withdrawal. Experimental evidence supports the characterization of ibogaine as a "substance use disorder interrupter" suitable for clinical administration during detoxification. An open-label study of 33 patients with heroin dependence reported the following outcomes (K. R. Alper et al., 1999) of 33 patients addicted to heroin showed these results:

- 73% (25 patients) experienced no opioid withdrawal and did not exhibit drug-seeking behavior during the 72-hour post-ibogaine-treatment observation period
- 12% (4 patients) — "drug-seeking behavior without withdrawal symptoms"
- 6% (2 patients) — "drug abstinence with attenuated withdrawal signs"
- 3% (1 patient) — "drug-seeking behavior with continued withdrawal"
- 3% (1 patient) died, "possibly involving surreptitious heroin use"

Of particular clinical significance, ibogaine enabled 73% of these patients to complete detoxification without withdrawal symptoms, with reductions in short-term drug craving that may have extended beyond the 72-hour observation window (Coleman et al., 2019; Glue, Winter, et al., 2015).

Subsequent observational studies have broadly corroborated these findings. Marked reductions in opioid withdrawal severity have been documented within 72 hours of ibogaine administration, with significant reductions in opioid use relative to pretreatment baseline persisting at twelve-month follow-up in a subset of participants (T. K. Brown & Alper, 2017). Similar sustained reductions in drug use and depressive symptomatology over twelve months have been described in a small cohort of opioid-dependent individuals (Noller et al., 2018). In an inpatient, medically supervised detoxification cohort of 191 patients, substantial reductions in opioid withdrawal severity and significant decreases in opioid and cocaine craving were documented (Mash et al., 2018). Earlier case series provided the initial human observations of rapid withdrawal suppression that would motivate three decades of subsequent investigation 81, 83).

Post-Traumatic Stress Disorder and Trauma-Related Conditions

Human research investigating ibogaine for the treatment of PTSD and trauma-related conditions remains in its earliest stages, with available evidence derived predominantly from small, open-label investigations conducted in veteran populations, frequently incorporating co-administered psychedelic agents or adjunctive psychotherapeutic interventions. A prospective open-label study evaluated the magnesium–ibogaine protocol (MISTIC) in 30 male Special Operations Forces veterans presenting with predominantly mild traumatic brain injury and high comorbid rates of PTSD, depression, and anxiety (Rolle et al., 2025). At one-month follow-up, clinician-rated assessments demonstrated substantial reductions in PTSD, depressive, and anxiety symptomatology, with a large effect size for PTSD symptom reduction (Cohen's $d = 2.54$), alongside marked improvements in global functioning. The prophylactic intravenous administration of magnesium within the protocol reflected the established cardiac liability of ibogaine; no serious or unexpected adverse events were reported.

Additional evidence has emerged from a clinical program in Mexico utilizing sequential administration of ibogaine and 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) with psychotherapeutic support. In a prospective open-label cohort of 86 trauma-exposed Special Operations Forces veterans, large improvements were observed across self-reported measures of PTSD, depression, anxiety, insomnia, post-concussive symptomatology, life satisfaction, psychological flexibility, and cognitive functioning, with preliminary signals of durability extending to six months (Armstrong et al., 2023; Davis et al., 2023). A subgroup analysis of 45 participants with concurrent alcohol misuse and PTSD symptomatology demonstrated substantial reductions in risky alcohol consumption maintained at six-month follow-up, with participants exhibiting improvement in alcohol use also demonstrating significantly greater reductions in PTSD symptoms relative to non-responders. The combined administration protocols employed in these investigations preclude attribution of therapeutic effect to ibogaine alone.

While these preliminary data are encouraging, the methodological limitations are substantial: all available studies are open-label and uncontrolled, enrollment has been restricted to highly selected veteran populations, and the frequent co-administration of additional agents and psychotherapeutic interventions complicates causal inference. Ibogaine cannot at present be characterized as an established treatment for PTSD, and rigorously controlled trials remain necessary.

Recent United States Policy Developments

The therapeutic potential of ibogaine for both substance use disorder and trauma-related conditions has increasingly attracted attention at the level of United States federal and state policy. An initial effort in Kentucky, where the chair of the state Opioid Abatement Advisory Commission proposed allocating opioid settlement funds toward ibogaine research, was ultimately blocked in late 2023 following political opposition and a change in commission leadership. In May 2025, the State of Texas enacted Senate Bill 2308 and House Bill 3717, appropriating $50 million in state funds to support FDA-approved clinical trials investigating ibogaine for the treatment of substance use disorder, trauma-related conditions, and traumatic brain injury; this is the largest publicly funded psychedelic research initiative undertaken by any government to date. The state subsequently selected UTHealth Houston, in collaboration with the University of Texas Medical Branch at Galveston, to lead a multi-institutional, two-year research consortium known as Ibogaine Medicine for PTSD, Addiction, and Cognitive Trauma (IMPACT).

At the federal level, an executive order issued on April 18, 2026 directed expanded federal coordination on the evaluation of psychedelic compounds, including ibogaine, for the treatment of severe mental illness and conditions affecting military veterans, and announcing a $50 million federal investment in ibogaine research. The order directs the Food and Drug Administration to issue priority review vouchers to accelerate approval timelines, expands right-to-try pathways for ibogaine, and dedicates $50 million in ARPA-H funding to psychedelic research. FDA Commissioner Marty Makary subsequently indicated that the agency would issue national priority vouchers enabling review of late-stage clinical trial data within one to two months of submission, rather than the standard one-year timeframe.

Regulatory Status and Conclusion

To date, no randomized, placebo-controlled clinical trials have evaluated the efficacy of ibogaine in the treatment of substance use disorders or PTSD, and all available human efficacy data derive from open-label observational studies, retrospective analyses, and case reports (Esperança et al., 2026). Within the European Union, no authorized medicinal products containing ibogaine are currently available, and *Tabernanthe iboga* is not listed in any European Medicines Agency (EMA) or Committee on Herbal Medicinal Products (HMPC) monograph; consequently, any current administration occurs outside regulated pharmaceutical frameworks. The World Health Organization has similarly acknowledged the increasing interest in ibogaine as a potential therapeutic agent while emphasizing the absence of robust clinical data regarding its safety and efficacy, urging that research involving psychoactive plant-based substances adhere to rigorous standards of pharmaceutical quality, safety, and ethical oversight (World Health Organization, 2013; *World Health Statistics 2024*, 2024).

Safety

Ibogaine therapy is associated with substantial safety concerns that distinguish it from the classical serotonergic psychedelics, including psilocybin, mescaline, and lysergic acid diethylamide (LSD). Of greatest clinical significance, ibogaine and its primary metabolite noribogaine inhibit the hERG potassium channel, producing concentration-dependent prolongation of the QT interval that can progress to torsades de pointes, ventricular tachycardia, and fatal arrhythmias (K. Alper et al., 2016; K. R. Alper et al., 2012; Hoelen et al., 2009; Koenig & Hilber, 2015; Thurner et al., 2014). Multiple fatal case reports and forensic investigations have documented deaths temporally associated with ibogaine exposure, frequently occurring in the context of pre-existing cardiac or hepatic disease, electrolyte disturbances, polysubstance use, or non-standardized preparations (K. R. Alper et al., 2012; Chèze et al., 2008; Kontrimaviciute et al., 2006; Mazoyer et al., 2013; Papadodima et al., 2013). Non-fatal cases have similarly documented severe QTc prolongation and life-threatening arrhythmias following ibogaine administration (Mestre et al., 2024; Pleskovic et al., 2012; Steinberg & Deyell, 2018).

The cardiotoxic risk profile is further complicated by substantial interindividual variability in ibogaine metabolism, attributable in large part to CYP2D6 polymorphisms, as well as by the extensive lipophilic tissue sequestration of the parent compound and the prolonged systemic persistence of noribogaine. These pharmacokinetic features generate an extended window of cardiac vulnerability that may persist for several days following ingestion (Glue, Winter, et al., 2015; Henstra et al., 2017). These considerations impose a narrow therapeutic window and necessitate rigorous risk-mitigation strategies, including pre-treatment cardiac screening, continuous electrocardiographic monitoring, and careful management of electrolyte status.

In response to the established cardiac liabilities of ibogaine, medicinal chemistry efforts have yielded structural congeners designed to preserve anti-addictive efficacy while attenuating cardiotoxicity. These compounds include 18-methoxycoronaridine (18-MC), tabernanthalog (TBG), and oxa-iboga derivatives, each of which has demonstrated improved safety profiles in preclinical models (Cameron et al., 2021; Glick et al., 2000; Havel et al., 2024; Iyer et al., 2021). However, these analogues also raise complex design challenges, as reduced engagement of certain neurotrophic and plasticity-related pathways may compromise the durability of therapeutic response (Carnicella et al., 2010; Esperança et al., 2026).

Doses administered in the treatment of substance use disorders vary considerably across clinical and non-clinical settings, with typical therapeutic doses falling within the range of 15 to 20 mg/kg. The Global Ibogaine Therapy Alliance recommends that ibogaine administration not exceed 24 mg/kg within any 24-hour period, with adjustments indicated for underweight or overweight patients. The Alliance further

references preclinical evidence supporting the use of CYP2D6 phenotyping to identify poor and rapid metabolizers who may require dose adjustment (Dickinson, 2015).

Given its prolonged systemic persistence, noribogaine is considered a principal contributor to both the anti-addictive and cardiotoxic effects of ibogaine. At the receptor level, noribogaine attenuates withdrawal-related somatic and affective symptomatology through sustained modulation of μ- and κ-opioid signaling, without inducing the pronounced euphoria associated with full μ-opioid agonists. Additional anxiolytic and antidepressant-like effects during the post-acute withdrawal period have been attributed to modulation of serotonergic transmission within corticolimbic circuitry. Accordingly, data pertaining to noribogaine are included throughout this Investigator's Brochure (see Appendix for summaries on 18-MC and noribogaine).

Chemical Properties & Formulations

Chemical Properties of Ibogaine

Ibogaine is an organic heteropentacyclic compound that is ibogamine in which the indole hydrogen para to the indole nitrogen has been replaced by a methoxy group (Figure 1a). It has a role as a oneirogen, an inhibitor, a hallucinogen and a plant metabolite. It is an aromatic ether, an organic heteropentacyclic compound and a monoterpenoid indole alkaloid. It is functionally related to an ibogamine. It is a conjugate base of an ibogaine(1+) (Pubchem). Ibogaine is rapidly demethylated by first-pass metabolism to a long-acting metabolite noribogaine (Figure 1b (Mash, 2023).

The chemical name for the compound is ibogaine HCl. Ibogaine is also known as 12-methoxyibogamine (Fig. 1a). The hydrochloride salt has a protonated tertiary amine in the aliphatic fused ring (e.g., nonindolic nitrogen atom). The indole nitrogen of ibogaine is a tertiary amine. Ibogaine free base has a chemical formula of C20H26N2O. The molecular weight of the free base is 310.4 g/mole and 346.9 for the hydrochloride salt. The molecular formula of noribogaine is $C_{19}H_{25}N_2O \cdot Cl$ for the hydrochloride salt. The molecular weight is 296.4 for the free base and 332.9 for the hydrochloride salt. Ibogaine in the form of white to off-white powder has the IUPAC name (1 R,15 R,17 S,18 S)− 17-ethyl-7-methoxy-3,13-diazapentacyclo[13.3.1.02,10.04,9.013,18]nonadeca-2(10),4(9),5,7-tetraene. Ibogaine is obtained either by extraction from the roots of the iboga plant or by semi-synthesis from the precursor compound voacangine (Mash, 2023).

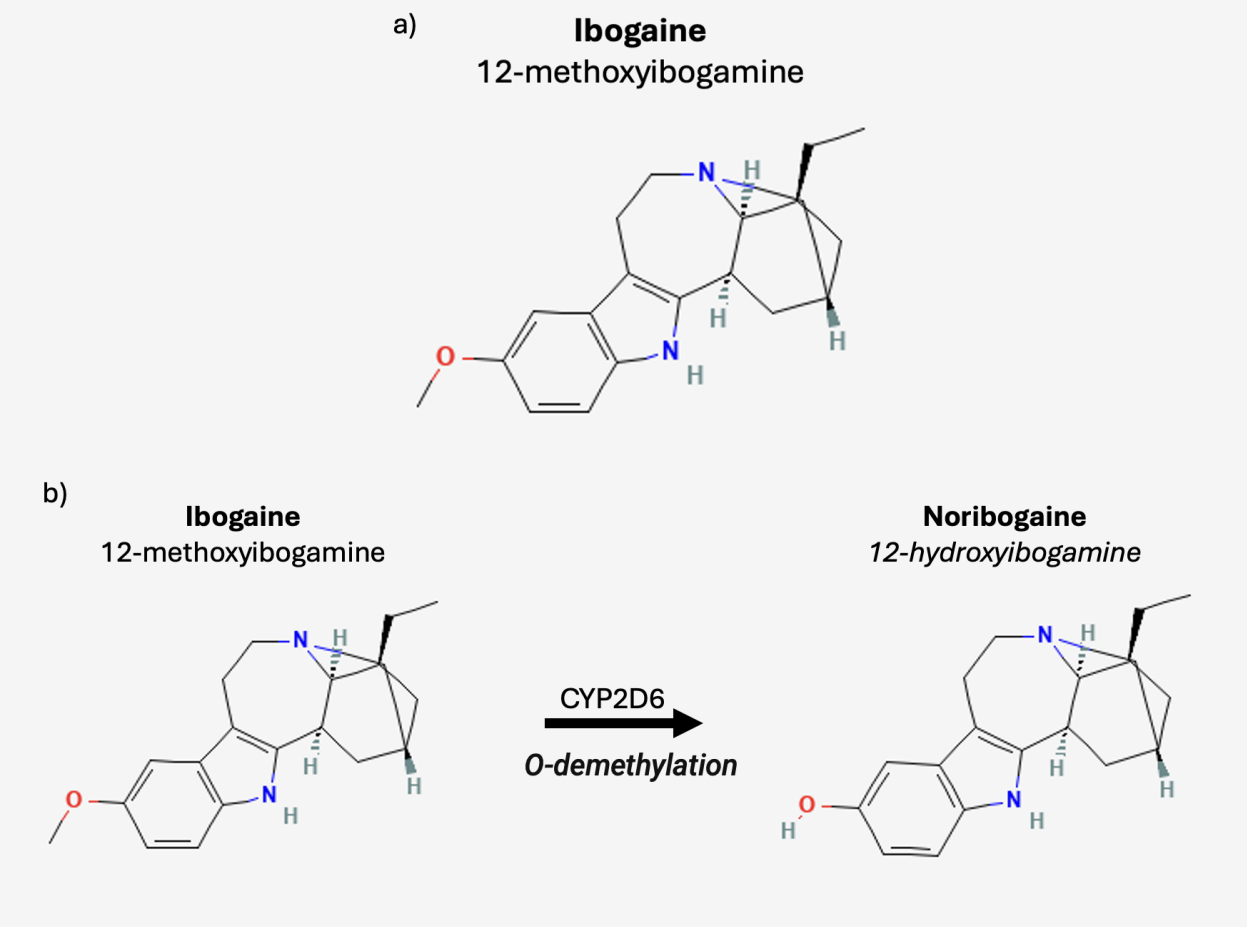

Figure 1: Chemical Structure of Ibogaine (a) and biosynthesis of noribogaine via O-demethylation by the action of cytochrome P4502D6 (CYP2D6) (b).

Table 3: Chemical Properties of Ibogaine

REGULATORY IDENTIFIERS	
UNII (FDA, ibogaine free base)	3S814I130U
UNII (FDA, ibogaine hydrochloride)	MRI8GKD98X
CAS Registry Number	83-74-9
PubChem CID (ibogaine)	197060
PubChem CID (ibogaine HCl)	197059
PubChem CID (noribogaine)	3083548
MeSH Descriptor ID	D007050
ChEBI ID	5852
EPA CompTox DTXSID	DTXSID20894069
ECHA / EINECS	201-498-4
Merck Index	m6184
NSC Number	NSC-249764
DEA Schedule	Schedule I (Hallucinogenic substance, DEA No. 7260)
NOMENCLATURE	
Approved Name (WHO-DD)	Ibogaine
Chemical Name	12-Methoxyibogamine
IUPAC Name	(1R,15R,17S,18S)-17-ethyl-7-methoxy-3,13-diazapentacyclo[13.3.1.$0^{2,10}$.$0^{4,9}$.$0^{13,18}$]nonadeca-2(10),4(9),5,7-tetraene

Other Names / Synonyms	(−)-Ibogaine; 12-Methoxyibogamine; Endabuse; Ibogamine, 12-methoxy-; NIH-10567; NSC-249764
MOLECULAR PROPERTIES	
Molecular Formula (ibogaine)	$C_{20}H_{26}N_2O$
Molecular Formula (ibogaine HCl)	$C_{20}H_{27}ClN_2O$
Molecular Formula (noribogaine)	$C_{19}H_{24}N_2O$
Molecular Weight (ibogaine)	310.43 g/mol
Molecular Weight (ibogaine HCl)	346.89 g/mol
Molecular Weight (noribogaine)	296.41 g/mol
Stereochemistry	Absolute; 5 defined stereocenters (1R, 15R, 17S, 18S configuration)
InChIKey (ibogaine)	HSIBGVUMFOSJPD-CFDPKNGZSA-N
PHYSICOCHEMICAL PROPERTIES	
Physical Form	Solid; crystallizes as prismatic needles (colourless) from ethanol
Melting Point (ibogaine)	152–153 °C
Melting Point (ibogaine HCl)	299–300 °C (with decomposition)
pKa	8.1 (in 80% 2-methoxyethanol)
Chirality (ibogaine)	Levorotatory; $[\alpha]_D = -53°$ (c, 95% EtOH)
Chirality (ibogaine HCl)	Levorotatory; $[\alpha]_D = -63°$ (MeOH); $-37.3°$ (H_2O)
Stability	Decomposed by light and heat; ibogaine HCl decomposes at 299 °C
SOLUBILITY	
Ibogaine (free base)	Freely soluble in methanol and ethanol; soluble in chloroform, acetone, and benzene; slightly soluble in acetone and chloroform; insoluble in diethyl ether and water (~257 mg/L at 25 °C, estimated)
Ibogaine hydrochloride	Soluble in water, methanol, and ethanol; slightly soluble in acetone and chloroform
SPECTROSCOPIC DATA	
Spectrofluorometry — Excitation λ	300 nm (Zetler et al., 1972)
Spectrofluorometry — Emission λ	360 nm (Zetler et al., 1972)

Sources: FDA Global Substance Registration System (GSRS); PubChem (National Library of Medicine, NIH); NLM Medical Subject Headings (MeSH); CAS Common Chemistry; ChEBI; ECHA; Büchi et al., J. Am. Chem. Soc. 1966, 88, 3099; Zetler, Singbartl & Schlosser, Pharmacology 1972, 7(4), 237–248.

Clinical Formulations

The identification of ibogaine's molecular targets, in conjunction with established drug design methodologies, revealed the early pharmacological promiscuity of both ibogaine and noribogaine. This observation provided the impetus for the development of analogs incorporating activity across multiple targets for the treatment of substance use disorders (Efange et al., 1998); US Patent 5,616,575). The overarching aim of this research program was to develop synthetic ibogaine-like compounds with the potential to surpass the therapeutic efficacy of the parent molecule. Given the relative structural complexity of ibogaine, the immediate objective was to identify the simplest ibogaine-derived fragment capable of retaining anti-addictive activity. Systematic examination of the 5-methoxytryptamine and isoquinuclidine fragments led to the discovery of a novel series of phenyl-substituted hexahydroazepino[4,5-b]indole analogs of ibogaine as compositions of matter (Efange et al., 1998). It should be noted, however, that this body of work was conducted during a period in pharmacological research characterized by a prevailing focus on highly selective, single-target therapeutics, which ultimately limited the broader application of these findings.

Ibogaine drug product is provided as ibogaine hydrochloride, administered most commonly as oral tablets or capsules. These tablets or capsules are stored in hermetically sealed containers at room temperature or refrigerated. The earliest commercial oral tablet formulations of ibogaine include: *Dragées Nyrdahl* (≈8

mg ibogaine HCl per tablet), *Lambarène* (0.2 g *Tabernanthe manii* extract per tablet, corresponding to ~8 mg ibogaine), and *Iperton* (analytically confirmed to contain ~1.5 mg ibogaine per tablet) represent, although these products were not manufactured under modern pharmaceutical quality standards and have all been withdrawn from the market (Ona & Marie, 2026).

Across contemporary clinical research, oral ibogaine HCl remains the dominant formulation. In the large open-label inpatient case series reported by (Mash et al., 2018), 191 opioid- and cocaine-dependent participants received oral doses of ibogaine HCl in gel caps at 8–12 mg/kg, with whole blood concentrations of ibogaine and noribogaine quantified by validated GC/MS methods to support pharmacokinetic characterization (Mash et al., 2018). Similarly, (T. K. Brown & Alper, 2017) administered a mean total dose of 1,540 ± 920 mg of ibogaine HCl (approximately 19 mg/kg) to 30 participants with DSM-IV opioid dependence in short-stay inpatient settings. (Knuijver et al., 2022), in a descriptive open-label observational safety study conducted at a university medical center in the Netherlands, administered a single oral dose of 10 mg/kg ibogaine HCl to 14 patients with opioid use disorder who had been converted to morphine sulphate prior to dosing. Stanford has recently integrated magnesium into their treatment protocol through the Magnesium–Ibogaine: the Stanford Traumatic Injury to the CNS (MISTIC) protocol (Cherian et al., 2024). 30 male U.S. Special Operations Forces veterans with traumatic brain injury received 1 gram of intravenous magnesium sulfate together with an oral gastrointestinal protective agent 1–2 hours prior to dosing. Oral ibogaine HCl was then administered at an initial dose of 2–3 mg/kg, with an additional dose of up to <14 mg/kg provided approximately 40 minutes later based on clinical response. At 12 hours post-dose, participants received additional intravenous magnesium sulfate alongside oral and intravenous antioxidants and metabolic supporting agents (Cherian et al., 2024).

In parallel, dedicated pharmaceutical development of ibogaine has advanced under Good Manufacturing Practice (GMP) conditions. DemeRx IB, Inc., in partnership with atai Life Sciences, has developed DMX-1002, a GMP-manufactured oral formulation of ibogaine HCl, which received approval from the UK Medicines and Healthcare products Regulatory Agency (MHRA) in 2021 to initiate the first Phase 1/2a clinical trial of ibogaine for opioid use disorder (DemeRx, n.d.) More recently, an intravenous ibogaine formulation, IBX-210, has been developed with the explicit objective of improving safety, reducing pharmacokinetic variability, and achieving shorter and more predictable in-clinic dosing times compared with oral administration (atai Life Sciences, 2021). A Phase 1 study of IBX-210 reported that 9 mg/kg intravenous ibogaine produced a tolerable safety profile, supporting advancement to a Phase 1/2a trial in opioid use disorder populations. From a manufacturing and supply-chain perspective, contemporary ibogaine HCl drug substance is most commonly produced by semisynthesis from voacangine, an iboga alkaloid obtained in higher yield (~0.9–1%) from the root bark of *Voacanga africana*, rather than by direct isolation from *Tabernanthe iboga* root bark (which contains only ~0.3–0.4% ibogaine by weight) (González et al., 2021; Iyer et al., 2021). This semisynthetic approach addresses both the low natural abundance of ibogaine in T. iboga and the sustainability and cultural concerns associated with uncontrolled exploitation of the plant in Gabon and neighboring countries (González et al., 2021). In 2025, researchers at UC Davis reported a gram-scale, seven-step total synthesis of ibogaine from pyridine, along with an enantioselective synthesis of (+)-ibogaine and access to several structurally related analogues (Iyer et al., 2025). Although total synthesis is not yet the primary manufacturing route for clinical-grade ibogaine, this advance offers the potential for fully synthetic, supply-chain-independent GMP production and for the generation of structurally diversified analogues with improved safety profiles.

Nonclinical Studies and Preclinical Findings

Findings from nonclinical animal research, retrospective studies of ibogaine administration, and case reports in human populations are presented in this section. In the 1950s, Jurg Schneider, a scientist at Ciba Pharmaceutical Products, Inc. (Summit, New Jersey), conducted murine studies investigating the capacity of ibogaine (marketed as Bogadin) to potentiate the analgesic effects of opiates (J. A. Schneider

& McArthur, 1956). These investigations led to Ciba's patenting of ibogaine for the reduction of opiate tolerance. Through potentiation and prolongation of morphine's analgesic effects, ibogaine permitted reductions in administered opioid doses, thereby attenuating the risk of toxic sequelae (J. A. Schneider, 1957), including the development of opioid use disorder and respiratory depression in patients receiving morphine. This reduction of drug tolerance is now recognized as one of three proposed therapeutic effects of ibogaine, the others comprising attenuation of withdrawal symptomatology and reduction of drug craving. In the decades following Schneider's initial rodent experiments, a substantial body of literature has accumulated, encompassing animal investigations of therapeutic activity in substance use disorder, toxicological profiling, pharmacological characterization, and effects on neurotransmitter systems.

Preclinical Evidence in Opioid Use Disorder

Although the face validity of animal models in substance use disorder research has been subject to recent scrutiny (Spanagel, 2017), in vivo pharmacological studies nonetheless demonstrate translational relevance for ibogaine. Specifically, the drug has been shown to attenuate the rewarding effects of opioids following single-dose administration (Glick et al., 1991; Spanagel, 2017) and to reduce naloxone-precipitated opioid withdrawal signs (Cappendijk et al., 1994; Dzoljic et al., 1988; Glick, Rossman, et al., 1992; Leal et al., 2003; Parker et al., 2002). Two reports, however, indicated that ibogaine was ineffective in blocking withdrawal signs in animal models (Francés et al., 1992; Sharpe & Jaffe, 1990). In morphine-dependent rhesus monkeys, subcutaneous administration of ibogaine (2 and 8 mg/kg) only partially suppressed the total number of withdrawal signs. Similarly, ibogaine administered subcutaneously (5, 10, 20, and 40 mg/kg) fifteen minutes prior to a naloxone challenge (0.5 mg/kg, s.c.) failed to reduce precipitated withdrawal in a morphine-dependent rat model (Sharpe & Jaffe, 1990). These negative outcomes may be attributable to the subcutaneous route of administration, which circumvents the first-pass hepatic metabolism of ibogaine to its active metabolite noribogaine.

Research conducted by our group has demonstrated that noribogaine dose-dependently attenuates naloxone-precipitated withdrawal signs in opioid-dependent mice (Mash et al., 2016). The approximate ED_{50} for suppression of withdrawal signs following oral noribogaine administration was 13 mg/kg. At a dose of 10 mg/kg, noribogaine achieved plasma concentrations of 26 ng/mL and brain concentrations of 533 ng/g, corresponding to approximately 0.6 μM and 5.8 μM, respectively. These findings provide additional support for the hypothesis that noribogaine contributes substantively to the clinical efficacy of ibogaine in the management of opioid withdrawal following oral administration in humans (Mash et al., 2000).

Preclinical Evidence Across Other Substance Classes

Beyond its effects on opioid reward, ibogaine produces dose-dependent reductions in stimulant-induced locomotion and psychostimulant self-administration (Broderick et al., 1994; Cappendijk & Dzoljic, 1993; Glick et al., 1994; Maisonneuve, Mann, et al., 1997; Sershen, Harsing, et al., 1992). Preclinical studies have further demonstrated that ibogaine reduces ethanol self-administration in rats, with greater efficacy observed following intraperitoneal versus subcutaneous administration, a finding consistent with first-pass conversion of ibogaine to noribogaine (A. H. Rezvani et al., 1995). The rewarding properties of ethanol (1.8 g/kg, i.p.) and ibogaine (10 or 30 mg/kg, p.o.) have also been examined using the conditioned place preference (CPP) paradigm (Henriques et al., 2021). These investigations revealed that ethanol, but not ibogaine, induced CPP in mice. Furthermore, oral administration of ibogaine following ethanol conditioning suppressed the reinstatement of ethanol-induced CPP, both during a drug-primed reinstatement test and during a drug-free assessment conducted after re-exposure to ethanol.

A seminal series of experiments conducted by Dorit Ron and colleagues at the Ernest Gallo Clinic and Research Center in both rat and mouse models definitively established that ibogaine reduces alcohol consumption (He et al., 2005). That study further demonstrated that ibogaine attenuated binge drinking

following a period of abstinence through upregulation of glial cell line-derived neurotrophic factor (GDNF).

Subsequent work confirmed that noribogaine exerts comparable effects to ibogaine on GDNF expression and ethanol self-administration (Carnicella et al., 2010). Noribogaine has also been shown to dose-dependently reduce nicotine self-administration in rats with an efficacy comparable to varenicline, a pharmacotherapy approved for smoking cessation (Chang et al., 2015). This finding supports a role for noribogaine at neuronal nicotinic acetylcholine receptors (nAChRs) as a shared substrate mediating treatment effects across both nicotine and alcohol dependence (Henriques et al., 2021). Collectively, the preclinical effects of ibogaine and noribogaine across multiple models of substance use disorder support continued investigation of this compound class as a pharmacotherapeutic strategy for modulating brain reward circuitry.

Consistent with the established role of active metabolites in drug discovery, Belgers and colleagues conducted a meta-analysis of in vivo animal studies of ibogaine and reported that the most pronounced reductions in drug self-administration occurred within the first 24 hours following intraperitoneal administration, with effects persisting for more than 72 hours (Belgers et al., 2016). The rapid biotransformation of ibogaine to noribogaine (Hearn et al., 1995; Hough et al., 1996) supports the characterization of ibogaine as a prodrug whose bioactivation to noribogaine substantially contributes to the in vivo pharmacological effects observed in humans (Mash et al., 2001). Noribogaine, as a pharmacologically active metabolite, may be responsible for the primary therapeutic effects of ibogaine treatment (on-target activity) or may contribute off-target activities distinct from those of the parent compound. Further investigation using noribogaine as an isolated pharmacological agent is warranted in both human and animal studies to systematically delineate its on- and off-target contributions to ibogaine's overall therapeutic profile.

Neither noribogaine nor ibogaine exhibits the conditioned place preference associated with potent mu-opioid receptor agonists, nor the conditioned place aversion observed with kappa agonists (Skoubis et al., 2001) or mu antagonists (Mash et al., 2016; Parker et al., 1995). Consistent with in vitro binding data, noribogaine does not substitute for the discriminative stimulus properties of morphine or the kappa agonist U50,488 (Parker et al., 1995; Zubaran et al., 1999). The discriminative stimulus profile of ibogaine has been characterized in rats trained to discriminate phencyclidine (PCP; 2.0 mg/kg, i.p.) (Jones, 1998). Ibogaine (5.6–17.6 mg/kg, i.p.) failed to substitute for PCP in rats, and similarly did not generalize to the PCP discriminative cue in rhesus monkeys (0.5–4.0 mg/kg, i.m.) trained to discriminate PCP (0.1 mg/kg, i.m.) from vehicle injections. Notably, lysergic acid diethylamide (LSD), included as a reference compound, produced only partial substitution for PCP in rats and minimal responding on the PCP-associated lever in monkeys. Given that noribogaine is pharmacologically inactive as a glutamate channel blocker (Mash, Staley, Pablo, et al., 1995), the extensive first-pass metabolism of ibogaine to noribogaine warrants careful consideration when interpreting the behavioral effects of ibogaine in preclinical models of substance use disorder and reward.

These findings highlight meaningful distinctions between the ketamine-like behavioral profile of PCP and those of other psychoactive substances, including LSD and ibogaine. Despite demonstrating some affinity at the NMDA receptor channel (Mash, Staley, Pablo, et al., 1995; Popik, Layer, Fossom, et al., 1995; Staley et al., 1996), ibogaine does not appear to replicate the dissociative psychic effects characteristic of ketamine and PCP in humans. In rats trained to discriminate ibogaine from saline, complete generalization to noribogaine was obtained (Zubaran et al., 1999). Ibogaine is not classifiable as a conventional hallucinogen; rather, it is more accurately described as an oneirogenic substance that induces a prolonged dream-like state. Rodent studies indicate that ibogaine administration produces electroencephalographic (EEG) gamma band alterations and REM sleep-like characteristics that are qualitatively comparable to natural REM sleep (González et al., 2021), providing novel neurobiological

evidence for a possible mechanistic link between ibogaine's psychedelic phenomenology and REM sleep architecture.

Nonclinical Pharmacology

Ibogaine presents a complex pharmacological profile because both the drug and its primary metabolite noribogaine act on multiple neurotransmitter systems to produce pharmacological effects that last for hours and anti-addictive effects that can last for days, weeks, or months. In the following sections, the pharmacology of ibogaine is presented based on nonclinical animal studies and epidemiological reports.

Primary Pharmacodynamics

The effects of ibogaine and noribogaine on neurotransmitter systems are complex and multifaceted. Both compounds exhibit micromolar affinity for multiple receptor systems within the central nervous system, including NMDA receptors; opioid receptors (κ_1, κ_2, μ, and σ_2); serotonin receptors (5-HT_2 and 5-HT_3); muscarinic receptors (M_1 and M_2); dopamine, acetylcholine, and nicotinic receptors; as well as the dopamine, norepinephrine, and serotonin reuptake transporters (Maciulaitis et al., 2008; Sweetnam et al., 1995). Ibogaine binding sites in the brain are summarized in Table 3, with values averaged across multiple sources where available, including the National Institutes of Health Psychoactive Drug Screening Program K_i database. Table 4 compares the binding profiles of ibogaine and noribogaine at the sites considered most relevant to the pharmacology of substance use disorder.

The pharmacological basis of the therapeutic effects of ibogaine, noribogaine, and structurally related compounds remains incompletely characterized, but is likely the product of concurrent interactions at multiple central nervous system binding sites (Sweetnam et al., 1995). A pharmacokinetic mechanism is additionally thought to contribute to the persistence of therapeutic effects: ibogaine is lipophilic and distributes into adipose tissue, from which it may be slowly released into systemic circulation over an extended period (Hough et al., 1996). Subsequent biotransformation of the released parent compound into noribogaine is hypothesized to sustain therapeutic effects following single-dose administration.

To explain these longer-lasting anti-craving and anti-addiction effects, research has focused on antagonism of $\alpha3\beta4$ nicotinic acetylcholine receptors (Arias et al., 2011; Arias, Feuerbach, et al., 2010; Arias, Rosenberg, et al., 2010; Fryer & Lukas, 1999; Mah et al., 1998; A. S. Schneider et al., 1996), a potential mechanism shared by ibogaine, noribogaine, and 18-methoxycoronaridine; the latter a derivative of ibogaine invented in 1996. The binding site of ibogaine on $\alpha3\beta4$ acetylcholine receptors appears to overlap with the binding sites of both the dissociative anesthetic phencyclidine (PCP) and the antidepressant and smoking-cessation medication bupropion (Arias et al., 2017; Arias, Feuerbach, et al., 2010; Arias, Rosenberg, et al., 2010). A more recent alternative hypothesis for longer-lasting therapeutic effects of ibogaine focuses on the increased expression of glial cell derived neurotrophic factor (GDNF) in the brain (He et al., 2005; He & Ron, 2006; Marton et al., 2019).

Regarding the therapeutic effects of ibogaine and noribogaine in substance use disorder, Ona and colleagues argued that rather than identifying individual key molecular targets, the activity of ibogaine should be conceptualized as a complex modulation of multiple receptor systems producing potential synergistic effects, and that the elucidation of ibogaine pharmacology may be advanced through methodologies grounded in the polypharmacology paradigm (Ona et al., 2023). Earlier work by Glick and colleagues had similarly emphasized this "dirty drug" profile as a therapeutic strength rather than a liability in the treatment of substance use disorder, given that the disorder itself involves dysregulation across multiple neurotransmitter systems (Sershen et al., 2001). This framework was subsequently extended by ranking ibogaine's receptor affinities according to their relevance to neurorestoration and remyelination, with the proposal that affinity at κ-opioid receptors (KOR; ibogaine 2.1–13.8 μM, noribogaine 0.61–0.96 μM), NMDA receptors (1–5.6 μM and 15–31.4 μM, respectively), and σ_2

receptors (0.2–0.3 μM) positions ibogaine uniquely among psychedelic compounds for the promotion of white matter repair via oligodendrocyte differentiation, attenuation of excitotoxicity, and support of axonal repair (Calvey et al., 2026).

Acute Psychoactive Effects and Receptor Mechanisms

The initial dream-like psychoactive effects of ibogaine may be partially mediated by antagonism at the *N*-methyl-D-aspartate (NMDA) receptor via MK-801 binding sites, and by agonism at the 5-hydroxytryptamine 2A (5-HT_{2a}) and 5-hydroxytryptamine 2C ($5\text{-HT}_{2}c$) receptors (Helsley et al., 2001). Both ibogaine and noribogaine function as μ-opioid antagonists and κ-opioid partial agonists, which may further contribute to the acute psychoactive profile. Psychological experiences during this dream-like state may additionally contribute to the therapeutic effects of ibogaine in substance use disorder.

Among the pharmacological mechanisms by which ibogaine could acutely modify the effects of drugs of abuse, it can be noted that 5-HT3 and kappa-opioid receptors are situated in the brain in such a way that they can modulate dopamine release (Sershen et al., 1995).

Sigma Receptors

σ_2 receptors are widely distributed throughout the brain and participate in multiple functions encompassing both neuronal and non-neuronal signaling. Although ibogaine exhibits only moderate affinity at σ_2 receptors (Bowen et al., 1995; Mach et al., 1995), it demonstrates 43-fold selectivity for σ_2 over σ_1 receptors, suggesting a potentially significant role for σ_2 receptors in the actions of ibogaine (Bowen et al., 1995). Nevertheless, ibogaine inhibits voltage-activated potassium channels associated with σ_1 receptors, including those expressed in neonatal rat intracardiac neurons (H. Zhang & Cuevas, 2005).

Second Messenger Systems

In the male rat brain, both ibogaine and noribogaine selectively enhanced the receptor-mediated inhibition of adenylyl cyclase activity produced by maximally effective concentrations of morphine or 5-HT; however, the inhibitory action of the muscarinic acetylcholine agonist carbachol on adenylyl cyclase activity was not modified by either compound (Rabin & Winter, 1996b). Ibogaine produces a physiologically negligible inhibition of acetylcholinesterase and does not appear to participate substantively in muscarinic acetylcholine transmission (K. Alper et al., 2012). Ibogaine has been shown to inhibit cholinergic contractions of the male guinea pig ileum, enhance purinergic contractions in the isolated rat vas deferens, and increase spontaneous contractions of the isolated male rat portal vein (Mundey et al., 2000).

NMDA Receptor Interactions

The therapeutic effects of ibogaine in substance use disorder may be partially mediated by competitive inhibition of [^{3}H]MK-801 (dizocilpine; an NMDA antagonist with anti-addictive properties) binding to NMDA-receptor-coupled cation channels (Popik et al., 1994). In isolated organ tissue (frog spinal cord and male human caudate and cerebellum), ibogaine showed 4 to 6 times the potency of noribogaine in binding to the [3H]MK-801 binding sites on the NMDA receptor, though they were both far less potent in binding compared to MK-801 (Mash, Staley, Pablo, et al., 1995). In male rats, ibogaine interacts with high- and low-affinity PCP binding sites located in the ionophore of the NMDA receptor complex in the cortex, but only with low-affinity PCP binding sites in the cerebellum. NMDA receptor agonists are believed to attenuate opiate withdrawal and cocaine sensitization, so the binding of ibogaine to the PCP sites may contribute to its anti-addictive properties. In the male rat cortex and cerebellum, ibogaine had

no affinity for [3H]-CGP 39653 (an NMDA antagonist) binding sites, whereas it had low-molecular affinities for sigma1 and sigma2 binding sites, similar to that of harmaline (Itzhak & Ali, 1998).

Ibogaine functions as an open-channel NMDA receptor antagonist. In male mice, ibogaine produced complete protection in the maximal electroshock test (ED_{50} = 31 mg/kg, i.p.). Although ibogaine afforded only partial protection against NMDA-induced lethality, these findings demonstrated effective in vivo blockade of NMDA receptors by the compound. In cultured hippocampal neurons from rat embryos, ibogaine blocked NMDA-induced currents in a slow, concentration-dependent manner, while failing to affect either kainate- or γ-aminobutyric acid-evoked currents (K. Chen et al., 1996).

Ibogaine is characterized as a low-affinity ion-channel blocker and NMDA antagonist acting at non-glycine sites of the NMDA receptor (Witkin et al., 1995). The NMDA antagonist activity of ibogaine may underlie its capacity to reduce the expression of morphine dependence (Popik, Layer, & Skolnick, 1995). Administration of ibogaine at 40 mg/kg (i.p.) reduced withdrawal symptomatology in morphine-dependent male mice, an effect attributable in part to antagonism at NMDA glutamate receptors (Leal et al., 2003).

Phosphoinositide Hydrolysis

The effects of ibogaine and noribogaine on phosphoinositide hydrolysis have been examined in rat striatal and hippocampal slices. While phosphoinositide turnover was not altered by ibogaine in either tissue, noribogaine produced a concentration-dependent increase in [^{3}H]inositol phosphate generation. As this effect was not secondary to neurotransmitter release, the authors proposed that it may represent a mechanism through which noribogaine contributes to the behavioral effects of ibogaine (Rabin & Winter, 1996a).

Opioid Receptor Interactions

Early receptor binding studies conducted in 1980 indicated that ibogaine exhibited minimal interaction with κ-opioid receptors and was largely inactive at μ- and δ-opioid receptors. However, a 1995 investigation in male mouse forebrain demonstrated that ibogaine appears to function as an agonist recognizing two distinct agonist affinity states of the μ-opioid receptor. This activity may account for the analgesic properties of ibogaine, its attenuation of opioid withdrawal symptomatology, and its reduction of drug-seeking behavior (Codd, 1995). A subsequent study in male mice concluded that ibogaine selectively inhibits the development of tolerance to the antinociceptive effects of μ-opioid receptor agonists, but not to those of κ- or δ-opioid receptor agonists (Cao & Bhargava, 1997). In contrast, a radioligand binding study demonstrated that noribogaine exhibits highest affinity for κ-opioid receptors, lower affinity for μ-opioid receptors, and no detectable affinity for δ-opioid receptors, with noribogaine demonstrating greater affinity than ibogaine across all three opioid receptor subtypes (Pearl, Herrick-Davis, et al., 1995).

Serotonin Transporter

Ibogaine inhibits the serotonin transporter (SERT), which mediates termination of serotonergic signaling by transporting 5-HT into the presynaptic neuron (Moller et al., 2019; Staley et al., 1996). Unlike typical SERT inhibitors, ibogaine produces inhibition through binding at a distinct extracellular site, which subsequently induces inhibition of both serotonin transport and serotonin-induced ionic currents (Bulling et al., 2012). Ibogaine stabilizes an inward-open (as opposed to outward-open) conformation of SERT (Coleman et al., 2019; Jacobs et al., 2007; Y. W. Zhang et al., 2016), an effect likely also true of noribogaine (Koldsø et al., 2013). When bound to SERT, ibogaine can partially correct SERT mutations that impair proper folding (El-Kasaby et al., 2010). Although ibogaine is considered a noncompetitive inhibitor of SERT, it reduces binding of selective serotonin reuptake inhibitors (Bulling et al., 2012; Jacobs et al., 2007). The ibogaine-SERT interaction has more recently inspired structure-based drug

design; a virtual docking study used ibogaine as a structural template against the SERT crystal structure to identify potent and selective ibogaine-related SERT inhibitors with efficacy in mouse models of depression and substance use disorder (Singh et al., 2023).

Comparative Pharmacology of Ibogaine and Noribogaine

Noribogaine displays high affinity for the 5-HT transporter, increases extracellular 5-HT, and elevates synaptic levels of 5-HT, and that ibogaine and noribogaine are equipotent at the dopamine transporter (Mash, Staley, Baumann, et al., 1995). Ibogaine and noribogaine have similar binding profiles. They show equipotency at vesicular dopamine and monoamine transporters and on the 5-HT transporter, both have high potency values at the cocaine recognition site and lower potencies for the [3H]paroxetine binding sites. Compared to ibogaine, noribogaine shows higher affinity at the kappa-1 receptor but lower affinity at the NMDA receptor complex. The combined pharmacological actions of both compounds appear to underlie the observed therapeutic effects on tolerance and withdrawal (Staley et al., 1996).

Noribogaine has certain distinct pharmacological activities compared to those of ibogaine. Ibogaine shows a higher affinity for NMDA receptors in brain tissue (Baumann, Pablo, et al., 2001) and more strongly stimulates the hypothalamic-pituitary-adrenal axis (Baumann, Rothman, et al., 2001). Noribogaine is an indirect 5-HT agonist that inhibits 5-HT uptake, thereby increasing extracellular concentration of serotonin in the male rat brain approximately 10 times more than does ibogaine (Baumann, Rothman, et al., 2001). Noribogaine also shows comparatively greater affinity for opioid receptors, acting as an agonist of mu and kappa1, whereas ibogaine shows greater affinity for the kappa2 opioid receptor (Maciulaitis et al., 2008). In functional studies, ibogaine has been shown to exert a non-competitive, antagonist effect on nicotinic receptors, binding to the same area as phencyclidine (PCP) (Arias, Feuerbach, et al., 2010). Noribogaine may bind to the orthosteric morphinan binding site of the opioid receptors. Noribogaine is a weak mu antagonist and a G-protein biased kappa agonist able to inhibit kappa β-arrestin recruitment induced by dynorphin. This biased agonist/antagonist activity featured by noribogaine is not found with ibogaine (Maillet et al., 2015). Maillet et al. suggested that because elevated levels of dynorphins are correlated with "anxiety, dysphoric effects, and decreased dopaminergic tone, a therapeutically relevant functional inhibition bias to endogenously released dynorphins by noribogaine might be worthy of consideration for treating anxiety and substance related disorders" (Maillet et al., 2015).

Next-Generation Analogues

More recently, Tabernanthalog (TBG), a novel water-soluble, non-toxic azepinoindole analog of ibogaine synthesized by David E. Olson at UC Davis has been licensed by Delix Therapeutics (Mash, 2023; Olson, 2018). Tabernanthelog has antidepressant and antiaddictive effects in rodents similar to ibogaine with the hope of similar efficacy but better safety parameters (Peters & Olson, 2021).

Table 4: Ibogaine's Binding Affinities

Target / Receptor	Ibogaine Ki or IC50	Noribogaine Ki or IC50	Pharmacodynamics	References
Monoamine Transporters				
SERT ([³H]5-HT reuptake, rat)	0.5 μM	0.3 μM	Serotonin reuptake blocker	*(Mash, Staley, Pablo, et al., 1995)*
SERT (paroxetine binding, human)	2.0 μM	0.9 μM	Serotonin reuptake blocker	*(Mash, Staley, Pablo, et al., 1995)*
SERT (RTI-55 binding, human)	0.5 μM	0.04 μM	Serotonin reuptake blocker	*(Mash, Staley, Pablo, et al., 1995)*

SERT (RTI-55 binding, rat)	0.2 µM	0.2 µM	Serotonin reuptake blocker	*(Mash, Staley, Pablo, et al., 1995)*
SERT (RTI-55, HeLa cells)	2.5 µM	—	Non-competitive serotonin reuptake blocker	*(Mash, Staley, Pablo, et al., 1995)*
DAT (RTI-55 binding, human)	1.5–4.0 µM (≈1.98 µM)	3.4 µM	Dopamine reuptake blocker	*(Mash, Staley, Pablo, et al., 1995)*
DAT (RTI-55 binding, rat)	1.5–4.0 µM	—	Dopamine reuptake blocker	*(Mash, Staley, Pablo, et al., 1995)*
Serotonin Receptors				
5-HT$_{1a}$	>10 µM (>10,000 nM)	—	Minimal direct activity	*(Glick et al., 2000; Glick & Maisonneuve, 2000; Roth & Driscol, 2018; Toll et al., 1998)*
5-HT$_{1}$^{b}	>100 µM (>100,000 nM)	—	Inactive	*(Deecher et al., 1992; Glick & Maisonneuve, 2000)*
5-HT$_{1}$^{d}	>100 µM (>100,000 nM)	—	Inactive	*(Deecher et al., 1992; Glick & Maisonneuve, 2000)*
5-HT$_2$ (ketanserin, rat cortex)	4.8 µM; >100 µM	Inactive	Unknown; weak direct affinity	*(Deecher et al., 1992)*
5-HT$_{2a}$	≈12.8 µM (12,833 nM)	—	Low-affinity; not a primary target	*(Glick et al., 2000; Glick & Maisonneuve, 2000; Roth & Driscol, 2018; Toll et al., 1998)*
5-HT$_{2}$^{c}	>10 µM (>10,000 nM)	—	Low affinity	*(Glick et al., 2000; Glick & Maisonneuve, 2000; Roth & Driscol, 2018; Toll et al., 1998)*
5-HT$_3$ (GR65630, N1E-115; area postrema)	3.8 µM; >100 µM	Inactive	Unknown	*(Roth & Driscol, 2018; Toll et al., 1998)*
Dopamine Receptors				
D$_1$	>10 µM (>10,000 nM)	—	Inactive	*(Glick et al., 2000; Glick & Maisonneuve, 2000; Roth & Driscol, 2018; Toll et al., 1998)*
D$_2$	>10 µM (>10,000 nM)	—	Inactive	*(Glick et al., 2000; Glick & Maisonneuve, 2000; Roth & Driscol, 2018; Toll et al., 1998)*
D$_3$	≈70 µM (70,000 nM)	—	Negligible direct binding	*(Glick et al., 2000)*
D$_4$	IC50 >100 µM	—	Inactive	*(Sweetnam et al., 1995)*
Opioid Receptors				
µ (mu; naloxone binding, mouse/rat)	0.13–3.6 µM	5.8 µM	Agonist; partial agonist; mixed agonist–antagonist	*(Glick et al., 2000; Pablo & Mash, 1998; Pearl, Herrick-Davis, et al., 1995; Sweetnam et al., 1995)*
µ (DAMGO; human cortex)	5.6–11.0 µM	1.5 µM	Antagonist (in DAMGO assay)	*(Glick et al., 2000)*
µ (HEK-MOR, DAMGO)	IC50 19 µM	1.1 µM; 0.2 µM	Functional activity varies with assay	*(Pablo & Mash, 1998)*
κ (kappa; U69,593 binding, human)	2.0–4.0 µM (≈2.2 µM); IC50 16 µM	0.7 µM	Partial agonist; biased agonist	*(Deecher et al., 1992; Glick & Maisonneuve, 2000; Pearl, Herrick-Davis, et al., 1995; Sweetnam et al., 1995)*
δ (delta; DPDPE, calf caudate)	>100 µM	24.7 µM	Inactive at ibogaine; weak at noribogaine	*(Deecher et al., 1992; Pearl, Herrick-Davis, et al., 1995)*

NMDA / Glutamate				
NMDA (MK-801, rat cortex/forebrain)	1.0–3.2 µM; IC50 5.2 µM	—	Non-competitive channel blocker	
NMDA (MK-801, human caudate; frog cord)	5.2–9.8 µM	31.4 µM	Channel blocker	*(Popik et al., 1994)*
NMDA (voltage-dependent, rat hippocampus)	3.2 µM	—	Channel blocker	*(K. Chen et al., 1996)*
PCP site	IC50 50.5 µM	—	Low-affinity channel activity	*(Sweetnam et al., 1995)*
Sigma Receptors				
σ_1 (pentazocine binding, human cerebellum)	10 µM (≈9.3 µM)	Inactive	Unknown	*(Mach et al., 1995)*
σ_2 (rat liver / guinea pig brain)	0.10–0.4 µM	Inactive	High-affinity binding; functional role unclear	*(Glick et al., 2000)*
Nicotinic Acetylcholine Receptors				
Ganglionic nAChR (PC-12, Na^+ influx)	0.02 µM	1.5 µM	Non-competitive inhibitor	*DemerRx laboratory data*
α3β4 nAChR (HEK cells, human)	0.22–1.0 µM; 3.7 µM	6.8 µM	Non-competitive antagonist (desensitised/resting state)	*DemerRx laboratory data*
α3β4 nAChR (SH-SY5Y cells)	5.2 µM; 9.8 µM	0.5 µM	Non-competitive antagonist	*DemerRx laboratory data*
Muscarinic Acetylcholine Receptors				
M_1 muscarinic	Ki 31.6 µM; IC50 7.6 µM	—	Weak antagonist activity	*(Repke et al., 1994; Sweetnam et al., 1995)*
M_2 muscarinic	Ki 50.1 µM; IC50 5.9 µM	—	Weak antagonist activity	*(Repke et al., 1994; Sweetnam et al., 1995)*
M_3 muscarinic	Ki 12.5 µM	—	Low-affinity binding	*(Repke et al., 1994)*
Other Targets				
β_1 adrenergic	>100 µM	—	Inactive	*(Deecher et al., 1992)*
H_1 histamine	IC50 >10 µM	—	Inactive	*(Sweetnam et al., 1995)*
$GABA_a$	>100 µM	—	Inactive	*(Deecher et al., 1992)*
$GABA^b$	>100 µM	—	Inactive	*(Glick et al., 2000)*

Table 5: Ibogaine's Binding Sites Relevant to Addictive Drugs

Receptors, Reference	Ibogaine	Noribo-gaine	Addictive Drugs
Kappa opioid (Glick & Maisonneuve, 1998)	Binds	Binds	Ibogaine's kappa agonist actions reduce opioid and cocaine intake
NMDA (Glick & Maisonneuve, 1998)	Binds	Binds	Ibogaine's NMDA antagonism reduces opioid intake and withdrawal
Serotonin uptake sites (Glick & Maisonneuve, 1998)	Binds	Binds	Ibogaine's serotonergic actions may reduce alcohol intake
Sigma2 (Glick & Maisonneuve, 1998)	Binds		Sigma 2 appears to be involved in ibogaine's neurotoxicity though this has yet to be confirmed mechanistically (Mash, 2023)

Alpha-3 beta-4 nicotinic acetylcholinereceptors (Arias, Rosenberg, et al., 2010)	Binds to location that overlaps with the PCP binding site		Ibogaine's nicotinic receptor antagonism reduces nicotine intake
Dopamine (Glick et al., 1998)			Ibogaine as a pretreatment can reduce morphine-induced and elevate cocaine- and amphetamine-induced DA levels

Although the authors of a study referenced in Table 4 (Glick & Maisonneuve, 1998) stated that both ibogaine and its primary metabolite bind to NMDA and kappa opioid sites, it should be noted that a drug-discrimination study in rats found noribogaine apparently lacking discriminative effects for both a prototypic NMDA antagonist and kappa-opioid agonist (Zubaran et al., 1999).

Central Nervous System

Given the central role of dopamine in the neurobiology of substance use disorder, considerable research has examined how ibogaine modulates dopaminergic function both independently and in the context of co-administered substances of misuse. Findings, summarized in Table 4, have been inconsistent across studies but broadly suggest that ibogaine produces either no effect on or an acute reduction in extracellular dopamine, except at supraphysiological concentrations unlikely to be achieved through therapeutic dosing.

Table 6: Ibogaine's Effect on Levels of Dopamine and its Metabolites in Rats

		Nucleus Accumbens			Striatum			
Dose	**Route**	**Dopamine**	**DOPAC**	**HVA**	**Dopamine**	**DOPAC**	**HVA**	**Ref**
1 µMol	Central perfusion	—	—	Not measured	—	—	Not measured	(Reid et al., 1996)
10 µMol	Central perfusion	—	—	Not measured	—	—	Not measured	(Reid et al., 1996)
100 µMol	Central perfusion	Decrease	—	Not measured	Decrease	—	Not measured	(Reid et al., 1996)
500 µMol	Central perfusion	Increase	—	Not measured	—	—	Not measured	(Reid et al., 1996)
1000 µMol	Central perfusion	Increase	—	Not measured	—	—	Not measured	(Reid et al., 1996)
50 mg/kg	i.p.	Not measured	Not measured	Not measured	Decrease	Increase at 30, 60, and 120 minutes;	Increase at 30, 60, and 120 minutes;	(Ali et al., 1996)

						decrease at 24 hours	decrease at 24 hours	
1 µMol	Central perfusion	—	—	—	—	—	—	(Glick et al., 1993)
10 µMol	Central perfusion	—	Decrease	—	—	Decrease	—	(Glick et al., 1993)
40 µMol	Central perfusion	—	—	—	—	—	—	(Glick et al., 1993)
80 µMol	Central perfusion	—	—	—	—	—	—	(Glick et al., 1993)
200 µMol	Central perfusion	Decrease	Increase	Increase	Decrease	Increase	Increase	(Glick et al., 1993)
400 µMol	Central perfusion	Decrease	Increase	Increase	Decrease	Increase	Increase	(Glick et al., 1993)
1 mg/ kg	i.v.	—	Not measured	Not measured	Not measured	Not measured	Not measured	(Baumann, Rothman, et al., 2001)
10 mg/ kg	i.v.	—	Not measured	Not measured	Not measured	Not measured	Not measured	(Baumann, Rothman, et al., 2001)
40 mg/kg	i.p.	Decrease	Decrease	Increase	Decrease	Decrease	Increase	(Maisonneuve, Rossman, et al., 1992)

10 mg/kg	i.p.	Decrease	Increase	Increase	Decrease	Increase	Increase	(Baumann, Rothman, et al., 2000)
100 mg/kg	i.p.	Decrease	Increase	Increase	Decrease	Increase	Increase	(Baumann, Rothman, et al., 2000)

Direct Brain Infusion Studies

Direct intracerebral infusion of ibogaine in female rats produced decreases in dopamine concentrations within the nucleus accumbens and striatum at perfusion concentrations of 200 and 400 μM, with no detectable changes observed at concentrations of 80 μM or lower (Glick et al., 1993). A separate investigation reported that local perfusion of ibogaine produced a biphasic, concentration-dependent effect on dopamine release in the male rat nucleus accumbens and striatum: a lower concentration (100 μM) decreased extracellular dopamine, whereas higher concentrations (500 and 1000 μM) produced pronounced increases (Reid et al., 1996). The decrease in dopamine release was attenuated by the κ-opioid receptor antagonist norbinaltorphimine (NorBNI), suggesting mediation through κ-opioid receptor stimulation, while the elevation in extracellular dopamine at higher concentrations may reflect direct ibogaine activity at the dopamine transporter (Reid et al., 1996), consistent with in vitro evidence of ibogaine binding to and inhibition of the transporter (Baumann, Rothman, et al., 2001; Mash, Staley, Baumann, et al., 1995).

Parenteral Administration Studies

Administration of ibogaine via alternative parenteral routes has yielded inconsistent effects on extracellular dopamine. In isoflurane-anesthetized male rats, ibogaine (50 mg/kg, i.p.) produced decreases in caudate dopamine concentrations with concurrent increases in dopamine turnover, alongside elevated 5-HT concentrations in the frontal cortex (Z. Binienda et al., 1998). A separate study in male rats demonstrated that ibogaine at 10 and 100 mg/kg (i.p.) substantially reduced tissue dopamine levels while concurrently increasing concentrations of the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). This profile of reduced dopaminergic transmission was observed in the striatum, hypothalamus, and olfactory tubercle; however, no appreciable effects on serotonergic systems were detected (Baumann et al., 1998).

In contrast, ibogaine at either 1 or 10 mg/kg (i.v.) produced no detectable effects on extracellular dopamine in the male rat nucleus accumbens, although increased extracellular 5-HT was observed in the same region (Baumann, Rothman, et al., 2001). Given the higher bioavailability associated with intravenous administration, this inconsistency is unlikely to be attributable to dose-related factors alone. Similarly, ibogaine at 40 mg/kg (i.p.) in male rats has been reported to leave dopamine overflow in the nucleus accumbens unchanged, with no effect on locomotor activity; however, dopamine and 5-HT concentrations in the medial prefrontal cortex were reduced (Benwell et al., 1996).

In female rats, ibogaine (40 mg/kg, i.p.) has been shown to increase extracellular dopamine in the prefrontal cortex while decreasing concentrations in the striatum, with extracellular dopamine in the nucleus accumbens unaffected (Maisonneuve et al., 1991). At the same time, extracellular levels of dopamine in the nucleus accumbens were not affected. Dopamine remained decreased in the striatum at

19 hours after administration. Levels of dopamine metabolites were initially raised and then decreased in all three examined regions.

The effects of ibogaine on the dopamine-related neuropeptides neurotensin and dynorphin have additionally been investigated. A single administration of ibogaine (40 mg/kg, but not 20 mg/kg, i.p.) to male rats has been shown to increase neurotensin-like immunoreactivity in the striatum, with no detectable changes in the nucleus accumbens, frontal cortex, or substantia nigra (Alburges & Hanson, 1999a). Daily administration of ibogaine at lower and the same doses for 4 consecutive days dose- and time-dependently increased neurotensin in the striatal, nigral, and nucleus accumbens but not the frontal cortex at 12 hours after the last drug administration. Neurotensin might contribute to an interaction between ibogaine and the dopamine system as a participant in the pharmacological actions of this drug (Alburges & Hanson, 1999a). In contrast, when investigated for responses in the same brain regions except the frontal cortex, the same 4-day regimen of ibogaine (40 mg/kg i.p.) in male rats failed to affect levels of dynorphin, another dopamine-linked neuropeptide (Alburges & Hanson, 1999b).

Interactions with Substances of Misuse

Studies examining whether ibogaine modifies the acute effects of substances of misuse in rodent models are summarized in Table 5. Pretreatment with ibogaine (40 mg/kg, i.p.) has been shown not to alter the electrophysiological response of ventral tegmental area (VTA) dopaminergic neurons to morphine or cocaine in male rats (French et al., 1996). These findings indicate that ibogaine does not produce long-term alterations in dopaminergic neuronal activity or in the capacity of VTA neurons to respond to cocaine or morphine, and that alternative mechanisms must therefore be considered to account for the durable inhibitory effects of ibogaine on cocaine and morphine self-administration.

Additional evidence in male mice administered ibogaine (40 mg/kg, i.p.) suggests that the compound may block the effects of cocaine on serotonergic transmission, which in turn modulates dopamine release, with κ-opioid modulation of serotonergic transmission additionally contributing to this effect (Sershen et al., 1996).

Differential Effects in Drug-Experienced Animals

Ibogaine frequently exerts differential effects in substance-experienced animals as compared with substance-naïve animals (Blackburn & Szumlinski, 1997), and has been hypothesized to reverse the neuroadaptations underlying drug craving and compulsive substance-seeking behavior. In support of this hypothesis, ibogaine has been shown to enhance the elevation in accumbal dopamine produced by acute administration of stimulant compounds, and to potentiate the expression of stimulant-induced motor behaviors in both acutely and chronically stimulant-treated animals (Szumlinski, Maisonneuve, et al., 2001).

Table 7: Differential Effects of Ibogaine in Drug-Experienced Animals

Stimulants: Methamphetamine, D-Amphetamine, and Cocaine				
Ibogaine Dose and Route of Administration	**Other Drug and Route of Administration**	**Effect Measured**	**Interaction**	**Ref**
50 mg/kg i.p. pretreatment	Methamphetamine, 20 mg/kg i.p.	Changes in body temperature and induction of heat shock protein (HSP-72) in the caudate nucleus of female mice	Ibogaine decreased methamphetamine-induced hypothermia and HSP-72 expression	(Yu et al., 1999)

40 mg/kg i.p., 19 hours earlier	Methamphetamine, 2 and 4 mg/kg i.p.	Methamphetamine-induced behavioral sensitization in female rats	Ibogaine augments the stereotypy effects of methamphetamine in the same manner as it augments them for cocaine	(Szumlinski, Balogun, et al., 2000)
40 mg/kg i.p., 19 hours earlier	Methamphetamine, 0.1 mg/kg, i.p.	Methamphetamine-induced changes in behavior in an elevated plus maze and changes in corticosterone in female rats	Ibogaine antagonized the behavioral disinhibiting effects of methamphetamine "without altering locomotor activity." Ibogaine antagonized the increase in plasma corticosterone induced by methamphetamine	(Szumlinski, Haskew, et al., 2001)
40 mg/kg i.p., one or two injections at 2 and 24 hours earlier in mice, and at 18 hours earlier in rats	D-Amphetamine, 1, 5, and 10 mg/kg s.c. in mice and 1.25 mg/kg i.p. in rats	D-Amphetamine-induced locomotor stimulation in male mice and female rats	Ibogaine reduced D-amphetamine-induced locomotor stimulation in mice from 1 and 5 mg/kg, but not 10 mg/kg, and potentiated the locomotor activity induced in rats	(Sershen, Harsing, et al., 1992)
40 mg/kg i.p., 1 day before behavioral testing	D-Amphetamine, four doses at 1.5 mg/kg i.p.	D-Amphetamine-induced locomotor behavior in amphetamine-pretreated and -naïve male rats	Ibogaine reduced hyperlocomotion in D-amphetamine-treated rats more than in amphetamine-naïve rats	(Blackburn & Szumlinski, 1997)
40 mg/kg i.p., 19 hours earlier	D-Amphetamine, 1.25 mg/kg i.p.	Brain levels of D-amphetamine in female rats	Ibogaine increased brain levels of D-amphetamine	(Glick, Gallagher, et al., 1992)
40 mg/kg i.p., 24 hours earlier	D-Amphetamine, 3 mg/kg i.p.	D-Amphetamine-induced place preference in male rats	Ibogaine pretreatment interfered with establishing an amphetamine-induced conditioned place preference after one amphetamine trial but much less so after four amphetamine trials, when rats apparently developed tolerance to ibogaine's effects on place preference	(Moroz et al., 1997)

40 mg/kg i.p., 19 hours earlier	D-Amphetamine, to measure dopamine (DA) levels: 1.25 mg/kg i.p.; to measure motor activity: 0.625, 1.25, 2.5 or 5 mg/kg i.p.	D-Amphetamine-induced neurochemical and motor changes in female rats	Ibogaine potentiated D-amphetamine-induced increases in extracellular DA in the striatum and nucleus accumbens and enhanced amphetamine-induced motor stimulation	(Maisonneuve, Keller, et al., 1992)
10 μM (local perfusion); pretreatment:40 mg/kg i.p., 19 hours earlier	D-Amphetamine, 1.25 mg/kg i.p.; 1–10 μM locally	D-Amphetamine-induced extracellular DA increases in female rats	Locally administered ibogaine enhanced the effects of systemically administered D-amphetamine on DA, and systemically administered ibogaine enhanced the effects of locally administered D-amphetamine on DA	(Glick et al., 1993)
40 mg/kg i.p.	Cocaine, 25 mg/kg s.c.	Cocaine-induced locomotor stimulation in male mice	Ibogaine antagonized cocaine-induced locomotor stimulation when administered at 2 hours before a single cocaine injection, at 24 hours after a second cocaine injection, and when administered at 1 and 2 hours after mice received cocaine daily for 3 and 4 days, respectively	(Sershen, Hashim, et al., 1992)
40 mg/kg i.p.	Cocaine, 0.25, 0.5, 1, 2, and 4 mg/kg i.v.	Ventral tegmental area (VTA) DA neuron firing in rats	Ibogaine pretreatment at 6–8 and 19 hours before cocaine did not significantly alter cocaine-induced, nor spontaneous VTA DA firing	(French et al., 1996)
40 mg/kg i.p., one dose, three consecutive daily doses, and once weekly dosing for 3 consecutive weeks	Cocaine, ad libitum i.v. perfusions	Cocaine self-administration in male rats	Ibogaine depressed cocaine consumption in cocaine-dependent rats at all dosing regimens	(Cappendijk & Dzoljic, 1993)
40 mg/kg s.c., one or two injections	Cocaine, 10(-6) M, in vitro	Electrically evoked efflux of DA and 5-HT	Ibogaine pretreatment	(Sershen et al., 1996)

		in male mouse striatum ex vivo	prevented the in vitro cocaine-induced increased efflux of 5-HT, but not that of DA	
40 mg/kg s.c., two pretreatment injections 6 hours apart, the first at 18 hours prior to the second	Cocaine, 10 or 25 mg/kg s.c.	Cocaine-induced increase in locomotor activity in male mice	DA increased; 5-HT not increased. Ibogaine pretreatment antagonized cocaine-induced increase in locomotor activity	(Sershen et al., 1996)
40 mg/kg i.p., once or twice weekly, 19 hours before cocaine	Cocaine, 5, 10, 20 and 40 mg/kg i.p. in female rats habituated to the drug (15 mg/kg i.p. daily)	Cocaine-induced locomotor activity	Ibogaine-treated rats with previous cocaine use showed a markedly greater increase in cocaine-induced locomotor activity from subsequent cocaine at 5, 10, or 20 mg/kg i.p., and a decreased locomotor response from cocaine at 40 mg/kg i.p.	(Szumlinski et al., 1999)
40 mg/kg i.p. on 4 consecutive days	Cocaine, 30 mg/kg i.p. daily for 4 consecutive days and on day 5	Cocaine-induced changes in striatal, nigral, cortical and accumbens neurotensin-like immunoreactivity (NTLI) content in male rats	Ibogaine pretreatment prevented cocaine-induced increases of nigral, striatal, and accumbens NTLI 12 hours after cocaine and 36 hours after last dose of ibogaine	(Alburges & Hanson, 1999a)
40 mg/kg i.p. daily for consective 4 days	Cocaine, 20 mg/kg s.c., 2 hours after final dose of ibogaine	Cocaine-induced changes in DA and 5-HT in the nucleus accumbens of male rats	Compared to baseline of ibogaine pretreatment, cocaine increased DA release and decreased 5-HT release; ibogaine downmodulated the cocaine-induced increase in DA and potentiated the cocaine-induced decrease in 5-HT release	(Broderick et al., 1994)
40 mg/kg s.c., two doses 6 hours apart	Cocaine, 300 and 200 mg/L in drinking water consecutively for	Cocaine self-administration and brain levels of cocaine in male mice	Ibogaine reduced cocaine self-administration for 5 days and lowered	(Sershen et al., 1994)

	2 weeks; acute cocaine challenge of 25 mg/kg s.c.		locomotor and stereotypy activity. At 35 min after cocaine injection, levels of cocaine in the brain were approximately 25% higher in the mice treated with ibogaine	
40 mg/kg i.p.	Cocaine, 15 mg/kg i.p. daily for 5 days	Stereotypic effects of acute cocaine (20 mg/kg i.p.) in cocaine-sensitized (5×15 mg/kg i.p.) and in acutely treated female rats 19 hours after pretreatment with ibogaine	No significant change in dopamine levels in rats only acutely treated with cocaine; however, ibogaine decreased dopamine in rats sensitized to cocaine	(Szumlinski, Maisonneuve, et al., 2000)
40 and 80 mg/kg i.p.	Cocaine, 0.33 mg/infusion	Self-administration of cocaine in male rats on FR10 schedule reinforcement	Only pretreatment with the higher dose of ibogaine at 60 or 90 minutes, but not 24 hours beforehand, suppressed cocaine self-administration for 48 hours in habituated rats	(Dworkin et al., 1995)
2.5 mg/kg i.p. after abrupt cessation of cocaine	Cocaine, 1 mg/kg i.p. for 14 days	Cocaine withdrawal behavior in mice in the plus-maze (i.e., decreased time spent in open arm of maze)	Ibogaine blocked withdrawal symptoms	(Onaivi et al., 1998)
40 mg/kg i.p. administered to mice prior to decapitation	Cocaine, 10(-6) M	Electrical-field stimulation-induced release of tritium in ex vivo striatal tissue from male mice	Ibogaine pretreatment did not alter cocaine-induced DA outflow	(Sershen et al., 1995)
40 mg/kg i.p., three times, usually at intervals of 1 week/injection	Cocaine, self-administered at 50 µL (~0.4 mg/kg) via intravenous cannula	Cocaine self-administration in cocaine-habituated female rats	Cocaine self-administration was reduced on Day 1 and into the next day	(Glick et al., 1994)
10 µMol/L	Cocaine, 10 µMol/L	The effect of ibogaine-induced tritium efflux on isolated male mouse striatum preloaded with DA	The DA-releasing effect of ibogaine was reduced by the DA uptake-inhibitor, cocaine	(Harsing et al., 1994)
Local perfusion with ibogaine (10(-6) M-10(-3) M) via microdialysis probes	Cocaine, 15 mg/kg i.p.	Extracellular DA levels in male rats	Cocaine pretreatment reduced striatal DA levels stimulated by ibogaine (10(-3)M)	(Reid et al., 1996)

40 mg/kg i.p., 1 hour prior	Cocaine, 20 mg/kg i.p.	Cocaine-induced hyperactivity in female rats	Pretreatment with ibogaine both acutely inhibited and delayed cocaine-induced hyperactivity	(Maisonneuve, Visker, et al., 1997)
50 mg/kg i.p.	Cocaine, 20 mg/kg i.p., alone and 1 hour after ibogaine	Effect of the drugs on brain waves (electrocorticogram) in male rats	Increased power in the alpha1, delta, and theta bands; the increase in alpha1 suggesting a role for the serotonergic system in the response to cocaine mediated by ibogaine, and the increases in delta and theta suggesting the threshold for seizures induced by cocaine is lowered by ibogaine at high doses	(Z. K. Binienda et al., 2011)
Opiates: Heroin and Morphine				
Ibogaine Dose and Route of Administration	**Other Drug and Route of Administration**	**Effect Measured**	**Interaction**	**Ref**
40 and 80 mg/kg i.p.	Heroin, 18 micrograms/infusion, 60 minutes after ibogaine	Self-administration of heroin in male rats on FR10 schedule of reinforcement	Heroin intake was almost completely suppressed by both pretreatment doses of ibogaine for 24 hours	(Dworkin et al., 1995)
20 or 40 mg/kg i.p.	Morphine, 10 mg/kg s.c. 10 minutes after ibogaine	Morphine antinociception as shown by sensitivity to pain in male mice tolerant to morphine	Morphine antinociception was dose-dependently enhanced by pretreatment with ibogaine, but the enhancement was absent in morphine-naive mice	(Sunder Sharma & Bhargava, 1998)
1–40 mg/kg i.p. as co-treatment and 40 mg/kg i.p. as 19 hours pretreatment	Morphine, 4 mg/kg s.c.	Morphine antinociception in morphine-naïve male rats	Co-administration of ibogaine and morphine dose-dependently enhanced morphine antinociception, whereas ibogaine as pretreatment decreased morphine antinociception	(Bagal et al., 1996)

2.5–80 mg/kg i.p., 15 minutes prior to morphine self-administrations	Morphine, 0.01 mg i.v./infusion	Self-administration of morphine in morphine-naïve female rats	Ibogaine dose-dependently reduced morphine intake, whereas individual rats varied in how much and for how long they exhibited the effect	(Glick et al., 1991)
40 mg/kg i.p.	Morphine, 0.5 and 1 mg/kg i.v.	Ventral tegmental (VTA) dopamine (DA) neuronal firing in rats	Ibogaine pretreatment at 6–8 and 19 hours before morphine did not significantly alter spontaneous VTA DA firing, nor in response to morphine	(French et al., 1996)
40 mg/kg i.p., 5 or 19 hours earlier	Morphine, 5 mg/kg i.p.	Morphine-induced locomotor activity and brain and plasma levels of ibogaine in male and female rats	Ibogaine pretreatment at both 5 and 19 hours produced antagonism to morphine-induced locomotor activity in female but not in male rats, and brain and plasma levels of ibogaine were higher in the females compared to males	(Pearl et al., 1997)
40 and 80 mg/kg i.p., 2 hours after a daily regimen of morphine, and 45 minutes before naloxone	Morphine, 175, 250, and 375 mg/kg i.p./day, respectively, on 3 consecutive days	Naloxone-induced morphine withdrawal signs (e.g., jumping) in morphine-dependent male mice	Jumping was significantly inhibited by ibogaine at either dose	(Leal et al., 2003)
40 mg/kg i.p., 19 hours earlier	Morphine, 10 mg/kg i.p.	Brain morphine levels in female rats	Ibogaine produced little or no enhancement to brain levels of morphine 30 minutes and 2 hours after morphine injection	(Glick, Gallagher, et al., 1992)
30 mg/kg i.p., 1 minute after naloxone for withdrawal signs; co-injected or injected 75 minutes before naloxone for antinociceptive activity	Morphine, 50 and 100 mg/kg i.p., repeated over several days; 6.5 mg/kg i.p. for antinociceptive activity	Withdrawal signs in morphine-naïve and -dependent mice	In the tail-flick test in morphine-naïve mice, ibogaine did not produce antinociception but did potentiate the antinociceptive effect of morphine, both in duration and intensity. In morphine-dependent	(Francés et al., 1992)

			mice, ibogaine did not eliminate naloxone-precipitated withdrawal symptoms but rather increased the number of repetitive vertical jumps induced by naloxone	
40 mg/kg i.p., 19 hours earlier	Morphine, 5 mg/kg i.p.	Effect on DA levels in the striatum, prefrontal cortex, and nucleus accumbens of female rats	Ibogaine prevented the morphine-induced increase in DA levels in each brain region	(Maisonneuve et al., 1991)
40 mg/kg i.p., three times, usually at intervals of 1 week/injection	Morphine, self-administered at 20 µL (~0.04 mg/kg) via intravenous cannula	Morphine self-administration in morphine-habituated female rats	Morphine self-administration was reduced on Day 1 and into the next day	(Glick et al., 1994)
40 mg/kg i.p., 12 hours after last dose of morphine	Morphine, 5–25 mg/kg s.c., b.i.d., followed by 25 mg/kg (b.i.d.) for 4–7 days	Local cerebral glucose utilization (LCGU) in drug-naive and morphine-dependent male rats	In contrast to morphine-dependent rats in which LCGU showed only minor alterations compared to drug-naive controls, LCGU globally decreased in morphine-dependent rats treated with ibogaine, most notably in the flocculus, inferior colliculus, locus coeruleus, preoptic areas (medial and lateral), thalamus (anterior), and nucleus of the diagonal band	(Levant & Pazdernik, 2004)
40 mg/kg i.p., 19 hours earlier	Morphine, 0.5, 1.25, 5, 10, 20, and 30 mg/kg i.p.	Morphine-induced locomotor activity in female rats	Ibogaine pretreatment decreased locomotor activation effects for the first 2 hours after each dose of morphine except 30 mg/kg. The locomotor inhibiting effect against morphine (5 mg/kg)	(Maisonneuve, Rossman, et al., 1992)

			persisted for 1 week but not 1 month after	
20, 40 or 80 mg/kg i.p., 30 minutes prior to challenge with naltrexone (1 mg/kg i.p.). Also, 40 mg/kg 4 hours prior to naltrexone	Morphine, 0.5 mL of 50 mg/mL s.c. daily for 5 days via implanted reservoirs	Naltrexone-precipitated withdrawal signs in morphine-dependent male rats	Ibogaine (40 and 80 mg/kg) at both 30 minutes and 4 hours prior to naltrexone reduced withdrawal symptoms	(Glick, Rossman, et al., 1992)
10, 20 or 40 mg/kg i.p., 10 minutes, 4 hours, or 24 hours earlier	Morphine, 7 or 10 mg/kg s.c.	Morphine-induced antinociception in male mice	Antinociceptive effects of morphine were not modified by ibogaine; however, noribogaine (40 or 80 mg/kg i.p.) injected 10 minutes before morphine (5 mg/kg s.c.) enhanced the antinociceptive activity of morphine	(Bhargava et al., 1997)
40 mg/kg i.p., 4 hours prior to naloxone and 20 hours after morphine	Morphine, 20 mg/kg s.c.	Naloxone-induced morphine withdrawal signs in male rats	Ibogaine attenuated both somatic and motivational morphine withdrawal reactions acutely induced by naloxone	(Parker et al., 2002)
40 mg/kg i.p., 4, 12 or 24 hours prior; 80 mg/kg i.p. 24 hours prior; or two doses of 40 mg/kg i.p. 24 and 48 hours or 4 and 24 hours prior to place preference testing	Morphine, 5 mg/kg i.p.	Morphine-induced conditioned place preference in male rats	Ibogaine did not attenuate an established one-trial morphine place preference	(Luxton et al., 1996)
4–16 micrograms, i.c.v. 15 minutes prior to naloxone	85-mg morphine pellets implanted s.c., 72 hours prior to naloxone	Naloxone-precipitated withdrawal syndrome in chronic morphine-dependent male rats	Ibogaine decreased locomotion and dose-dependently reduced the frequency of certain withdrawal symptoms (rearing, writhing, jumping, digging, chewing, salivation, head hiding, and teeth chattering), but not that of others (ptosis, head shakes, 'wet-dog' shakes, grooming, stretching, urination, paw tremor, scratching, diarrhea, rhinorrhea,	(Dzoljic et al., 1988)

			and vocalization on touch)	
5, 10, 20 or 40 mg/kg s.c., 15 minutes before naloxone	75-mg morphine pellet implanted s.c. 3 days before ibogaine	Naloxone-precipitated withdrawal signs in male rats	Ibogaine had no effect on 10 out of 12 withdrawal signs in this model, the two exceptions being increased teeth chatter and a decrease in grooming	(Sharpe & Jaffe, 1990)
3, 6, or 24 mg/kg s.c.	Morphine, 3 mg/kg s.c.	Morphine-induced analgesia in female mice	Co-administered with morphine, ibogaine dose-dependently increased morphine-induced analgesia	(J. A. Schneider & McArthur, 1956)
20, 40 or 80 mg/kg i.p., 10 minutes before each morphine injection	20 mg/kg s.c., b.i.d. for 4 days	Morphine-induced analgesia in male mice	At 40 and 80 mg/kg, ibogaine inhibited the development of tolerance to the antinociceptive action of mu- but not to delta- or kappa-opioid receptor agonists	(Cao & Bhargava, 1997)
40 mg/kg i.p., 30 minutes before naloxone	Morphine pellets implanted s.c., 75 mg/rat, 72 hours prior to naloxone	Naloxone-precipitated withdrawal signs in morphine-dependent male rats	Ibogaine attenuated naloxone-induced morphine withdrawal signs, diarrhea, chewing, teeth-chattering, and penile licking	(Cappendijk et al., 1994)
40 mg/kg, i.p., 15 minutes prior to morphine (self-administration study), & 19 hours prior to morphine (locomotor study)	Morphine, ~0.04 mg/kg/dose i.v. (self-administration); morphine, 5 mg/kg i.p. (locomotor study)	Morphine self-administration and morphine-induced locomotor stimulation in female rats	Ibogaine reduced morphine self-administration and inhibited morphine-induced locomotor stimulation	(Glick et al., 1997)
40–80 mg/kg i.p., 2.25 hours after morphine on day 4	Morphine, 30 mg/kg i.p. b.i.d. for 3 days, with an added dose of 30 mg/kg on day 4	Naloxone-precipitated morphine withdrawal signs in male mice	Ibogaine dose-dependently (ED50, 72 mg/kg) reduced naloxone-precipitated jumping in morphine-dependent mice	(Popik, Layer, Fossom, et al., 1995)
Ethanol				
Ibogaine Dose and Route of Administration	**Other Drug and Route of Administration**	**Effect Measured**	**Interaction**	**Ref**

Systemic: 20 or 40 mg/kg i.p., 2 months after continuous access to ethanol. Microinjection for VTA: 0.1 µM/0.5 µL (0.05 pmol), 1 µM/0.5 µl (0.5 pmol), and 10 µM/0.5 µL (5.0 pmol). Microinjection for substantia nigra: 10 µM/0.5 µL (5.0 pmol).	Ethanol in drinking water ad libitum	Effect of ibogaine on self-administration of ethanol in male rats using: 1) two-bottle choice & operant self-administration paradigms 2) relapse model 3) Microinjection of ibogaine into the brain	Systemic ibogaine (40 mg/kg) decreased ethanol intake for effects 1 & 2. Ethanol self-administration was reduced by injection of ibogaine into the VTA, but not into the substantia nigra	(He et al., 2005)
10, 30, or 60 mg/kg s.c. & i.p. after ethanol	Drinking water containing 10% ethanol for over 2 weeks	Ethanol & food intake in male rats	Administered i.p. or i.g., but not s.c., ibogaine reduced alcohol intake. Only the highest dose decreased food intake	(A. H. Rezvani et al., 1995)
60 mg/kg via gavage, daily for 5 consecutive days after daily, stabilized ethanol intake	Drinking water containing 10% ethanol	Tolerance to ethanol in male rats	Ibogaine significantly reduced alcohol intake without the development of tolerance; no significant effect on food and water intake	(A. H. Rezvani et al., 1995)
60 mg/kg i.p., 15 minutes before ethanol	Ethanol (16% v/v), 2.5 g/kg i.p.	Blood alcohol levels in alcohol-naïve male rats	No effect	(A. H. Rezvani et al., 1995)
Nicotine				
Ibogaine Dose and Route of Administration	**Other Drug and Route of Administration**	**Effect Measured**	**Interaction**	**Ref**
40 mg/kg i.p., after daily nicotine	Nicotine, 0.4 mg/kg s.c. daily for 5 consecutive days	Nicotine-induced dopamine overflow in the nucleus accumbens and hyperlocomotion in the plus-maze test in male rats	Ibogaine decreased the dopamine overflow induced by nicotine without affecting hyperlocomotion	(Benwell et al., 1996)
40 mg/kg i.p., 19 hours earlier	Nicotine, 0.32 mg/kg i.v.	Nicotine-induced increases in DA levels in male rats	Ibogaine attenuated the increase in extracellular dopamine induced by nicotine	(Maisonneuve, Mann, et al., 1997)
5.0 or 10 mg/kg i.p. daily for 21 consecutive days	Nicotine, 0.4 mg/kg s.c. daily with ibogaine for 21 consecutive days	Sensitization to nicotine-induced locomotor stimulant effects in male rats	Co-administered with nicotine, ibogaine had no effect on nicotine-induced locomotor activity	(Zubaran et al., 2000)

10–40 mg/kg i.p., 15 minutes earlier	Nicotine, 4 mg/mL, p.o. in drinking water	Nicotine self-administration in nicotine-preferring male rats	All doses of ibogaine decreased rates of nicotine intake	(Glick et al., 1998)

Table 8: Comparison of Ibogaine and Noribogaine at 1 or 10 mg/kg i.v. in Male Rats (Baumann, Pablo, et al., 2000)

	Ibogaine	**Noribogaine**
Tremors	Tremors	No tremors
Plasma levels of corticosterone	More potent at Elevating dose	Less potent at elevating
Plasma levels of prolactin	Elevated	Elevated
Extracellular levels of dopamine in the nucleus accumbens	No effect	No effect
Extracellular levels of 5-HT in the nucleus accumbens	Less potent at elevating	More potent at elevating

Table 9: Preclinical Research on Ibogaine's Pharmacology

Animals Male (m), Female (f), or Not Stated (n.s.)	**No. of Animals Per Group**	**Ibogaine Dose and Route of Administration**	**Type of Study**	**Single or Repeated Dose**	**Follow-up After Administration**	**Ref**
Mice (m)	10	10, 20, 40, and 80 mg/kg i.p.; Noribogaine, 10, 20, 40, and 80 mg/kg i.p.	Effects on opioid receptors	Single	NA	(Bhargava et al., 1997; Cao & Bhargava, 1997)
Mice (m)	10	20, 40, and 80 mg/kg i.p.	Tolerance to opioid receptor agonists	Single and repeat	NA	(Cao & Bhargava, 1997)
Mice (m)	8	Varying doses; 40 to 80 mg/kg i.p.	Morphine withdrawal	Single	NA	(Layer et al., 1996; Popik, Layer, Fossom, et al., 1995)
Mice (m)	10	20 and 80 mg/kg i.p.	Tonic extensor seizures	Single	NA	(G. Chen & Bohner, 1958)
Mice (m)	10	10, 12.1, and 20.9 mg/kg s.c.; 34.8 µmol/kg s.c.	Tremorolytic potency	Single	1 hour	(Zetler et al., 1972)
Mice (m)	16	40 mg/kg i.p.	Cocaine-induced locomotor activity	Repeated	5 and 9 days	(Sershen, Hashim, et al., 1992)
Mice (CDF1)	10	30 mg/kg i.p.	Morphine withdrawal	Single	5 days	(Francés et al., 1992)

Mouse (m), rat & guinea pig forebrains (in vitro); mice (m) in vivo	-	40 and 80 mg/kg i.p.	NMDA antagonist activity in vitro & morphine withdrawal in vivo	Single	NA	(Layer et al., 1996)
Mice (n.s.)	5	1–5 mg/kg i.p.; 2.5 mg/kg i.p.	Open-arms maze test; cocaine withdrawal	Repeated	14 days	(Ali et al., 1999; Onaivi et al., 1998)
Mice (m & f)	10	5 mg/kg i.p.	Candida albicans infection	Repeated	10 days	(Yordanov et al., 2005)
Mice (ns)	32	Ibogaine, 100, 300, 400, and 500 mg/kg i.g; noribogaine, 300, 500, 700, and 900 mg/kg i.g.	LD50	Single	NA	(Kubiliene et al., 2008)
Rats (m)	4	1–40 mg/kg i.p.	Morphine anti-nociception	Single	19 hours	(Bagal et al., 1996; Hough et al., 1996)
Rats (m)	12	10 mg/kg and variable doses i.p.	Introceptive stimuli, stimulus generalization	Repeated	NA	(Schechter & Gordon, 1993)
Rats (m)	6	10, 20, and 30 mg/kg i.p.	Discrimination from fenfluramine	Single	NA	(Schechter, 1997)
Rats (m)	12	1, 3, 10, 30, 46 and 50 mg/kg i.p.	8-Armed radial maze	Repeated	7 days	(Helsley, Fiorella, et al., 1997)
Rats (m)	27	1, 3, 10, 15, and 20 mg/kg i.p.	Stimulus effects in drug-trained rats	Repeated	NA	(Palumbo & Winter, 1992)
Rats (m)	8	10, 20, 30, 40 and 60 mg/kg i.p.	Activity, spatial learning, & sensory-motor function	Repeated	24 hours, 7 days	(Kesner et al., 1995)
Rats (m)	32	40 and 80 mg/kg i.p.	Morphine place preference	Single and repeated	NA	(Luxton et al., 1996; Parker et al., 1995)
Rats (m)	32	0.025, 0.25, or 2.5 mg/kg i.p.	Mental retrieval in the Morris maze spatial navigation task	Single	NA	(Popik, 1996)
Rats (m)	10	50 mg/kg, i.p.	EEG, EKG and monoamines	Single	NA	(Z. Binienda et al., 1998)
Rats (m & f)	3 to 4	Ibogaine, 10 to 60 mg/kg i.p.; 40 mg/kg s.c.; noribogaine, 5 to 40 mg/kg i.p.	Sex differences morphine-induced in locomotor activity	Single	1, 5, and 19 hours	(Hough et al., 1996; Pearl et al., 1997)

Rats (f)	12	40 mg/kg i.p.	Morphine-induced locomotor activity; brain dopamine metabolism	Single	1 month	(Glick, Rossman, et al., 1992; Maisonneuve, Rossman, et al., 1992)
Rats (f)	16	Ibogaine or noribogaine, 40 mg/kg i.p.	Cocaine-induced hyperactivity	Single	NA	(Maisonneuve, Visker, et al., 1997)
Rats (n.s.)	18	0.25, 1, 2, and 4, and 40 mg/kg i.v.	Dopaminergic neuronal responses to cocaine & morphine	Repeated	Up to over 19 hours	(French et al., 1996)
Rats (n.s.)	50	100 mg/kg i.p.	Purkinje cell toxicity	Single and repeated	Up to 2 weeks	(O'Hearn & Molliver, 1993)
Rats (f)	2 to 12	2.5, 20, 40, 60, and 80 mg/kg i.p.	Morphine self-administration	Single and repeated	30 days	(Glick et al., 1991)
Rats (f)	12	40 mg/kg i.p.	Brain levels of morphine & amphetamine	Single	19 hours	(Glick, Gallagher, et al., 1992)
Rats (f)	3 to 8	10 to 40 mg/kg i.p.	Cocaine & morphine intake, tremors, & DA release	Repeated	27 days	(Glick et al., 1994)
Rats (m)	10	10, 20, and 40 mg/kg i.p.	Cocaine intake	Single and repeated	NA	(Cappendijk & Dzoljic, 1993)
Rats (m)	10	40 mg/kg i.p.	Morphine withdrawal	Single	NA	(Cappendijk et al., 1994)
Rats (m)	6	40 mg/kg i.p.	Nicotine-induced locomotor responses, dopamine overflow, and 5-HT levels	Single	7 days	(Benwell et al., 1996)
Rats (m)	12	40 and 80 mg/kg i.p.	Cocaine and heroin intake	Single	Up to 24 hours	(Dworkin et al., 1995)
Rats (m)	8	10, 30, and 60 mg/kg i.p., s.c., and i.g.	Alcohol intake	Single and repeat	NA	(A. H. Rezvani et al., 1995)
Rats (m)	30	4, 8, and 16 µg, i.c.v.	Morphine withdrawal	Single	NA	(Dzoljic et al., 1988)
Rats (m)	24	5, 10, 20, and 40 mg/kg s.c.	Morphine withdrawal	Single	1 hour	(Sharpe & Jaffe, 1990)
Rats (f)	24	25, 50, 75, and 100 mg/kg i.p.	Neurotoxicity	Single	24 hours	(Xu et al., 2000)
Rats (m)	6	Ibogaine and nor-ibogaine, 1 and 10 mg/kg i.v.	Neurobiological effects on of DA and 5-HT	Single	24 hours	(Baumann, Rothman, et al., 2001)

Rats (m) and mice (m)	Unclear	20 and 40mg/kg i.p.;various doses via microinjection into ventral tegmental area	Ethanol intake and GDNF regulation	Repeat and single	Up to 48 hours	(He et al., 2005)
Rats (m)	16	40 mg/kg, i.p.	Amphetamine-induced locomotor activity	Single	7 days	(Blackburn & Szumlinski, 1997)
Rats (m)	19	40 mg/kg i.p.	Cerebral glucose in morphine-dependent and -naïve animals	Single	45 minutes	(Levant & Pazdernik, 2004)
Rats (n.s.)	26	20 and 40 mg/kg i.p.	Effects on sleep and waking state; motor behavior	Repeated	6 and 2 hours	(Gonzalez et al., 2018)
Rats (m)	36	50 mg/kg i.p.	Methods for detecting ibogaine in tissues	Single	Up to 24 hours	(Dhahir et al., 1971)
Rats (m) and mice (m)	12 rats; 18 mice	10 mg/kg i.p.	Aggressiveness and muricide	Single	30 and 90 minutes	(Kostowski et al., 1972)
Catss (n.s.), dogs (n.s.), and mice (n.s.)	Cats (n.s.), dogs (n.s.), and 30 (mice)	2–10 mg/kg i.v.; 10 and 20 mg/kg s.c. (mice)	Behavioral changes (cats and dogss), EEG, blood pressure, and heart rate (cats); electroshock-seizure threshold (mice)	Single	NA	(J. A. Schneider & Sigg, 1957)
Zebra fish (m and f)	20–30	10 and 20 mg/L submersions	Social behavior and locomotor activity	Single	NA	(Cachat et al., 2013)
Rats (f)	~118	5–60 mg/kg, i.p.	Antagonism of morphine-induced locomotion	Single	2 and 3 hours	(Pearl, Johnson, et al., 1995)

Neuroendocrine Effects of Ibogaine and Noribogaine

Ibogaine and noribogaine both cause time-limited increases in plasma corticosterone and prolactin, with ibogaine more potently stimulating corticosterone secretion (Baumann, Rothman, et al., 2001). In male rats administered a single injection of ibogaine (50 mg/kg i.p.), plasma prolactin rapidly elevated and then declined to control levels after 60 minutes (Ali et al., 1996). Corticosterone increases were comparatively more persistent as concentrations showed a continuing increase for 120 minutes after drug administration and levels, although they had returned to baseline at 24 hours post-dosing. 5-HT neurotransmission showed mild and transient effects. At 60 minutes following ibogaine injection, levels of serotonin and its metabolite 5-hydroxyindole acetic acid (5-HIAA) were decreased, though only in the striatum.

Effects on Gene Expression and Markers of Metabolic Activity in Animals

Ibogaine is not known to produce epigenetic modifications or to exert adverse effects on gene expression. However, ibogaine does influence gene expression in animal models, and these alterations may be

mechanistically related to its therapeutic effects. More broadly, changes in gene expression or metabolic activity within the brain serve as informative markers of regional susceptibility to ibogaine action.

A single injection of ibogaine (50 mg/kg, i.p.) in male mice has been shown to produce significant induction of immediate early gene expression across multiple brain regions (Ali et al., 1999). Specifically, *egr-1* messenger RNA was induced in the nucleus accumbens (NAc), caudate-putamen (CPu), frontal cortex (FCx), septum, dentate gyrus (DG), and CA3 region of the hippocampus, while *c-fos* induction was observed in the CPu, FCx, DG, septum, and CA1 region of the hippocampus.

Ibogaine demonstrates measurable effects on cellular metabolic activity. In a standard yeast model of housekeeping metabolism, ibogaine has been shown to decrease the cellular ATP pool (Paskulin et al., 2010). Effects on cellular energy metabolism, including elevations in cerebral concentrations of metabolic enzymes involved in glycolysis, may contribute to the therapeutic profile of ibogaine (Paskulin et al., 2006).

Ibogaine has been shown to increase glial cell line-derived neurotrophic factor (GDNF) expression both in vivo and in vitro. A single intraperitoneal administration of ibogaine at 40 mg/kg, but not 20 mg/kg, produced elevated GDNF concentrations in the male rat ventral tegmental area at 24 hours following administration (Marton et al., 2019). In cell culture models, short-term exposure of a dopaminergic-like cell line to ibogaine produced sustained increases in GDNF mRNA, leading to elevated protein expression and upregulation of the GDNF signaling pathway (He & Ron, 2006). Given that GDNF reduces ethanol consumption in rats (Ron & Janak, 2005), therapies that activate GDNF signaling have been proposed as potentially useful approaches in the treatment of substance use disorder (Ron & Janak, 2005).

Research using in vivo and in vitro models suggests that ibogaine may influence genes implicated in the central effects of psychostimulants (Onaivi et al., 2002). Defined signal transduction pathways are associated with psychostimulant administration, and broad-spectrum regulation of these signals by ibogaine has been described. The actions of methamphetamine have been shown to parallel those of cocaine, including the capacity to alter long-term potentiation (LTP) in the rat hippocampus—an effect suggesting that excessive brain stimulation associated with compulsive psychostimulant use may exceed a threshold beyond which LTP becomes occluded. The influence of ibogaine on immediate early genes and other candidate genes regulated by psychostimulants and additional substances of misuse warrants further evaluation in models of compulsive use, reward, relapse, tolerance, craving, and withdrawal. These findings have prompted the hypothesis that ibogaine may modulate gene products relevant to substance use disorder pathophysiology, although the mechanism remains to be fully characterized.

The first transcriptomic analysis of ibogaine effects on gene expression has been reported (Biosca-Brull et al., 2024). A single oral dose of ibogaine (60 mg/kg, corresponding to approximately 10–25 mg/kg human equivalent) administered to C57BL/6J mice produced significant alterations in frontal cortex gene expression at four hours post-administration. Notable upregulation was observed in genes involved in hormonal signaling pathways, including oxytocin (*Oxt*; $\log_2$FC = 5.23, $p = 0.016$) and vasopressin (*Avp*; $\log_2$FC = 4.72, $p = 0.045$), as well as in synaptogenesis-related genes including cerebellin 4 (*Cbln4*; $\log_2$FC = 0.77, $p = 0.016$) and cerebellin 2 (*Cbln2*; $\log_2$FC = 0.40, $p = 0.001$). Downregulated transcripts included *Usp35* (deubiquitinase) and *Ap5b1* (adaptor protein), implicating apoptotic and endosomal transport processes. Marked sex differences were evident in the transcriptomic response: eight differentially expressed genes were identified in males, compared with 28 in females. The upregulation of oxytocin and vasopressin transcripts represents a mechanistically novel finding and may contribute to the prosocial subjective effects reported during ibogaine therapy.

Effects on Folding of Neurotransmitter Transporters and Other Proteins

Pharmacological chaperones are molecules that function as molecular scaffolding to facilitate the correct folding of otherwise misfolded mutant proteins. Both ibogaine and its primary metabolite noribogaine have demonstrated the capacity to act as pharmacological chaperones at serotonin and dopamine transporters, although the clinical implications of this activity remain to be established.

Serotonin Transporter Chaperone Activity

In vitro studies have shown that ibogaine can bind to the inward-facing conformation of the serotonin transporter (SERT) (Bulling et al., 2012) and provide a partial rescue of mutations that impair proper folding (El-Kasaby et al., 2010); effects that apparently extend to noribogaine (El-Kasaby et al., 2014).

Dopamine Transporter Chaperone Activity

Ibogaine has similarly been shown to act as a pharmacological chaperone capable of restoring normal function to misfolded dopamine transporter (DAT) protein in vitro. This activity has been proposed as potentially applicable to dopamine transporter deficiency syndrome (DTDS), a rare hereditary condition caused by autosomal recessive loss-of-function mutations in the DAT that frequently disrupt transporter trafficking and folding (Beerepoot et al., 2016). Available evidence suggests that ibogaine promotes DAT maturation by functioning as a pharmacological chaperone within the endoplasmic reticulum, with successful rescue of DAT maturation and functional activity demonstrated for the DTDS-associated mutations A314V and R445C. These findings represent the first demonstration of pharmacological chaperoning of DAT and suggest a potentially viable approach to increasing DAT expression in DTDS and other conditions associated with reduced DAT function. Depending on the effective dose, patients with this genetic disorder would likely not employ ibogaine on a maintenance basis; however, the pharmacological activity of ibogaine may inspire the development of novel therapeutic agents capable of exerting sustained effects.

Genetic mutations affecting the human dopamine transporter (hDAT, *SLC6A3*) produce a clinical syndrome of infantile and juvenile dystonia accompanied by parkinsonism. In *Drosophila* models, three such mutations have been corrected through pharmacochaperoning with noribogaine (Asjad et al., 2017). Given the demonstrated capacity of noribogaine to restore dopamine transport in *Drosophila melanogaster*, the prospect of functional rescue of misfolded DATs in living organisms through pharmacochaperoning has been proposed as offering novel therapeutic possibilities for protein folding disorders—not only those affecting hDAT, but also those involving other SLC6 transporters, particularly mutants of the creatine transporter-1, which give rise to X-linked intellectual disability (Sucic et al., 2016).

Ibogaine noncompetitively inhibited transport by dopamine transporter (DAT) (Bulling et al., 2012). Because ibogaine and noribogaine can restore DAT function, they are of interest in the pursuit of treatments for children afflicted with disease-relevant mutations of DAT. Ibogaine and noribogaine are likely to serve as valuable tools for investigating the folding trajectory of the transporter, with the expectation that improved mechanistic understanding of SLC6 transporter folding will facilitate the rational design of pharmacological chaperones (Freissmuth et al., 2018).

Noribogaine is a pharmacochaperone that inhibits heat-shock proteins involved with misfolded SERT (El-Kasaby et al., 2014). For patients with genetic protein-folding disorders who pursue ibogaine treatment for substance use disorder, consultation between treating clinicians and specialists in protein-folding disease may be warranted to evaluate whether ibogaine administration produces measurable short-term or long-term benefits with respect to the concomitant disease.

Structure-Activity and Translational Considerations

A systematic structure–activity relationship investigation has compared 15 ibogaine analogues and 37 bupropion analogues for DAT pharmacological chaperone activity (Sutton et al., 2022). Ibogaine and noribogaine were identified as the most efficacious DAT chaperones examined, with ibogaine increasing wild-type DAT surface expression to 222 ± 7.9% of vehicle and noribogaine reaching 251 ± 17.8%. Other ibogaine analogues demonstrated lower efficacy, including ibogainalog (169 ± 13.7%), coronaridine (147 ± 7.3%), and voacangine (125 ± 3.1%). β-carbolines (pinoline 141 ± 4.4%; tetrahydroharmine 137 ± 6.8%) and tryptamine analogues were substantially less efficacious. The isoquinuclidine ring was identified as essential for ibogaine-class chaperone activity, and DAT binding affinity did not predict chaperone capacity, indicating that pharmacochaperoning and transport inhibition represent pharmacologically distinct processes.

The translational viability of ibogaine-class compounds for the treatment of DTDS has subsequently been challenged by in vivo investigation in an A313V DAT knock-in mouse model (Russo et al., 2026). Despite extensive pharmacokinetic optimization—including an oral dosing regimen of 500 + 250 mg/kg achieving brain noribogaine concentrations exceeding 100 μM for ≥19 hours—noribogaine did not rescue DAT protein expression as assessed by Western blot in either wild-type or A313V animals, in contrast to the successful rescue previously demonstrated in cell-based studies. Noribogaine did produce reductions in locomotor activity in both genotypes (wild-type vehicle 3687.86 ± 336.01 vs. noribogaine 1912.71 ± 311.13 cm, $p < 0.0001$; A313V vehicle 7939.86 ± 836.61 vs. noribogaine 4491.25 ± 525.87 cm, $p < 0.0001$); however, α-methyl-para-tyrosine and amphetamine demonstrated superior efficacy as disease-modifying interventions. These findings indicate that, although the noribogaine regimen examined was capable of attenuating hyperactivity in both wild-type and A313V animals, it did not produce increases in DAT expression on Western blot analysis, in contrast to results obtained in cell-based studies.

Neurobiological Effects in Animals

At higher doses, ibogaine modulates neuronal excitability and synaptic transmission within the parabrachial nucleus by depolarizing parabrachial neurons, producing increased firing rates and excitability, while concurrently depressing non-NMDA receptor-mediated fast synaptic transmission, with both effects involving dopamine receptor activation (Kombian et al., 1997).

High doses of ibogaine produce neurotoxicity in rats. However, no detectable neurotoxicity has been observed in rats, mice, dogs, or rabbits administered ibogaine at the therapeutic dose of 25 mg/kg. Postmortem analysis of one human ibogaine user did not reveal evidence of neurotoxicity following four ibogaine sessions employing doses of up to 30 mg/kg. Therapeutic doses of ibogaine up to at least 25 mg/kg therefore do not appear to pose neurological risks to adult human recipients.

Electroencephalographic and Sleep Effects

In anesthetized male rats administered ibogaine (50 mg/kg, i.p.), EEG power was reduced in the delta, theta, alpha, and beta frequency bands during the initial 30 minutes following administration, with return to baseline within the subsequent 15 minutes (Z. Binienda et al., 1998).

In male rats, ibogaine has been shown to produce stimulant effects, including dose-dependent increases in locomotor activity at doses of 1 and 10 mg/kg (i.v.) (Baumann, Rothman, et al., 2001) and prolonged waking hours following doses of 20 or 40 mg/kg (i.p.) (Gonzalez et al., 2018). The extended period of wakefulness corresponded with reduced overall sleep duration, characterized by decreased slow-wave sleep during the first 2 hours following administration and decreased rapid eye movement (REM) sleep across the entire 6-hour polysomnographic recording period. Possible explanations for these findings are that ibogaine either inhibited serotonin reuptake (Wells et al., 1999) or activated cholinergic pathways (J. A. Schneider & Sigg, 1957).

Tremor Induction

Tremors have been observed in male mice following both subcutaneous and intracerebral administration of ibogaine (Singbartl et al., 1973; Zetler et al., 1972). At a low intravenous dose of 10 mg/kg, ibogaine produced tremors in male rats, whereas noribogaine did not (Baumann, Pablo, et al., 2000). Male rats experience tremors for 2 to 3 hours when given ibogaine in doses of 20, 40, or 80 mg/kg i.p (Glick, Rossman, et al., 1992). Ibogaine (40 mg/kg i.v.) produced fine tremors, flattening of body posture, and flaccid hindlimbs in rats in a matter of minutes and for up to 2 hours after administration (French et al., 1996). Even a low dose of ibogaine (10 mg/kg i.p.) produced general tremors in male rats within 10 minutes after administration (Helsley, Fiorella, et al., 1997). This study is in agreement with other research that showed ibogaine produces tremors in specific locations; the head and upper limbs seem to be vulnerable among both rats and mice (Costache, 1995). Unlike ibogaine at 10 mg/kg i.v., however, noribogaine did not produce tremors in male rats at the same or one-tenth the dose (Baumann, Pablo, et al., 2000).

Across five iboga alkaloids administered subcutaneously to male mice, tremors have been characterized as coarse and interrupted by quiet episodes that could persist for minutes (Zetler et al., 1972). The least tremorigenic compounds were also those with the lowest lipid solubility. Although lipid solubility represents an important determinant of initial cerebral concentration—reflecting a correlation between distribution coefficient and maximal brain concentration—maximal brain concentration in this context appears indicative of supply rather than pharmacological potency. Potency, by contrast, is most accurately assessed through drug concentration at tremor termination, a functional parameter that does not correlate with the distribution coefficient but rather with the subcutaneous ED_{50}. The subcutaneous ED_{50} was 12.1 mg/kg for ibogaine and 51.4 mg/kg for noribogaine. At 100 mg/kg (s.c.), noribogaine additionally produced salivation, convulsions, and running fits. The tremorigenic potency of these alkaloids appears to depend more on chemical structure than on lipid solubility, supporting the proposal of specific indole compound receptors within brain regions implicated in tremor generation. Additional evidence indicates that ibogaine is not subject to intracerebral drug metabolism (Zetler et al., 1972).

The induction of tremors by ibogaine might be partly attributable to interactions with the GABA-benzodiazepine receptor complex since the tremorigenic effect of a structurally related iboga alkaloid, tabernanthine, was ameliorated in male rats (20 mg/kg i.p.) by administration of either a benzodiazepine agonist (flunitrazepam) or antagonist (Ro 15-1788) after the alkaloid. In vitro binding studies suggest that tabernanthine acts as a benzodiazepine inverse agonist (Trouvin et al., 1987). Notably, the tremors produced by ibogaine (20 mg/kg s.c.) in male mice were more effectively blocked through the pre-administration of cholecystokinin octapeptide (CCK-8), ceruletide, or some ceruletide analogs rather than atropine, biperiden, clonazepam, methixene, haloperidol, ethopropazine, trihexyphenidyl, or prolyl-leucylglycine amide (Zetler, 1983).

Substance P and Neuropeptide Effects

Administered daily for 4 consecutive days, ibogaine (40 mg/kg i.p.) increases substance P-like immunoreactivity in the striata and substantia nigra but not in the nucleus accumbens of male rats; however, from 20 mg/kg daily, a substantial increase in substance P-like immunoreactivity was only found in the striatum and a daily dose of 10 mg/kg failed to produce an increase in either part of the brain (Alburges et al., 2000).

Antiseizure Activity

The first comprehensive evidence that ibogaine and structurally related ibogalogs—including DM506, ibogainalog, and nor-IBG—exert antiseizure activity in rodents through 5-HT_{2a}/2C receptor activation has been reported (Chagraoui et al., 2026). In the pentylenetetrazole (PTZ) model of seizures (PTZ 70 mg/kg, i.p., in C57BL/6J mice), nor-IBG (30 mg/kg, i.p.) and DM506 (25 mg/kg, i.p.) significantly reduced

seizure scores ($p < 0.0001$), and ibogaine (10 mg/kg, i.p.) demonstrated time-dependent protection. Repeated subthreshold dosing across 7–14 days (DM506 5 mg/kg/day; nor-IBG 3 mg/kg/day) produced more robust antiseizure effects than acute treatment ($p < 0.0001$), suggesting therapeutic augmentation without development of tolerance. In hippocampal CA3 slice preparations, both nor-IBG and DM506 (50 μM) completely blocked kainic acid-induced epileptiform discharges, with the selective 5-HT_{2a} antagonist volinanserin (1 μM) reversing the nor-IBG suppression of these discharges. Receptor pharmacology data confirmed activity at multiple 5-HT receptor subtypes: at 5-HT_{2a}, nor-IBG EC_{50} = 135 ± 13 nM; at 5-HT_2c, nor-IBG EC_{50} = 165 ± 126 nM; at 5-HT_1D, DM506 EC_{50} = 110 ± 20 nM, nor-IBG EC_{50} = 447 ± 134 nM, and ibogaine EC_{50} = 661 ± 182 nM. These findings indicate that ibogalogs induce antiseizure activity in rodents in a dose- and time-dependent manner involving 5-HT_{2a}/2C receptor activation, with nor-IBG suppression of kainic acid-induced discharges in the CA3 subfield clearly implicating 5-HT_{2a} receptor activation.

Complementary evidence demonstrates that ibogaine (30 mg/kg, i.p.) induces paroxysmal EEG activity and CNS depression, characterized by increased delta power and decreased alpha power, in freely moving mice (González-Trujano et al., 2022). Notably, this paroxysmal activity was not abolished by the 5-HT_{1a} antagonist WAY100635, in contrast to paroxysmal activity produced by *Tabernaemontana arborea* extract, which was attenuated by 5-HT_{1a} blockade. This dissociation suggests that the paroxysmal EEG effects of ibogaine involve mechanisms extending beyond 5-HT_{1a} receptor signaling.

Reopening of Critical Period Plasticity

A novel mechanism underlying the durable therapeutic effects of ibogaine has emerged from preclinical evidence demonstrating that ibogaine reopens critical period-like plasticity within the adult mouse visual cortex(Acuña et al., 2025). A single dose of ibogaine (40 mg/kg, i.p.) followed by four days of monocular deprivation reduced visual acuity in the deprived eye and decreased dendritic spine density—responses normally restricted to the juvenile critical period of development. Ibogaine produced approximately 30% reductions in perineuronal net (PNN) staining intensity and density, decreased the proportion of parvalbumin-positive (PV^+) interneurons enwrapped by PNNs, and lowered vGAT-positive puncta density, collectively indicating disinhibition of cortical circuits. Vehicle-treated controls demonstrated no such effects. These findings suggest that ibogaine reopens a window of heightened cortical adaptability in the adult brain, providing a candidate mechanism through which the therapeutic effects of ibogaine may persist beyond the systemic clearance of the compound.

Disruption of Cognitive Maps

Two-photon calcium imaging in head-fixed Thy1-GCaMP6m mice (n = 8; three female) has been employed to record from ensembles of 153–702 retrosplenial cortex (RSC) neurons before and after ibogaine administration (40 mg/kg, i.p.) (Ivan et al., 2024). Ibogaine destabilized position-related firing of RSC neurons: mutual information for non-cue locations decreased significantly ($p = 1.44 \times 10^{-9}$) while cue location information was preserved, and position decoding error increased by approximately 300% following ibogaine but not saline administration. Functional connectivity was reorganized, with the clustering coefficient of pairwise correlations decreasing and the explained variance of the top six principal components dropping from 72.9 ± 4.7% to 64.8 ± 2.6%, indicating increased neuronal independence. Neural avalanche dynamics shifted toward criticality, and the temporal integration window was shortened. These findings demonstrate that ibogaine destabilizes the firing fields of spatial neurons, impairs the decoding of animal position from neural population activity, reorganizes functional connectivity patterns, and alters neural avalanche dynamics, while preserving sensory-evoked responses. This cellular-level disruption of cognitive maps may underlie the psychedelic and therapeutic effects of ibogaine by transiently destabilizing rigid neural patterns associated with substance use disorder and trauma.

Behavioral and Physiological Effects in Animals

Locomotor activity refers to bodily motion associated with walking and ambulation. A slight increase in locomotor activity, manifested as running behavior, has been reported in male mice following administration of ibogaine (20 mg/kg, i.p.) (G. Chen & Bohner, 1958).

Morphine-induced locomotor activity is understood to depend upon dopaminergic release within the brain. Pretreatment with ibogaine (40 mg/kg, i.p.) inhibited locomotor activity in female rats administered morphine at 1 hour, 19 hours, and 1 week following ibogaine administration—an inhibition attributable to ibogaine-induced reductions in extracellular dopamine concentrations (Maisonneuve, Rossman, et al., 1992).

Ibogaine administered to male rats at doses ranging from 10 to 60 mg/kg (i.p.) produced dose-dependent behavioral effects (Kesner et al., 1995). At 20–60 mg/kg, animals exhibited slower response times across sensory and sensorimotor tasks, with impaired performance on evaluations of motor reflexes at the 40 and 60 mg/kg doses. At lower doses (10–40 mg/kg), motor and non-locomotor activities were markedly reduced alongside diminished emotional expression, while at the highest doses (40–60 mg/kg) animals were rendered inactive. Administration of a high dose of ibogaine (80 mg/kg, i.p.) to morphine-dependent male mice produced no observable changes in rotarod performance in the context of naloxone-precipitated withdrawal jumping (Layer et al., 1996).

Discriminative Stimulus Properties

Male rats trained to discriminate ibogaine (10 mg/kg, i.p.) from saline have demonstrated intermediate levels of generalization to the hallucinogens LSD and DOM (Helsley et al., 1998). These findings suggest that although ibogaine may produce some of its effects through interactions at 5-HT_{2a} receptors, such interactions do not appear essential to the discriminative stimulus properties of the compound.

Anxiety-Related Behavior

Male mice have demonstrated anxiety-related behavior on the elevated plus-maze 30 minutes following administration of ibogaine at either 20 or 40 mg/kg (i.p.) (Popik & Wrobel, 2001). Similarly, male rats administered ibogaine (40 mg/kg, i.p.) exhibited decreased entries into the open runways of the elevated plus-maze for 22 hours following administration, consistent with anxiogenic effects in rodent models (Benwell et al., 1996). These findings have been interpreted to suggest that the long-lasting anxiogenic effects of ibogaine warrant further investigation before clinical use can be recommended in smoking cessation populations.

However, the interpretation of these behavioral findings is complicated by several considerations. A subject, whether human or rodent, recovering from administration of a centrally acting compound may avoid brightly lit open spaces for reasons unrelated to anxiety, including heightened introspection, photophobia, or perceived impairment of coordination over surfaces presenting a fall risk. Additionally, a human recipient intentionally undertaking ibogaine administration for a specific therapeutic purpose may respond with less anxiety than a laboratory animal exposed to an unexpected administration of a centrally acting compound. Moreover, the presence of transient anxiety does not in itself preclude the therapeutic utility of ibogaine in smoking cessation or related indications.

Reduction of Drug Self-Administration

Another psychological effect can be seen in reduced drug craving. Ibogaine inhibits the self-administration of dependency-producing drugs in animal models. In preclinical studies, ibogaine reduced the self-administration of: Opioids (Dworkin et al., 1995; Glick et al., 1991); Alcohol intake was reduced by i.p. and i.g., but not s.c. injections (A. H. Rezvani et al., 1995); Cocaine (Cappendijk & Dzoljic, 1993; Glick et al., 1994); in some studies, for at least several days afterward (Glick et al., 1994; Sershen et al.,

1994). One study did not consistently replicate the effect of ibogaine on reduced self-administration of cocaine (Dworkin et al., 1995).

Suppression of cocaine and morphine self-administration has been shown to be dose-related, with higher doses of ibogaine producing more pronounced effects than lower doses (Glick et al., 1994). In some, but not all, animals, repeated administration on consecutive days or at weekly intervals produced more durable outcomes (Glick et al., 1991).

In a study of morphine self-administration in female rats, considerable interindividual variability in susceptibility to the therapeutic effects of ibogaine was documented (Glick et al., 1991). In some animals, persistent decreases in morphine intake were observed for several days or weeks following a single ibogaine injection; other animals demonstrated such persistent changes only after two or three weekly injections; and a small number of animals appeared resistant to prolonged aftereffects. The observed aftereffects could not be attributed to conditioned aversion.

Analogous variability is anticipated in clinical settings. Accordingly, ibogaine may not produce uniformly predictable outcomes when administered as a therapeutic intervention for substance use disorder. This expectation is consistent with the high relapse rates observed across currently approved pharmacotherapies for substance use disorder.

A dose-dependent reduction in alcohol self-administration has been demonstrated in male rats when ibogaine was administered via intraperitoneal or intragastric routes, but not via subcutaneous administration—a route that bypasses the first-pass hepatic metabolism through which CYP2D6 converts ibogaine to its primary metabolite noribogaine (A. H. Rezvani et al., 1995). This finding supports a substantive role for noribogaine in the therapeutic effects of ibogaine in substance use disorder.

Conditioned Place Preference and Translational Considerations

Animal models employ two principal paradigms to assess abuse liability: drug-induced conditioned place preference and drug self-administration. A meta-analysis of 27 animal studies on ibogaine concluded that the compound does not modify conditioned place preference in morphine- or amphetamine-dependent rats, with no significant differences observed across ibogaine doses or across the substance examined (morphine or amphetamine) (Belgers et al., 2016). The conditioned place preference paradigm is most appropriately applied to assess Pavlovian conditioning, an automatic and involuntary form of associative learning. The self-administration paradigm, by contrast, incorporates both Pavlovian and operant conditioning, the latter of which reflects clearly voluntary behavior. Data derived from self-administration studies therefore offer greater translational relevance for extrapolating preclinical findings to human behavioral outcomes.

Attenuation of Opioid Withdrawal

Ibogaine reduces the intensity of the withdrawal syndrome produced by morphine (Layer et al., 1996). Ibogaine (20, 40, or 80 mg/kg i.p.) pretreatment decreased the intensity of withdrawal syndrome induced by naloxone or naltrexone in morphine-dependent male rats (Glick, Rossman, et al., 1992). Similarly, treatment with ibogaine (40 to 80 mg/kg i.p.) before naloxone dose-dependently reduced the morphine withdrawal syndrome in male mice (Popik, Layer, Fossom, et al., 1995). Finally, pretreatment doses of ibogaine (2 or 8 mg/kg s.c.) reduced the naloxone-induced withdrawal signs for morphine in morphine-dependent nonhuman primates (Aceto et al., 1989).

The observation that pretreatment with glycine, which impedes the binding of noncompetitive antagonists of NMDA receptors, effectively abolishes the suppressing effect of ibogaine on naloxone-precipitated morphine withdrawal syndrome in male mice (Popik, Layer, Fossom, et al., 1995; Popik, Layer, &

Skolnick, 1995), would suggest that the antagonist action of ibogaine on NMDA receptors is, in part, responsible for its ameliorating effects on opiate withdrawal.

Cardiovascular System

Ibogaine can prolong the QT interval, an effect known to increase the risk of life-threatening torsades de pointes (TdP) arrhythmias. Additionally, heart rate may initially slow following ibogaine administration.

Ibogaine can disturb the heart's physiology by inhibiting heterologously expressed hERG (human ether a go-go gene) potassium channels (Koenig & Hilber, 2015; Litjens & Brunt, 2016). At higher in vitro doses, ibogaine also reduced human Nav1.5 sodium and Cavi.2 calcium currents (Koenig et al., 2013). While low micromolar concentrations of ibogaine in guinea pig cardiomyocytes failed to prolong the action potential and higher concentrations shortened the potential, researchers proposed that calcium-channel inhibition by ibogaine counteracts the prolonged action potential effects of hERG blockade. However, computational modeling of the human ventricular cardiomyocyte indicates that ibogaine is capable of prolonging the action potential in the human heart (Koenig et al., 2013).

A series of physiological investigations examining the cardiovascular effects of ibogaine in cats, dogs, frogs, rabbits, and isolated animal organ preparations was reviewed in 1957, encompassing studies conducted from 1901 through the 1940s and 1950s (J. A. Schneider & Rinehart, 1957). In anesthetized animals (32 dogs and 6 cats), ibogaine (2 to 5 mg/kg, i.v.) produced reductions in heart rate accompanied by decreased respiration and blood pressure. When perfused through an isolated cat heart preparation, ibogaine (5 µg/cc) substantially reduced the amplitude of contraction in association with bradycardia and decreased coronary flow. In anesthetized dogs, ibogaine (1 mg, i.v.) markedly slowed the heart rate while modestly increasing pulse pressure, whereas a higher dose (3 mg, i.v.) produced more pronounced reductions in heart rate alongside decreased aortic flow, with concurrent elevations in right atrial pressure indicative of cardiac failure.

Because depressed cardiac function in cats was produced at ibogaine doses one-tenth of those required to elicit vasodilation, the observed reductions in heart rate were attributed to depressed cardiac output rather than to vasodilation. Notably, the bradycardia and reduced blood pressure produced by ibogaine were observed only in anesthetized or curarized animals. In unanesthetized dogs, comparable doses of ibogaine produced a clear elevation in blood pressure, occasionally preceded by a transient pressure decrease. In summary, ibogaine demonstrated a depressant effect on cardiac function in anesthetized animals and a stimulant effect in unanesthetized animals.

An electrocardiographic investigation in rats demonstrated that heart rate decreased immediately following intraperitoneal injection of ibogaine at 50 mg/kg (Z. Binienda et al., 1998).

More recent investigation has demonstrated dose-dependent cardiotoxic necrosis in rats at 6 and 24 hours following single oral doses of 1 or 20 mg/kg ibogaine, an effect not associated with inflammatory infiltration and not consistently associated with alterations in antioxidant defense markers (Vidonja Uzelac et al., 2024).

Respiratory System

Dedicated respiratory function studies of ibogaine in animals are sparse, and no published whole-body or head-out plethysmography data appear to be available.

Hepatic System

Ibogaine undergoes extensive first-pass hepatic metabolism, and the liver is therefore both the primary site of biotransformation and a relevant target organ for toxicology. The available preclinical data indicate

that ibogaine produces dose- and sex-dependent histopathological and biochemical changes in rat liver following acute oral administration, while large clinical case series have not reported substantial hepatic enzyme abnormalities at therapeutic doses.

Ibogaine is rapidly absorbed following oral administration and undergoes extensive first-pass O-demethylation to 12-hydroxyibogamine (noribogaine) by cytochrome P450 2D6 (CYP2D6) in both the gut wall and the liver (Glue, Winter, et al., 2015; Mash et al., 2000). Plasma protein binding is in the range of 65–70%, and consistent with its lipophilic nature ibogaine accumulates in adipose tissue, with reported concentrations up to ~11,300 ng/g in fat at 1 hour after intraperitoneal dosing of 40 mg/kg in rats compared with ~106 ng/mL in plasma (Hough et al., 1996). This adipose sequestration, together with the long elimination half-life of noribogaine, contributes to a prolonged systemic exposure to active alkaloid that extends well beyond the parent compound's plasma half-life. CYP2D6 polymorphisms produce substantial interindividual variability in the rate of conversion of ibogaine to noribogaine, with poor metabolizers showing higher and more sustained ibogaine exposure (Glue, Winter, et al., 2015; Knuijver et al., 2024).

Single oral doses of ibogaine (1 or 20 mg/kg, body weight) in male rats have been shown to produce significant glycogenolytic activity within hepatocytes, accompanied by mild oxidative stress at both 6 and 24 hours following administration (Tatalović et al., 2019). A complementary investigation in female rats employing the same dosing regimen demonstrated substantially lower glycogenolytic activity compared to males—a finding consistent with the higher overall bioavailability and altered metabolic profile of ibogaine in female animals (Tatalović et al., 2021). Histopathological evaluation in female rats demonstrated dilatation of the central vein at both doses 6 hours following administration, and dilatation of both the central vein and smaller branches of the portal vein at 24 hours following the higher 20 mg/kg dose; hepatic tissue architecture was otherwise preserved, with no evidence of necrosis or inflammatory infiltrate. With respect to redox status, hepatic thiol concentrations were elevated at 6 hours, followed at 24 hours by increased catalase activity, increased lipid peroxidation, and decreased xanthine oxidase activity. Plasma ibogaine bioavailability was two- to three-fold higher in females than in males following oral administration, with otherwise comparable kinetic profiles. Collectively, these findings indicate that single oral doses of ibogaine in the 1–20 mg/kg range produce mild, transient alterations in hepatic vasculature and redox homeostasis without overt hepatocellular injury or necrosis at either dose examined, and that female rats experience these effects at higher tissue exposures than males administered equivalent mg/kg doses.

Renal System

Tissue distribution analysis has examined ibogaine concentrations in plasma, brain, kidney, liver, and adipose tissue following intraperitoneal and subcutaneous administration in rats (Hough et al., 1996). At 1 hour following ibogaine 40 mg/kg (i.p.), renal drug concentrations were intermediate between those measured in plasma (~106 ng/mL) and adipose tissue (~11,308 ng/g), with renal concentrations 10- to 20-fold lower at 12 hours following the same dose. These findings indicate that the kidney does not function as a major sequestration compartment for ibogaine in the manner observed for adipose tissue. Subcutaneous administration produced significantly higher tissue concentrations across all sampled sites, consistent with first-pass metabolic loss following intraperitoneal dosing.

Single oral doses of ibogaine (1 or 20 mg/kg, body weight) in male rats have been shown to alter redox homeostasis within the kidney, with changes in antioxidant enzyme activities consistent with mild oxidative stress (Tatalović et al., 2019). A complementary investigation in female rats employing the same dosing regimen demonstrated mild histopathological changes across all treated animals (Tatalović et al., 2021). Slight alterations at the level of the proximal tubules and tubular epithelial cells were observed at the 1 mg/kg dose at both 6 and 24 hours, with moderate changes in the same renal compartments

observed at the 20 mg/kg dose at both timepoints. Notably, these changes did not progress to overt tubular necrosis or interstitial inflammation.
With respect to antioxidant enzyme activity, glutathione reductase activity was reduced at 6 and 24 hours at both doses, catalase activity was elevated at 6 hours, and xanthine oxidase activity was elevated at both 6 and 24 hours. Importantly, ibogaine did not alter antioxidant enzyme activity within erythrocytes, suggesting that the observed renal redox changes reflect localized tissue effects rather than systemic oxidative stress.
The pattern of mild proximal tubular changes—affecting the renal segment most exposed to parent drug, metabolites, and their conjugates within the glomerular filtrate, and most active in xenobiotic transport and reabsorption—is consistent with the kidney functioning as a route of elimination for ibogaine and noribogaine. However, these findings do not establish a primary nephrotoxic mechanism at the doses examined.

Preclinical Evidence by Substance Class

Cocaine

In rats administered cocaine both acutely and chronically, ibogaine pretreatment (40 mg/kg, i.p.) has been shown to enhance the locomotor response to cocaine challenge administered 19 hours later. Due to the shape of the dose-response curve, ibogaine pretreatment in chronic—but not acute—cocaine-exposed animals enhanced the locomotor response to 5 and 10 mg/kg cocaine while attenuating the response to 40 mg/kg cocaine (Szumlinski et al., 1999). These findings indicate that the capacity of ibogaine to modulate sensitivity to the stimulant effects of cocaine on locomotor activity depends in part on the prior history of cocaine exposure.

In a single-dose investigation in cocaine-reinforced male rats, only the highest ibogaine dose administered intraperitoneally shortly prior to cocaine self-administration sessions produced reductions in cocaine intake (Dworkin et al., 1995). Neither 40 mg/kg ibogaine administered 60 minutes prior to the session nor 80 mg/kg administered 24 hours prior to the session suppressed responding maintained by cocaine infusions (0.33 mg/infusion). Pretreatment with 80 mg/kg ibogaine at either 60 or 90 minutes prior to the session suppressed cocaine self-administration on the day of administration, with the longer pretreatment interval producing suppression of responding for 48 hours.

In substance-naïve male rats administered cocaine, ibogaine pretreatment (50 mg/kg, i.p.) administered one hour prior to cocaine challenge produced sustained increases in alpha_1 band electrocorticographic activity for 120 minutes, alongside increases in low-frequency delta and theta band power (Z. K. Binienda et al., 2011). The elevation in low-frequency activity suggests that high-dose ibogaine in combination with cocaine may lower the threshold for cocaine-induced seizures. Given that rats chronically administered cocaine for two weeks exhibited reductions in delta and theta band activity, the high dose of ibogaine appears to have attenuated the cocaine-induced slow-wave electrocorticographic profile.

Within one hour of administration, acute doses of ibogaine (2.5 to 80 mg/kg, i.p.) produced dose-dependent reductions in cocaine and morphine intake in female rats self-administering these substances daily over a period of approximately two weeks (Glick et al., 1994). At a dose of 40 mg/kg, the effects of ibogaine persisted into the subsequent day. Following three weekly injections of ibogaine (40 mg/kg, i.p.), a subset of animals demonstrated reduced morphine intake for several days and reduced cocaine intake for several weeks following the final administration.

A single dose of ibogaine (2.5 mg/kg) in mice receiving cocaine daily for two weeks reduced withdrawal-related aversion produced by abrupt cocaine cessation, as measured by behavioral responses on the elevated plus-maze (Onaivi et al., 1998). In male rats, electrocorticographic recordings combined with neurochemical measurements have demonstrated that a high dose of ibogaine (50 mg/kg, i.p.)

administered one hour prior to cocaine produces an attenuated response to the stimulant, reflected in part by reduced dopamine concentrations within the caudate nucleus (Z. Binienda et al., 2000).

In cocaine-dependent male rats, a single injection of ibogaine (40 mg/kg, i.p.) produced significant reductions in cocaine intake that persisted for more than 48 hours (Cappendijk & Dzoljic, 1993). Given the relatively short plasma half-life of ibogaine, this prolonged effect implicates one or more active metabolites in the modulation of cocaine intake.

Two sequential injections of ibogaine (40 mg/kg, i.p.), administered six hours apart, reduced cocaine intake in cocaine-preferring male mice for five days (Sershen et al., 1994). Brain cocaine concentrations measured 35 minutes after cocaine administration were approximately 25% higher in ibogaine-treated animals; however, in a separate experiment in which mice received cocaine daily for four days, brain cocaine concentrations did not differ significantly between control animals and animals administered two doses of ibogaine on the third day.

Further investigation in cocaine-dependent male rats has confirmed and extended these findings (Cappendijk & Dzoljic, 1993). A single injection of ibogaine (40 mg/kg, i.p.) produced significant reductions in cocaine intake that persisted for more than 48 hours. Repeated administration of ibogaine across three consecutive days also produced pronounced reductions in cocaine intake; however, a more pronounced inhibitory effect was observed in animals administered ibogaine weekly across three consecutive weeks. These findings characterize ibogaine, or its active metabolites, as a durable interruptor of cocaine dependence, consistent with observations from uncontrolled clinical reports.

Alcohol

Ibogaine has been shown to suppress alcohol intake in a dose-dependent manner in Marchigian Sardinian high-alcohol-drinking Fawn-Hooded rats, a strain selectively bred for binge drinking and relapse-like ethanol consumption (A. H. Rezvani et al., 2003). At 24 hours following an acute injection of ibogaine (40 mg/kg, i.p.), both preference for ethanol and ethanol intake were reduced in male rats that had self-administered ethanol over the preceding two months, with comparable reductions in consumption observed in a rodent ethanol relapse model (He et al., 2005). Glial cell line-derived neurotrophic factor (GDNF) signaling within the ventral tegmental area (VTA) has been hypothesized to mediate the reduction in alcohol intake produced by ibogaine, as microinjection of ibogaine directly into the VTA produced dose-dependent reductions in operant responding for ethanol self-administration.

A follow-up investigation in male rats characterized the regional and dose-specific effects of ibogaine on neurotrophic factor expression (Marton et al., 2019). At 40 mg/kg (i.p.), but not at 20 mg/kg, ibogaine selectively upregulated GDNF expression within the VTA and substantia nigra (SN). At both 20 and 40 mg/kg, ibogaine increased brain-derived neurotrophic factor (BDNF) expression within the nucleus accumbens (NAc), SN, and prefrontal cortex (PFC), while only the higher dose significantly upregulated GDNF within the VTA. At 40 mg/kg, nerve growth factor (NGF) mRNA was upregulated across all examined regions (PFC, NAc, SN, and VTA), whereas 20 mg/kg selectively upregulated NGF mRNA within the PFC and VTA. The selective elevation of GDNF within the VTA 24 hours following 40 mg/kg ibogaine, but not 20 mg/kg, coincided with the dose previously identified as effective in rodent models of self-administration of substances of misuse.

Subsequent work has further demonstrated that ibogaine (10 and 30 mg/kg, oral) blocks both drug-primed and cue-induced reinstatement of ethanol-induced conditioned place preference in male mice at doses that produce no detectable rewarding effects in their own right (Henriques et al., 2021).

Additional preclinical evidence supporting the therapeutic relevance of iboga-class compounds in alcohol use disorder has emerged from investigations of structural analogues. Oxa-noribogaine administered as 30

mg/kg followed by 20 mg/kg three hours later has been shown to reduce alcohol self-administration in rats through aversive learning, with sustained therapeutic effects ($F(1,24) = 5.25$, $p = 0.031$, Hedges' $g = 1.14$, 95% CI 0.31–1.97) (Meinhardt et al., 2026). Oxa-noribogaine-treated animals demonstrated blunted recovery of alcohol-seeking behavior (44.9%) compared with control animals (78%). The κ-opioid receptor antagonist aticaprant partially blocked this effect, and both memantine (an NMDA receptor antagonist, 25 mg/kg) and U-50488 (a κ-opioid receptor agonist, 10 mg/kg) each partially reproduced the effects observed with oxa-noribogaine. These findings support both NMDA receptor inhibition and κ-opioid receptor activation as contributing mechanisms.

Amphetamine and Methamphetamine

Female rats administered ibogaine (40 mg/kg, i.p.) 19 hours after daily methamphetamine administration across seven days exhibited an enhanced stereotypic response following a challenge dose of methamphetamine (2 mg/kg, i.p., but not 4 mg/kg) administered subsequent to a seven-day withdrawal period (Szumlinski, Balogun, et al., 2000). These findings indicate that ibogaine produced a reduction in tolerance to methamphetamine, consistent with one of the proposed therapeutic effects of the compound in substance use disorder.

In female rats, ibogaine (40 mg/kg, i.p.) administered 19 hours prior to an acute dose of (+)-amphetamine (1.25 mg/kg, i.p.) produced significant increases in cerebral amphetamine concentrations at both 30 minutes and 2 hours following amphetamine administration (Glick, Gallagher, et al., 1992). This finding suggests that ibogaine may inhibit an amphetamine-metabolizing enzyme, plausibly of hepatic origin.

Additional investigation in freely moving female rats has demonstrated that ibogaine (40 mg/kg, i.p.) administered 19 hours prior to d-amphetamine (1.25 mg/kg, i.p.) potentiated the amphetamine-induced increase in extracellular dopamine concentrations within the nucleus accumbens and striatum, prolonged the reduction in 3,4-dihydroxyphenylacetic acid (DOPAC) concentrations across both regions, and enhanced amphetamine-induced motor activity (Maisonneuve, Keller, et al., 1992). These findings have been interpreted to suggest that ibogaine may render lower doses of amphetamine more rewarding while concurrently rendering higher doses less reinforcing.

Ibogaine pretreatment (40 mg/kg, i.p., administered 19 hours prior) has also been shown to antagonize methamphetamine-induced elevations in corticosterone and the behavioral disinhibiting effects of acute methamphetamine in female rats (Szumlinski, Haskew, et al., 2001). Locomotor activity on the elevated plus-maze was not altered in this investigation, an outcome potentially attributable to the relatively low methamphetamine dose employed.

In male rats, ibogaine pretreatment (40 mg/kg, i.p.) administered 24 hours prior to amphetamine challenge blocked amphetamine-induced conditioned place preference following one or two conditioning trials, with diminished efficacy observed following four trials (Moroz et al., 1997). This attenuation of effect appeared to reflect the development of tolerance to ibogaine.

Nicotine

Nicotine produces stimulant effects on locomotor activity in rats. Ibogaine (5 to 10 mg/kg, i.p.) co-administered with nicotine across 21 consecutive days in male rats did not suppress nicotine-induced sensitization as measured by locomotor activity (Zubaran et al., 2000). It is possible that the consecutive daily administration produced tolerance to ibogaine, and that pretreatment rather than co-administration would have been more effective in attenuating locomotor activity. In a separate investigation, an acute dose of ibogaine (40 mg/kg, i.p.) administered 22 hours prior to nicotine challenge in male rats failed to attenuate nicotine-induced hyperlocomotion (Benwell et al., 1996).

It is possible that the consecutive daily administration produced tolerance to ibogaine, and that pretreatment rather than co-administration would have been more effective in attenuating locomotor activity. In a separate investigation, an acute dose of ibogaine (40 mg/kg, i.p.) administered 22 hours prior to nicotine challenge in male rats failed to attenuate nicotine-induced hyperlocomotion (Maisonneuve, Mann, et al., 1997). Pretreatment with ibogaine (40 mg/kg, i.p.) 19 hours prior to the first nicotine infusion (0.32 mg/kg per infusion) significantly attenuated the increase in extracellular dopamine concentrations induced by nicotine, suggesting that ibogaine may reduce the rewarding effects of nicotine.

In cultured bovine adrenal chromaffin cells employed as a model neuronal system, ibogaine (<10 μM) selectively inhibited nicotinic receptor-mediated catecholamine release through a mechanism not mediated by the κ-opioid receptor (Mah et al., 1998). Although the inhibitory effect was rapidly reversible at lower concentrations, at higher concentrations of ibogaine (100 μM) inhibition persisted for at least 19 hours following washout. Cerebral concentrations of ibogaine following therapeutic dosing in animal models have previously been reported within the range of 1 to 100 μM, supporting the physiological relevance of these in vitro findings. Earlier investigation in cultured chromaffin cells demonstrated that ibogaine (1 to 10 μM) selectively inhibited acetylcholine-stimulated nicotinic receptor-mediated catecholamine release, with additional mechanisms of evoked catecholamine release inhibited at higher concentrations of ibogaine (100 μM) (A. S. Schneider et al., 1996). The site of selective inhibitory action of ibogaine at the nicotinic acetylcholine receptor has been postulated to be the receptor ion channel itself.

Patch-clamp investigations have demonstrated that ibogaine functions as a more potent antagonist at α3β4 nicotinic receptors than at NMDA, 5-HT_3, or α4β2 nicotinic receptors (Glick et al., 2002). In isolated rat pheochromocytoma PC12 cells, ibogaine has been shown to non-competitively block the influx of $^{22}Na^+$ through ganglionic-type nicotinic receptor channels (Badio et al., 1997). When administered in conjunction with the antinociceptive agent epibatidine, ibogaine (10 mg/kg, i.p.) completely blocked epibatidine-elicited antinociception in mice, a response mediated by central nicotinic receptor channels, with no significant blockade observed at 24 hours following administration of 40 mg/kg ibogaine. Blockade of nicotinic channels has been proposed to contribute to the therapeutic effects of ibogaine in substance use disorder.

The diverse subtypes of nicotinic acetylcholine receptors belong to the neurotransmitter-gated ion channel superfamily and serve critical roles in chemical signaling throughout the nervous system. These receptors are accordingly of significant interest both as targets of substances of misuse and as molecular targets for therapeutics in substance use disorder and smoking cessation (Fryer & Lukas, 1999).

Opioids

Ibogaine at doses ranging from 2.5 to 80 mg/kg (i.p.) produced dose-dependent reductions in morphine and cocaine self-administration in female rats within one hour of administration, with effects persisting into the following day (Glick et al., 1994). A subset of animals exhibited reduced substance intake for several days following a single ibogaine injection or after two or three weekly injections at 40 mg/kg.

A single dose of ibogaine (40 mg/kg, i.p.) has been shown to significantly attenuate several signs of naloxone-precipitated morphine withdrawal in morphine-dependent male rats (Cappendijk et al., 1994). In an additional investigation, ibogaine at 40 or 80 mg/kg (i.p.) significantly reduced four of seven withdrawal signs in morphine-dependent male rats when administered 30 minutes prior to naltrexone-precipitated withdrawal; the 40 mg/kg dose administered four hours prior to naltrexone also significantly reduced the same withdrawal symptomatology (Glick, Rossman, et al., 1992).

In male rats trained with heroin reinforcement, an injection of ibogaine (40 or 80 mg/kg, i.p.) produced near-complete suppression of heroin self-administration within one hour, although responding returned to control levels on the subsequent day (Dworkin et al., 1995).

A 1956 investigation in female mice demonstrated that ibogaine administered subcutaneously at doses up to 40 mg/kg did not produce analgesic effects when administered alone, but did dose-dependently potentiate the analgesic effects of morphine, ketobemidone, codeine, and meperidine, producing more pronounced and prolonged analgesia when co-administered at doses of 6 and 24 mg/kg (J. A. Schneider & McArthur, 1956). More than four decades later, an investigation in male mice confirmed that both ibogaine (20 or 40 mg/kg, i.p.) and noribogaine (10, 20, or 40 mg/kg, i.p.) dose-dependently enhance the analgesic activity of morphine in morphine-tolerant animals, consistent with the proposed therapeutic effects of these compounds in substance use disorder (Sunder Sharma & Bhargava, 1998).

Morphine pre-exposure has been shown to influence ibogaine activity, suggesting that variability in opioid exposure history may account for some of the interindividual differences in the efficacy of ibogaine in the treatment of opioid use disorder (Pearl, Johnson, et al., 1995). In a study in which female rats were pretreated with varying doses of morphine or saline across 1 to 4 days, a single dose of ibogaine ranging from 5 to 60 mg/kg (i.p.) was subsequently administered. At 29 hours following a 40 mg/kg dose, morphine-induced locomotor stimulation was significantly attenuated. Notably, low doses of ibogaine (5 and 10 mg/kg, i.p.) that did not antagonize morphine-induced locomotor activity in non-pretreated animals successfully inhibited morphine-induced locomotor activity in morphine-pretreated rats.

In an investigation of the capacity of noribogaine to attenuate morphine tolerance, twice-daily administration of noribogaine to morphine-dependent male mice attenuated tolerance at 20 mg/kg (i.p.) in animals implanted with a morphine pellet and at 40 mg/kg (i.p.) in animals receiving daily morphine injections (Bhargava & Cao, 1997). Given that prior work had demonstrated tolerance inhibition with ibogaine at 40 and 80 mg/kg, the capacity of noribogaine to attenuate morphine tolerance at lower doses than ibogaine has been interpreted to indicate that the attenuating effect of ibogaine on morphine tolerance may be mediated through its biotransformation to noribogaine.

Further evidence suggests that ibogaine may enhance morphine antinociception in male mice indirectly through its metabolite noribogaine, potentially via activity at μ-opioid receptors. Noribogaine at 40 and 80 mg/kg (i.p.), but not 20 mg/kg, enhanced morphine antinociception, whereas ibogaine at doses up to 40 mg/kg (i.p.) did not (Bhargava et al., 1997). As the primary metabolite of ibogaine, the capacity of noribogaine to potentiate the analgesic effect of morphine may contribute to the reduction of opioid tolerance produced by the parent compound. Consistent with these findings, noribogaine functions as a full μ-opioid agonist in rat thalamic membranes, comparable in efficacy to morphine, a finding that may partially explain the attenuation of opioid withdrawal symptomatology and reduction of morphine intake produced by ibogaine (Pablo & Mash, 1998).

A 19-hour pretreatment with ibogaine (40 mg/kg, i.p.) in male rats significantly decreased morphine antinociception, with ibogaine producing no antinociceptive effects in the absence of morphine (Bagal et al., 1996). Noribogaine pretreatment (40 mg/kg, i.p.) similarly failed to alter morphine antinociception. However, when either ibogaine (5, 20, or 40 mg/kg, i.p.) or noribogaine (40 mg/kg, i.p.) was co-administered with morphine, both combinations enhanced morphine antinociception, with noribogaine producing more pronounced potentiation than ibogaine at the equivalent 40 mg/kg dose. These findings suggest that noribogaine may mediate the acute potentiation of morphine antinociception by ibogaine, while the inhibition of morphine antinociception observed following ibogaine pretreatment is unlikely to be attributable to noribogaine.

Ibogaine did not weaken morphine-induced conditioned place preference in male rats that had a previously established one-trial morphine place preference. This was measured in both single and double

injections of ibogaine at 40 mg/kg i.p. administered 4, 12, 24, and 48 hours prior to testing and a single dose of 80 mg/kg i.p. 24 hours prior (Luxton et al., 1996).

Additional evidence supports the hypothesis that noribogaine mediates the capacity of ibogaine to attenuate opioid withdrawal symptomatology (Mash et al., 2016). In male mice, oral noribogaine (30 and 100 mg/kg) dose-dependently reduced naloxone-precipitated morphine withdrawal induced two hours following administration. Noribogaine demonstrated substantial brain penetration across all doses examined (10 to 100 mg/kg, p.o.). In conditioned place preference testing, male rats administered noribogaine (10, 30, and 100 mg/kg, p.o.) exhibited no behavioral indication that the compound itself was rewarding, suggesting that the therapeutic effect of noribogaine in opioid use disorder is not attributable to substitution for the hedonic effects of morphine.

In chronically morphine-dependent male rats, intracerebroventricular administration of ibogaine at doses ranging from 4 to 16 µg 15 minutes prior to naloxone produced dose-related attenuation of naloxone-precipitated withdrawal syndrome (Dzoljic et al., 1988). In contrast, subcutaneous administration of ibogaine (5, 10, 20, or 40 mg/kg) failed to alleviate naloxone-precipitated morphine withdrawal symptomatology when administered 15 minutes prior to naloxone in morphine-dependent male rats three days following subcutaneous implantation of a 75 mg morphine pellet (Sharpe & Jaffe, 1990). This negative outcome may be partially attributable to the subcutaneous route of administration and the brief pretreatment interval, such that biotransformation of ibogaine to noribogaine had not progressed sufficiently to produce therapeutic concentrations of the active metabolite. Similarly, ibogaine (30 mg/kg, i.p.) failed to reduce naloxone-precipitated morphine withdrawal in morphine-dependent mice when administered one minute following naloxone administration (Francés et al., 1992). Interestingly, ibogaine does potentiate opiate analgesia when both drugs are co-administered subcutaneously (J. A. Schneider & McArthur, 1956), suggesting that the temporal onset of distinct pharmacological effects of ibogaine may vary across mechanisms.

Pretreatment with ibogaine (40 mg/kg, i.p.) administered 5 hours prior reduced morphine-induced locomotor behavior in female but not male rats (Pearl et al., 1997). Pretreatment with ibogaine (10 to 60 mg/kg, i.p., administered 19 hours prior) or noribogaine (5 to 40 mg/kg, i.p., administered 1 hour prior) attenuated morphine-induced locomotor effects significantly more in female than in male rats, and at relatively lower doses. Ibogaine pretreatment reduced post-test locomotor activity in both sexes; however, brain and plasma concentrations of ibogaine and noribogaine were higher in female than in male animals receiving equivalent doses. Although antagonism of morphine-induced locomotor activity by ibogaine (40 mg/kg) as a 19-hour pretreatment was more pronounced via subcutaneous than intraperitoneal administration, the subcutaneous route also produced more pronounced locomotor antagonism in females than in males. The observed sex differences in response to ibogaine appear attributable to higher bioavailability in female animals.

The role of the 5-HT_{2a} receptor in noribogaine pharmacology has been investigated using genetic knockout mouse models (Villalba et al., 2024). Noribogaine (10 or 40 mg/kg, i.p.) was shown to reduce NMDA-mediated current density in medial prefrontal cortex (mPFC) pyramidal neurons in a 5-HT_{2a} receptor- and sex-dependent manner. In whole-cell patch-clamp recordings from layer V mPFC pyramidal neurons, noribogaine at 40 mg/kg significantly reduced NMDA current density only in male wild-type mice (vehicle 6.02 ± 1.37 pA/pF vs. noribogaine 1.48 ± 0.56 pA/pF, $p < 0.01$), with no significant effects observed in male knockout animals or in female animals of either genotype. NMDA/AMPA ratios in male wild-type animals were significantly reduced following 40 mg/kg noribogaine (vehicle 0.75 ± 0.04 vs. 0.56 ± 0.03, $p < 0.001$). Locomotor effects, immediate early gene expression (*Npas4*, *Egr1*, *cFos*), and 5-HT_{2a} receptor mRNA expression each demonstrated pronounced sex- and genotype-dependent patterns.

Subsequent investigation has extended these findings to thalamocortical neurons, demonstrating that noribogaine blocks T-type calcium channels in a sex- and 5-HT_{2a}-dependent manner (Villalba et al., 2025). Noribogaine blocked T-type calcium current density only in 5-HT_{2a} knockout female animals, with no effect observed in wild-type females, and no blocking effect was observed in male animals of either genotype. Calcium current density values were substantially elevated in ventrobasal neurons from female animals, providing additional evidence of sex-dependent differences in this circuitry. Notably, the noribogaine effects demonstrated an inverted dose-response relationship, with effects absent at 40 mg/kg.

Pharmacokinetics and Product Metabolism in Animals

The pharmacokinetic profile of ibogaine has been characterized across multiple animal species. Interpretation of certain findings should account for the fact that human administration occurs almost exclusively via the oral route, whereas the majority of preclinical investigations have employed intraperitoneal (i.p.) or subcutaneous (s.c.) administration. The potential significance of route of administration is supported by evidence that ibogaine administered via intraperitoneal or intragastric—but not subcutaneous—routes significantly reduces alcohol intake without affecting blood alcohol concentrations (A. H. Rezvani et al., 1995).

Absorption

Ibogaine demonstrates non-linear, dose-dependent bioavailability, indicating that both absorption and first-pass elimination of the compound exhibit non-linear pharmacokinetics. Following oral administration of 5 and 50 mg/kg in rats, ibogaine bioavailability was 16% and 71% in female animals and 7% and 43% in male animals, respectively (Jeffcoat et al., 1994). Consistent with these findings, plasma ibogaine concentrations 19 hours following intraperitoneal administration of 40 mg/kg were approximately three-fold higher in female than in male rats (Pearl et al., 1997).

The extent to which ibogaine absorption proceeds through active versus passive mechanisms remains incompletely characterized. Ibogaine has been shown to inhibit P-glycoprotein (P-gp) and, to a lesser extent, breast cancer resistance protein (BCRP) in a concentration-dependent manner (Tournier et al., 2010). At the blood–brain barrier, BCRP and P-gp function as the major efflux transporters. P-gp interactions were assessed via in vitro assays measuring efflux of the P-gp substrates calcein-AM and rhodamine-123 (Rh-123) using flow cytometry in BCRP-MDR1 cells, with and without ibogaine. Ibogaine significantly inhibited calcein-AM efflux, with accumulation ratios of approximately 9, 18, and 26 at concentrations of 25, 50, and 100 μM, respectively; these values were lower than those produced by the positive control (5 μM valspodar; accumulation ratio of approximately 40).

BCRP interactions were assessed using in vitro assays measuring efflux of the BCRP substrates mitoxantrone (MXR) and pheophorbide-a (Ph-a) via flow cytometry in BCRP-HEK293 cells. Ibogaine produced no detectable inhibition of BCRP at 25 or 50 μM, with only modest effects observed at 100 μM (MXR accumulation ratio of approximately 2.5, substantially below the accumulation ratio of approximately 15 produced by the positive control, 10 μM fumitremorgine C). Parallel experiments measuring Ph-a accumulation demonstrated that ibogaine inhibited accumulation at all three concentrations (25, 50, and 100 μM), although modestly, with accumulation ratios rising from approximately 1.5 to 2.1 as concentration increased; these values were lower than the accumulation ratio of 3.2 produced by the fumitremorgine C positive control.

Sex Differences in Bioavailability

Ibogaine demonstrates higher bioavailability in female than in male animals. Following intraperitoneal administration, peak plasma concentrations of ibogaine have been reported as two-fold higher and those of noribogaine three-fold higher in female compared with male rats (Pearl et al., 1997). Areas under the concentration–time curve (AUC) for ibogaine following intraperitoneal administration have been reported

as twice as high in preovulatory female rats with elevated circulating estrogen as in either male or postovulatory animals (Baumann, Pablo, et al., 2001). Areas under the concentration–time curve (AUC) for ibogaine following intraperitoneal administration have been reported as twice as high in preovulatory female rats with elevated circulating estrogen as in either male or postovulatory animals (Jeffcoat et al., 1994). When this dose was compared with a 50 mg/kg oral dose, mean residence time was substantially increased in female animals at the higher dose but not in male animals, and oral bioavailability was markedly higher in females (71%) than in males (43%). Corresponding oral bioavailabilities at the 5 mg/kg dose were similarly higher in females (16%) than in males (7%).

Distribution

In female rats, plasma levels of ibogaine after i.v. administration decline rapidly. Ibogaine pharmacokinetics in the same rats fit a two-compartment model well, with higher concentrations found in fat tissue than in plasma or organs (Hough et al., 2000).

Because ibogaine pharmacokinetics fit a two-compartment model in rats, two half-life values can be given: the alpha half-life (the rate of decline in plasma concentrations due to drug re-distribution from the central to peripheral compartment) and the beta or terminal half-life (the rate of decline due to elimination via metabolism). Hough et al. (Hough et al., 2000) estimated that i.v. ibogaine in female rats had a rapid distribution phase with a half-life of 7.3 minutes, followed by an elimination phase half-life of 3.3 hours (Hough et al., 2000). In other studies, however, the half-life of i.v. ibogaine in male rats is estimated to be 51 minutes and 142 minutes by the i.p. route (Baumann, Rothman, et al., 2001).

In male rats administered ibogaine at 40 mg/kg i.p., the maximum concentrations of ibogaine in the blood and the brain were 11.2 μM and 11 μM, respectively, while maximum concentrations of noribogaine were 21.9 μM and 9.8 μM, respectively. From 50 mg/kg p.o., the maximum concentration of ibogaine in the brain was 15.1 μM and of noribogaine, 11.3 μM (Mash et al., 2001). When ibogaine (40 mg/kg i.p.) was administered to female rats, brain levels were approximately 30 times greater than in plasma (Hough et al., 1996).

Concentrations of ibogaine in fat, brain, kidney, and liver, and plasma were considerably higher in female rats when administered by the subcutaneous route compared to the intraperitoneal route, demonstrating the importance of first-pass hepatic metabolism (Hough et al., 1996).

Levels of ibogaine are higher in laboratory animals when measured in the blood compared to the plasma, possibly due to the drug being sequestered in platelets (K. R. Alper et al., 2001; Glick & Maisonneuve, 1998).

Pharmacokinetic findings with noribogaine support the theory that this metabolite may contribute to the therapeutic effects of ibogaine. Noribogaine reaches the brain within 15 minutes when administered to male rats at 40 mg/kg i.p. or 50 mg/kg p.o., indicating swift first-pass metabolism of the parent drug (Mash et al., 2001). From ibogaine administered i.p., the AUC of noribogaine in the blood and in the brain was between 1.75 and 9.1 times greater, respectively, compared to ibogaine (Mash et al., 2001). These results show that noribogaine can reach pharmacologically relevant concentrations in the brain after either oral or intraperitoneal routes in rats.

Metabolism

Ibogaine is subject to extensive first-pass metabolism by liver enzymes, primarily by cytochrome P450 isozyme 2D6 (CYP2D6) with additional minor contributions from CYP2C9 and CYP3A4, producing its active metabolite, noribogaine, via *O*-demethylation at the 12-position (Obach et al., 1998). Pharmacokinetic measurements in humans show that the area under the curve (AUC) for ibogaine is about a third of that of noribogaine (Mash et al., 2001).

CYP2D6 activity is genetically determined and a significant portion of the population has reduced CYP2D6 functioning. The plasma AUC for both the parent drug and noribogaine varies according to the individual's genetic polymorphisms in CYP2D6 (Mash et al., 2001). Following an in vitro study using human hepatic microsomes, the results suggested that two or more enzymes were involved in the *O*-demethylation of ibogaine, except in poor metabolizers in whom only one enzyme is present. Two *O*-demethylases of ibogaine were identified, "one with a low KMapp (1.1 μM) and the other with a high KMapp (>200 μM)" (Obach et al., 1998).

Building on these in vitro findings, Martins and colleagues conducted the first in vivo investigation of the roles of drug transporters and CYP3A4 in ibogaine pharmacokinetics using genetically engineered mouse models (F. Martins et al., 2022). Following oral administration of 10 mg/kg ibogaine to female FVB mice, absorption was rapid (Tmax ~0.5 h), and ibogaine demonstrated substantial intrinsic brain penetration with a brain-to-plasma ratio of 3.4 in wild-type animals. In mice lacking both Abcb1a/1b (P-gp) and Abcg2 (BCRP), the ibogaine AUC 0–2h increased approximately 2.3-fold compared to wild-type controls ($p<0.05$), and the brain-to-plasma ratio rose to approximately 5.1, while fecal recovery of ibogaine decreased roughly 2-fold, indicating that ABCB1 in combination with ABCG2 limits ibogaine oral bioavailability, likely through hepatobiliary and/or direct intestinal excretion, and that ABCB1 additionally restricts brain penetration. Noribogaine was formed rapidly and extensively, with metabolite AUCs far exceeding those of the parent compound, and its systemic exposure was not meaningfully affected by these efflux transporters; mOatp1a/1b proteins modestly influenced plasma exposure of the noribogaine glucuronide. Notably, neither Cyp3a knockout nor humanized CYP3A4-transgenic mice showed meaningful pharmacokinetic differences from controls, confirming that CYP3A4 does not play a significant role in ibogaine metabolism and supporting CYP2D6 as the principal metabolic pathway. These findings suggest that (1) genetic variation in ABCB1/ABCG2 may modestly affect ibogaine exposure, (2) drug interactions involving P-gp inhibition could increase ibogaine levels, and (3) CYP3A4 inhibitors or inducers are unlikely to meaningfully alter ibogaine pharmacokinetics.

Elimination

In rats of either sex, 60–70% of the dose of ibogaine is excreted through the renal route and feces during the first 24 hours (Jeffcoat et al., 1994). Systemic clearance of ibogaine administered intravenously is rapid and exceeded hepatic plasma flow by a factor of 3 to 4, suggesting the possibility of significant extra-hepatic clearance (Jeffcoat et al., 1994).

Based on the available scientific literature, less than 5% of parenterally administered ibogaine is recovered unchanged in the urine of rats, with approximately 15% estimated to be excreted within 24 hours, presumed to be in the form of noribogaine (Dhahir et al., 1971). To date, no studies have reported on the urinary or fecal recovery of ibogaine or its metabolites in mice, nonhuman primates, or humans.

Elimination of ibogaine proceeds rapidly, with an estimated half-life ($t_{½}$) of approximately 0.9 to 3.8 hours in rats depending on the route of administration (Baumann, Rothman, et al., 2000; Dhahir et al., 1971; Hough et al., 2000), and approximately 2 hours in mice following intragastric administration (Kubiliene, 2017). In rats, the pharmacokinetic (PK) profile of ibogaine following intravenous administration was best described by a two-compartment model, characterized by a rapid distribution phase (7.3 minutes) and a subsequent elimination phase (3.3 hours) (Hough et al., 2000).

In a case series of patients with substance use disorders, whole blood samples for 24-hour PK analysis were obtained from a subset of CYP2D6-genotyped individuals who received weight-adjusted oral doses of ibogaine hydrochloride ranging from 500 mg to 1,200 mg (6.4 to 14.3 mg/kg), formulated as a simple powder-in-capsule preparation (Mash et al., 2018). Derived PK parameters were stratified by dose range and CYP2D6 metabolizer status for both ibogaine and noribogaine. Ibogaine was rapidly absorbed from

the gastrointestinal tract, with median time to peak concentration (Tmax) values ranging from 1.75 to 4 hours across all dose levels. No consistent differences in mean peak plasma concentration (Cmax) were observed between extensive and intermediate metabolizers; however, mean AUC values were appreciably greater in intermediate metabolizers. Both Cmax and AUC0–24h for ibogaine demonstrated substantial intersubject variability. Given the observational nature of the study, estimation of clearance and other key pharmacokinetic parameters was not conducted to the procedural standards of an industry-sponsored clinical trial. The median terminal half-life of ibogaine ranged from 2.4 to 7.6 hours, varying as a function of CYP2D6 metabolizer status.

Table 10 provides a list of preclinical studies assessing pharmacokinetics and metabolism.

Table 10: Preclinical Studies on Pharmacokinetics and Metabolism of Ibogaine

Type of study	Dose and Route	Animal
Absorption		
(Pearl et al., 1997)	40 mg/kg i.p.	Rats (males and females)
(Jeffcoat et al., 1994)	5 and 50 mg/kg p.o.; 5 mg/kg i.v.	Rats (males and females)
Distribution		
(Hough et al., 1996)	40 mg/kg i.p., s.c.	Rats (female)
(Hough et al., 2000)	20 mg/kg i.v. infusion	Rats (female)
(Zubaran et al., 1999)	10 mg/kg i.p.	Rats (male)
Metabolism		
(Hough et al., 1996)	40 mg/kg, i.p., s.c.	Rats (female)
(Obach et al., 1998)	0.1 to 500 μM	Human hepatic microsomes
(Baumann, Rothman, et al., 2001)	40 mg/kg i.p.; 1 and 10 mg/kg i.v.	Rats (male)
(Hearn et al., 1995)	25 mg/kg p.o.	Monkey (female)
Elimination		
(Cartoni & Giarusso, 1972)	5–20 mg/kg p.o.	Rabbits
(Hough et al., 1996)	40 mg/kg, i.p., s.c.	Rats (female)
(Jeffcoat et al., 1994)	5 mg/kg; oral	Rats (males and females)
(Baumann, Rothman, et al., 2001)	40 mg/kg i.p.; 1 and 10 mg/kg i.v.	Rats (male)

Pharmacokinetic Drug Interactions

A study in rats conducted by MPI Research (Mattawan, MI) for the National Institute on Drug Abuse examined the potential adverse drug interactions from acute doses of morphine combined with acute doses of ibogaine (Schaefer, 1996). MPI Research reported:

Rats were administered ibogaine alone (50 and 100 mg/kg), morphine alone (50, 89, 158, 281, and 500 mg/kg) or combinations of 100 mg/kg ibogaine and varying amounts of morphine. A single dose of ibogaine was administered followed by a dose of morphine 45 minutes later. The same dose was also administered after 4 and 24 hours. No animal died following ibogaine administration alone. In the males, morphine alone produced some deaths with the highest number occurring in the group receiving 500 mg/kg morphine. The number of deaths in each group increased in animals receiving combinations of 100

mg/kg ibogaine and morphine relative to animals receiving morphine alone. A similar outcome was seen in the females; however, with a few exceptions, fewer females died in each group than males. The administration of ibogaine alone did not produce test-article related clinical signs.

A number of clinical signs were seen in animals treated with morphine alone. With the addition of ibogaine to morphine, there was an increase in the incidence of tremors, cold to touch and decreased activity. A slight, but statistically significant decrease in platelet count in the females in the 100 mg/kg ibogaine: 0 mg/kg morphine group and modest, but statistically significant, increase in cholesterol in the females in the 50 mg/kg ibogaine: 0 mg/kg morphine group were observed. Because these were only seen in one sex and were not dose-related, the effects did not appear to be test-article related. In addition, several animals receiving morphine showed corneal opacity and urinary bladder distention/discoloration. These observations may have resulted from morphine's inhibition of the blink reflex and urinary tract function, respectively.

Catalepsy (rigid body) was seen with high frequency among all groups administered morphine alone and combinations of ibogaine and morphine. This was particularly true during the two and three-hour post-dose observation on Day 1 where 70% to 100% of the animals in each dose group showed this sign. Catalepsy continued to be observed at high frequencies during the four-hour post-dose observation and again on Day 2.

Ataxia was not observed in any animal on this study.

Tremors were seen during the Day 1 post-dose observations in all groups receiving either morphine alone or an ibogaine and morphine combination. The number of animals per group tended to be quite low (55% or less) with exceptions to this occurring among the male animals in the groups receiving ibogaine with 158 and 281 mg/kg morphine.

Convulsions were not observed in any animal on this study.

Several signs indicating abnormal respiratory function were observed during this study. Abnormal respiratory sounds were frequently observed during all three post-dose observations on Day 1 in all groups receiving morphine. The administration of ibogaine did not appear to affect the frequency seen at any dose. Labored breathing was seen primarily on Day 2 during both the morning and the afternoon observations. Increases in the frequency of labored breathing observations were seen among male animals receiving ibogaine with 158 or 281 mg/kg of morphine compared to animals receiving those doses of morphine alone. The one surviving male animal in the ibogaine: 500 mg/kg dose group showed labored breathing on Days 2–4 compared to 1 (20%) or none of the surviving animals in the 500 mg/kg morphine alone group. Females also showed a somewhat increased frequency of labored breathing on Days 2–4 among animals receiving the higher three doses of morphine administered with ibogaine compared to animals receiving those doses of morphine alone. Gasping was also observed in a few animals, with the greatest rate (3/9) seen in the ibogaine: 50 mg/kg morphine male group. Taken as a whole, the data on respiratory function indicate that respiratory depression was produced by morphine and that ibogaine may exacerbate this response at the highest doses of morphine.

In summary, the administration of morphine produced dose-related mortalities which were increased by the addition of ibogaine. The extent of these mortalities was also sex-dependent, with males being more sensitive to the lethal effects than females. The LD50 for males administered morphine alone was 587 mg/kg of morphine; for those administered 100 mg/kg ibogaine and morphine it was 237 mg/kg of morphine. The LD50 for females administered morphine alone was greater than 500 mg/kg; for those administered 100 mg/kg ibogaine and morphine the LD50 was 487 mg/kg of morphine (Schaefer, 1996).

In a study sponsored by the National Institute on Drug Abuse, acute drug interactions of ibogaine with ethanol and with diazepam were investigated by Southern Research Institute (SRI) according to the following dose procedure (Page, Rogers, et al., 1993):

On Day 1, single oral gavage (PO) doses of 0.5 percent methylcellulose (Groups A and B), 50 mg/kg of diazepam in 0.5 percent methylcellulose (Groups C and D), or 3 g/kg of ethanol in deionized water (Groups E and F) were administered to fasted Sprague Dawley rats, followed by single PO doses of 400 or 800 mg/k doses of ibogaine approximately 10 minutes later (Page, Rogers, et al., 1993).

In accordance with their results, the authors of the study arrived at the following conclusions:

Single oral doses of ibogaine (400 and 800 mg/kg) caused reversible clinical signs of toxicity, including ataxia, outstretched forelimbs, splayed hindlimbs, tremors, and convulsions. The mean body weight of the rats in the 800 mg/kg group was decreased approximately 10 percent on Day 8 compared to the rats in the 400 mg/kg dose group. One (1/5) rat in the 800 mg/kg dose group died on Day 4.

Combination treatment with ethanol (3 g/kg/dose X 6 hourly doses) or diazepam (50 mg/kg/dose X 2 doses) appeared to decrease some toxic effects of ibogaine including tremors and convulsions. However, these combination treatments also appeared to exacerbate the toxicity of ibogaine, as additional clinical signs, including cyanosis and hypothermia, were only seen in the combination dose groups. Diazepam did not appear to affect ibogaine-induced mortality; 1/5 rats in the 800 + 50 dose group died. The effect of ethanol on ibogaine-induced mortality is unknown. While all of the ibogaine plus ethanol-treated rats died on Day 1 or 2, mortality may have been due to ethanol treatment alone since the total dose of ethanol administered to these rats during the six-hour dose period (18 g/kg) exceeded the LD50 of ethanol in rats (13.7 g/kg). Since no ethanol-alone dose groups were included in this study, the effect of ethanol on ibogaine-induced mortality remains to be determined (Page, Rogers, et al., 1993).

A study in dogs (three males and three females) for the National Institute on Drug Abuse examined the potential of i.v. diazepam (1 mg/kg/dose) to prevent or attenuate the convulsions induced by a single dose of ibogaine (150, 200, or 400 mg/kg p.o. in capsules). On Day 1, the dogs were administered diazepam and ibogaine immediately thereafter. Added doses of diazepam were administered at around four and 8 hours after ibogaine (Page, Rodman, & Giles, 1994). The authors made the following clinical observations concerning convulsions:

Convulsions were not observed during the observation period on Day 1 for the male and female dogs in the 150 mg/kg dose group. Diazepam pretreatment did not prevent convulsions during the first four hours after the ibogaine dose in dogs in the 200 and 400 mg/kg dose groups. Convulsions were noted in the male (200 mg of ibogaine/kg dose group) and the female (400 mg of ibogaine/kg dose group) dogs at 1.6 hours and between 1.0-3.5 hours, respectively, after the ibogaine dose on Day 1. Dogs in the 200 (females) and 400 (male) mg of ibogaine/kg dose groups (i.e., [dogs] BF848 and AM669, respectively) had repeated convulsions starting 2.1 and 1.0 hours after the ibogaine dose on Day 1, respectively. Additional doses of diazepam 1.8 ([dog] AM669) or 2.4 ([dog] BF848) hours after the ibogaine dose rescued these dogs from the ongoing convulsions. No convulsions were observed in all dogs between 4 and 9 hours after the ibogaine dose on Day 1. Convulsions were observed on Day 2 for both dogs in the 150 mg/kg dose group and on Days 2 and/or 3 in the 200 mg of ibogaine/kg dose group (Page, Rodman, & Giles, 1994).

Toxicology

Single-Dose Toxicology Studies

Many pharmacological studies have been conducted on the safety of ibogaine in animals. The most relevant risks to consider are cardiovascular, hepatic, and neurotoxic effects.

The lethal dose for ibogaine had been estimated for different species and routes of administration, as summarized in Table 11.

Table 11: LD50 for Ibogaine and Noribogaine in Various Animals

Substance	Dose	Species	References
Ibogaine	589 mg/kg p.o. 360 mg/kg p.o. 297 mg/kg i.p. 254 mg/kg i.p.	Rats (male) Rats (female) Rats (male) Rats (female)	(Page, Rodman, Rogers, et al., 1993)
Ibogaine	500 mg/kg p.o. 482 mg/kg p.o.	Rats (male) Rats (female)	(Page, Rodman, Rogers, et al., 1993)
Ibogaine	82 mg/kg i.p.	Guinea pigs	(Delourme-Houde, 1946; Popik, Layer, & Skolnick, 1995)
Ibogaine	145 mg/kg i.p. (alcohol 2 g/kg increased toxicity of ibogaine by a factor of 1.4.)	Rats	
Ibogaine	263 mg/kg i.g.	Mice	(Kubiliene et al., 2008)
Noribogaine	630 mg/kg i.g.	Mice	

One study determined that in mice, the LD50 for ibogaine is 263 mg/kg i.g. and the LD50 for noribogaine is 630 mg/kg i.g. Ibogaine was determined to be 2.4 times more toxic than noribogaine. At high doses, the two compounds produced nervous behavior, limb paralysis, convulsions, and death (Kubiliene et al., 2008).

Toxicity of ibogaine was investigated in rats from once-daily oral gavage administration for 14 days using a broad range of doses in male (15 to 150 mg/kg) and female (10 to 125 mg/kg) rats (Page, Rodman, Rogers, et al., 1993). Significant findings were summarized as follows:

The objectives of this study were to determine the range of doses of ibogaine that produce toxicity in rats and to determine the onset, duration, and severity of ibogaine-induced toxicity. Oral gavage doses of ibogaine were administered once daily for 14 consecutive days. Reversibility of ibogaine-induced toxicity was assessed during a 16-day, drug-free recovery period that followed the last dose of ibogaine. There were two deaths in this study: 1/10 in the male 15 mg/kg/dose group and 1/10 in the male 150 mg/kg/dose group. The male rat in the 15 mg/kg/dose group may have died as a result of the gavage procedure; however, no data were documented at necropsy to suggest a procedure-related death. The death of the male rat in the 150 mg/kg/dose group was most likely drug induced.

Clinical signs of toxicity that were generally dose related occurred in male and female rats from all ibogaine-treated groups between Days 1 and 24, and included a red crusty material around the nose, ataxia, hypoactivity, hyperexcitable, tense bodies, splayed hindlimbs, and outstretched forelimbs. However, on Day 1, these observations were generally noted only in female rats in the high dose group. Other abnormal clinical observations noted were hunched bodies, red and/or squinting eyelids, eye discharge, wet fur and/or excessive salivation, and thinness. Lethargy, tremors, and tonic and clonic convulsions were observed only in male and female rats in the high dose groups. Clinical signs of ataxia, splayed hindlimbs, hypoactivity, tense bodies, and lethargy persisted beyond Day 15. All male rats appeared normal by Day 25, while all female rats appeared normal by Day 20. Reduced body weight gain was noted in male and female rats in the high-dose groups between Days 1 and 4. No drug-related effects were observed on any hematology parameter, whereas slightly elevated levels of serum phosphorus were detected in male and female rats on Day 15. Possible drug-related decreases in the absolute liver and kidney weights and the corresponding organ/brain weight ratios were noted in the male rats only at Day 30. There were no drug-related gross lesions in rats of either sex.

In conclusion, daily oral gave doses of 15 to 150 mg of ibogaine/kg/dose (males) or 10 to 125 mg of ibogaine/kg/dose (females) to Sprague Dawley rats for 14 consecutive days produced clinical signs of toxicity that disappeared during the 16-day, drug-free recovery period. An initial decrease in body weight gain and an increase in serum phosphorus levels (Day 15) were reversible. A "no-observed-effect level" was not demonstrated in this study (Page, Rodman, Rogers, et al., 1993).

A similar 14-day study using a higher range of single doses (62.5 to 500 mg/kg i.p. and 200 to 800 mg/kg p.o.) investigated potential dose-related toxicity and lethality of ibogaine in 30 male and 30 female rats. The oral LD50 of ibogaine was estimated to be 589 mg/kg in males and 360 mg/kg in females. IP LD50s were estimated at 297 mg/kg for males and 254 mg/kg for females (Page, Rodman, Rogers, et al., 1993). Conclusions of the study are summarized as follows:

Single PO and IP doses of ibogaine caused mortality, clinical signs of toxicity, and reversible body weight loss or decrease in body weight gain of rats. Ibogaine was more toxic when administered IP than it was following oral gavage. For both routes of administration, female rats were more sensitive to the lethal effects of ibogaine than were male rats. More severe and prolonged effects were seen in animals dosed with ibogaine orally. The most common clinical signs of toxicity were related to skeletal muscle function (i.e., ataxia, abnormal posture, outstretched forelimbs, splayed hindlimbs, tense bodies, tremors, labored or slow breathing, erratic breathing, Straub tails), while diarrhea, lacrimation, salivation, and nasal and eye discharges were related to the parasympathomimetic effects of ibogaine. Ataxia, abnormal posture, tense bodies, and tremors were noted in all dose groups (IP and PO), whereas splayed hindlimbs (≥200 mg/kg), outstretched forelimbs (≥200 mg/kg), and salivation (200 and 400 mg/kg) were observed in only those animals dosed by the oral route. Labored, slow, or erratic breathing was observed in all dose groups (IP and PO), except for the 250 and 500 mg/kg (IP) dose groups. Straub tail (62.5 and 125 mg/kg dose groups) and lacrimation (≥62.5 mg/kg dose groups) were noted in the IP dose groups; these signs were also noted in all PO dose groups (≥200 mg/kg). Diarrhea and nasal or eye discharges were noted sporadically in animals dosed by the IP and PO routes of administration. All surviving rats dosed orally with ibogaine were normal by Day 9, whereas female and male rats dosed IP were normal by Days 2 and 3, respectively. This indicated that toxic effects induced by oral and IP doses of ibogaine were reversible in Sprague Dawley rats (Page, Rodman, Rogers, et al., 1993).

In an extended dose-range toxicity study (Page, Rodman, Giles, Heath, & Martin, 1994), 40 male and 40 female rats were observed over 32 days following 14 days of daily oral dosing with ibogaine (0, 125, 250, or 375 mg ibogaine/kg). Findings of significance were summarized as follows:

Dose- and drug-related mortality occurred between Days 2 and 8 for males and Days 2 and 13 for the females. There were 1/10 and 7/10 deaths (males) and 5/10 and 10/10 deaths (females) in the 250 and 375 mg/kg dose groups, respectively. In general, mean body weights for rats in all ibogaine dose groups declined on Days 2 and 3. Mean body weights for the rats in the 375 mg/kg/day dose groups on Day 3 were 79 (male) and 85 (female) percent of the mean body weights of the rats in the corresponding vehicle control groups. Rats receiving 125 or 250 mg ibogaine/kg/day gained weight between Days 4 and 14, whereas animals in the 375 mg/kg/day dose groups either continued to lose weight or gained little weight between Days 4-14. Absolute mean body weights for the surviving rats in the 125 (males only) and 250 (males and females) mg/kg/day dose groups were significantly less than the absolute mean body weights for the animals in the vehicle control groups between Days 4 and 32.

Clinical signs of toxicity were observed in the ibogaine-treated dose groups on Days 1-20 and occurred as early as 1 hour after dosing. Drug-related, but not dose-related, clinical observations that were observed during the dose period included hyperexcitability, hyperactivity, tense body, outstretched forelimbs, splayed hindlimbs, lethargy, eye discharge, and red crusty material around the eyes or nose. Clinical signs of toxicity that occurred during the dose period and were generally dose related included ataxia, tremors, excessive salivation, squinting eyelids, abnormal breathing, labored breathing, cool to touch, thinness, and

prostration. Male and female rats developed some tolerance to the ibogaine during the dose period, as evidenced by a decrease in the incidences of hyperexcitability, hypothermia, abnormal breathing, red crusty material around eyes and nose, eye discharge, splayed hindlimbs, and outstretched forelimbs. Convulsions were noted sporadically in a few rats in the 375 (male) and 250 (female) mg/kg/day dose groups between Days 1 and 15. Tremors, hypoactivity, lethargy, tense bodies, hunched bodies, squinting eyelids, ataxia, labored breathing, poor grooming, emaciated, and red crusty material around the nose were noted during the recovery period between Days 15 and 20. Surviving male and female rats were normal after Days 20 and 16, respectively. Female rats appeared to be more sensitive to the effects of ibogaine as noted by the increased mortality and increased incidences of clinical signs of toxicity.

Mean serum potassium values on Day 15 were significantly decreased at doses ≥ 250 mg ibogaine/kg/day; values were 78 to 88 (males) and 80 (females) percent of the mean potassium values for rats in the vehicle control group. Lesions of dark adrenal and thyroid gland, dark lymph nodes, dark or mottled thymus, and urinary bladder dilatation were noted for rats in the 250 and/or 375 mg/kg/day dose groups. Most of these lesions were found in animals that were found dead. In the absence of histopathology, the relationship between drug treatment and the nature of these lesions could not be established. Possible drug-related gross necropsy finding consisted of dark adrenal and thyroid glands, dark lymph nodes, dark or mottled thymus, mottled pituitary gland, and urinary bladder dilatation. A "no-observed-effect level" was not established in this study (Page, Rodman, Giles, Heath, & Martin, 1994).

In another toxicity study conducted for the National Institute on Drug Abuse, beagle dogs were orally administered ibogaine daily in capsules for 14 days with a male and a female dog in each of three dose groups: 10, 30, and 100 mg/kg (Page, Rodman, & Giles, 1993a). In contrast to a previous oral dosing study in only two dogs (Page, Rodman, & Giles, 1993b), the researchers concluded that rather than 100 mg/kg, the maximum tolerated daily oral dose of ibogaine was 30 mg/kg when administered daily for 14 days (Page, Rodman, & Giles, 1993a). Findings of significance were summarized as follows:

Dogs were judged moribund and sacrificed on Day 1 (female) or 2 (male) after administration of single doses of 100 mg of ibogaine/kg. Dogs in the 30 mg/kg/dose group lost 16 percent (male) and 23 percent (female) of their baseline body weights during the 14-day dose period with little or no gain in weight during the one-week drug-free recovery period. Decreased food and water consumption values were recorded throughout the dose period in both dogs in the 30 mg/kg/dose group; slight, but inconsistent effects on food consumption and water consumption were noted in dogs in the 10 mg/kg/dose group. Water consumption increased in dogs in both groups later in the study. A functional observational battery was used to augment clinical observations and assess changes in behavior. Most changes were recorded on Day 1, with the incidence and severity of the effects generally decreasing over the dose period. In general, a dose-related elevation in body (rectal) temperatures was recorded on the initial day of dosing; no consistent effects on body temperature was [sic] noted during the remainder of the dose period. Hematology and clinical chemistry values were affected in one or both dogs in the 30 mg/kg/dose group. The female dogs had a transient leukopenia with a corresponding decrease in segmented neutrophils. Thrombocytopenia was evident in the same dog between Days 8 and 15. An unexplained increase in nRBC vales was recorded on Days 8 and 15 for the same dog. Although slightly elevated ALP values were noted by Day 15 as compared to baseline values (Day 1), biologically significant alterations in the clinical chemistries were not detected in dogs in the 10 mg/kg/dose group. Both dogs in the 30 mg/kg/dose group had elevated ALP, ALT, and AST values and decreased serum albumin values, which indicated a possible ibogaine-induced effect on the liver. The effects were greater in the female dog than the male dog. ALP, ALT, and AST values had decreased at the end of the 7-day drug-free period compared to values after the last day of dosing (Day 15). ALP, ALT, and AST (females only) values were still slightly elevated on Day 21 compared to baseline values on Day 1. No drug-related effects were observed grossly at necropsy, and no drug-related changes in organ weight were recorded (Page, Rodman, & Giles, 1993a).

Repeat-Dose Toxicology Studies

Toxicity in Purkinje cells of rats has been demonstrated following single and multiple injections of ibogaine at high doses (100 mg/kg) (O'Hearn & Molliver, 1993). In contrast, administration of ibogaine at 10 mg/kg (i.p.) every other day across 60 days produced no detectable damage to Purkinje cells (Helsley, Dlugos, et al., 1997).

Repeat-dose oral toxicity studies of ibogaine administered in gelatin capsules (5, 15, and 30 mg/kg daily for 14 days) in male and female dogs were conducted by the Southern Research Institute (SRI) on behalf of the National Institute on Drug Abuse (NIDA) (Page, Rodman, Giles, Heath, & Wood, 1994). A subsequent re-evaluation of these results was performed by MPI Research (Birmingham, AL) (Kirby et al., 1996).

The protocol included pre-test electrocardiographic recordings on days −7 and −3, with additional electrocardiograms obtained on days 1, 7, and 14, both immediately prior to and approximately two hours following ibogaine or vehicle administration. Hematological and biochemical parameters were assessed in blood samples collected prior to ibogaine administration on days 2, 7, 15, and 31. All animals were examined for macroscopic and microscopic pathological findings following euthanasia on days 14 and 31.

The electrocardiographic re-evaluation determined that the minimally prolonged QT intervals observed during the study fell within normal limits or were near the 95% confidence limit for this parameter in Beagle dogs. Additional electrocardiographic changes initially reported by SRI were determined to be artifactual rather than test article-related.

Administration of ibogaine produced increased segmented neutrophil counts, decreased lymphocyte and monocyte counts, elevated serum activity of alkaline phosphatase and alanine aminotransferase, and decreased serum albumin concentrations. These alterations were most consistently observed during the 7- and 15-day intervals of the test period. Alkaline phosphatase serum activity remained mildly elevated at the 31-day recovery interval. The re-evaluation findings were broadly consistent with the original SRI analysis; however, the elevation in alanine aminotransferase and reduction in serum albumin, now considered ibogaine-related effects, had not been identified as test article-related findings in the original report.

Microscopic re-evaluation confirmed the presence of ibogaine-related lesions across multiple organs in both male and female dogs in all dose groups following 14 days of drug administration, indicating that the no-observable-effect level (NOEL) was less than 5 mg/kg/day. Microscopic examination of organs from animals maintained for a 17-day recovery period demonstrated resolution of most ibogaine-related changes. The subacute inflammation observed across multiple organs at terminal sacrifice was either absent or only minimally present at recovery in male and female dogs across all study groups, including the control group.

Overall agreement was observed between the original SRI evaluation and the MPI re-evaluation of ibogaine-treated Beagle dogs. While the cardiovascular effects of repeat ibogaine administration were minimal, significant clinical and pathological alterations were documented, the majority of which resolved in animals permitted a 17-day recovery period. During the period of repeat-dose administration, however, daily doses of ibogaine as low as 5 mg/kg/day produced significant biological and biochemical changes.

Genotoxicity Studies

Ibogaine is not known to produce epigenetic modifications or have adverse effects on gene expression; however, ibogaine does influence gene expression in animals and these changes may be related to its

therapeutic effects. More generally, changed gene expression or metabolic activity in the brain can indicate brain regions that are particularly affected by ibogaine.
The National Institute on Drug Abuse (NIDA) sponsored a study on the mutagenic potential of ibogaine by Microbiological Associates, Inc. using the Salmonella Mutagenicity Assay with tester strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of Aroclor-induced rat liver S9 (San & Wyman, 1995). At doses up to 5000 µg per plate, no positive responses were observed with any of the tester strains in either condition, and no precipitate or appreciable toxicity was observed. The authors concluded that ibogaine hydrochloride did not cause a positive response in the Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay under the conditions of the study.

A further study on mutagenic potential, also for NIDA, employed the L5178Y/TK+/- Mouse Lymphoma Mutagenesis Assay (San & Clarke, 1995). Non-activated cultures treated with doses of 500 to 50 µg/mL exhibited total growth from 8% to 90%, and S-9 activated cultures at the same dose range produced 8% to 96% total growth. No cultures, whether activated or non-activated, exhibited a mutant frequency at least twice that of the solvent controls, and no dose-dependent response was observed. The results indicate that ibogaine hydrochloride was negative in both the absence and presence of exogenous metabolic activation.

Carcinogenicity

No data. The anthropological literature gives no indication that ibogaine causes cancer. There are no scientific studies on potential carcinogenicity.

Reproductive and Developmental Toxicity

No data.

Other Toxicity Studies

The mutagenic potential of ibogaine has been evaluated under sponsorship of the National Institute on Drug Abuse (NIDA) (San & Wyman, 1995). Ibogaine hydrochloride was assessed using the Salmonella mutagenicity assay (Ames test) across tester strains TA98, TA100, TA1535, TA1537, and TA1538, both in the presence and absence of Aroclor-induced rat liver S9 metabolic activation. The assay was conducted in two phases using the plate incorporation method: an initial dose range-finding study to establish appropriate concentrations for the mutagenicity assay, followed by the mutagenicity assay itself.

In the dose range-finding study, the maximum tested dose was 5000 µg per plate, a ceiling established by protocol, delivered to the test system as a white turbid suspension in 100% ethanol. No precipitate or appreciable toxicity was observed at this concentration, and the same maximum dose was therefore applied in the subsequent mutagenicity assay. In the mutagenicity assay, no positive mutagenic responses were observed across any of the tester strains, either in the presence or absence of Aroclor-induced rat liver S9 activation. No precipitate or appreciable toxicity was observed during the assay. Under the conditions of this investigation, ibogaine hydrochloride did not produce a positive mutagenic response in the Salmonella/mammalian microsome plate incorporation mutagenicity assay.

The mutagenic potential of ibogaine has additionally been evaluated using the L5178Y/$TK^{+/-}$ mouse lymphoma mutagenesis assay (San & Clarke, 1995). Ibogaine hydrochloride was tested in both the absence and presence of Aroclor-induced rat liver S9 metabolic activation. Non-activated cultures selected for cloning were treated with doses ranging from 50 to 500 µg/mL and exhibited total growth values of 8% to 90%. S9-activated cultures selected for cloning were similarly treated with doses ranging from 50 to 500 µg/mL, producing total growth values of 8% to 96%. No non-activated cultures demonstrated a mutant frequency at least two-fold above the mean mutant frequency of solvent controls, and no dose-dependent response was identified among the treated cultures. Similarly, no S9-activated cultures demonstrated a mutant frequency at least two-fold above the mean mutant frequency of solvent

controls, with no dose-dependent response observed. Under the conditions of this mutagenicity assay, ibogaine hydrochloride produced negative findings in both the absence and presence of exogenous metabolic activation.

Immunological Effects

As with many pharmacological agents, ibogaine has been shown to produce acute alterations in immune function; however, no evidence has emerged to indicate that these changes possess clinical significance.

In vitro immune function assays have demonstrated that ibogaine produces dose-dependent suppression of B-cell function, natural killer cell function, and T-cell regulatory and effector function, while failing to suppress macrophage function. Suppression of immune cell function has generally been observed only at high concentrations (10 to 100 μmol/L) (House et al., 1995).

Preclinical investigations have additionally suggested that ibogaine may possess antifungal activity. Ibogaine has been shown to reduce organ colonization in early-stage systemic and gastrointestinal *Candida albicans* infections in mice (Yordanov et al., 2005). When applied to cutaneous infection, ibogaine suppressed the symptomatology of *C. albicans* and accelerated elimination of the organism from the site of inoculation (Yordanov et al., 2008). The development of specific immune responses did not appear to be influenced by ibogaine, as delayed-type hypersensitivity reactions to *C. albicans* and the production of interferon (IFN)-γ were comparable between control and ibogaine-treated animals. Notably, the combined administration of amphotericin B and ibogaine in mice with gastrointestinal infection produced greater reductions in organ colonization than either compound administered alone.

Ibogaine has additionally demonstrated in vitro antimicrobial activity against the pathogenic mycobacteria *Mycobacterium tuberculosis*, *M. avium*, and *M. kansasii*, the latter primarily affecting livestock rather than humans (Rastogi et al., 1998).

Ibogaine is not known to produce toxicity through sustained alterations in body temperature. In clinical settings, ibogaine may produce sweating and transient increases or decreases in body temperature that have not been characterized as clinically meaningful.

Hyperthermia in Animals and Epidemiological Settings

In female mice, ibogaine (50 mg/kg) produced hypothermia. Pretreatment with this dose blocked methamphetamine-induced hyperthermia and the methamphetamine-induced expression of heat-shock protein within the caudate nucleus (Yu et al., 1999).

Cardiovascular Toxicity in Animals and Epidemiological Settings

Cardiotoxicity is the primary safety risk for patients who receive ibogaine treatment. Overall, it appears ibogaine and noribogaine can, individually and in combination, cause cardiotoxicity by interacting with human ether-a-go-go-related gene potassium channels.

A proposed mechanism for ibogaine-induced cardiac arrhythmias centers on inhibition of the hERG (human ether-à-go-go-related gene) I_Kr potassium channel, which plays an essential role in repolarization of the cardiac action potential (Koenig et al., 2013). This inhibition delays repolarization, prolongs the QT interval, and consequently produces arrhythmias that can lead to sudden cardiac death. At higher doses, ibogaine has additionally been shown to inhibit sodium and calcium currents within the ventricular cardiomyocyte (Koenig et al., 2013).

Detailed tissue-culture investigation of the interaction between ibogaine and hERG channels indicates that ibogaine blocks hERG channels from the cytosolic side—either in its charged form alone or in

conjunction with its uncharged form—and alters channel currents by modifying the relative contribution of channel states over time (Thurner et al., 2014).

In the human context, hERG potassium channels are vital to the repolarization phase of cardiac action potentials, and blockade by ibogaine delays repolarization, producing QT interval prolongation and consequent arrhythmias or sudden cardiac arrest (Litjens & Brunt, 2016). Twenty-seven fatalities have been reported following ibogaine ingestion, with pre-existing cardiovascular conditions implicated in the deaths of individuals for whom postmortem data were available. However, eight case reports have documented ventricular tachyarrhythmias and QT prolongation following ibogaine ingestion in individuals without identified pre-existing cardiovascular conditions or relevant family history. Noribogaine appears at least as cardiotoxic as the parent compound.

Work employing human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) combined with multi-electrode array (MEA) readouts and physiologically based kinetic (PBK) modeling for reverse dosimetry has highlighted the substantive contribution of noribogaine to the overall cardiotoxic profile of ibogaine (Shi, 2021). In vitro hiPSC-CM assays examining ibogaine alone, without PBK-modeling-facilitated reverse dosimetry, underestimate the role of noribogaine, as the longer plasma residence and distinct channel-interaction profile of the metabolite are not captured by such isolated assays. Integration of parent drug and metabolite exposures through PBK modeling provides more clinically relevant cardiac risk predictions than either in vitro or animal investigations considered in isolation.

Neurotoxicity in Animals and Epidemiological Settings

The available evidence indicates that therapeutic doses of ibogaine (up to 25 mg/kg p.o.) do not pose a risk for neurotoxicity in humans. Studies have detected neurotoxicity in Purkinje cells, a class of GABAergic neuron, in the cerebellum of rats, but no similar toxicity has been seen in monkeys nor mice.

A GLP-compliant video-EEG study in cynomolgus monkeys (Macaca fascicularis) provides the most rigorous primate CNS-safety data to date for noribogaine (Authier et al., 2016). Six monkeys (3M/3F, ~2 years old, 2.6–2.9 kg) received oral noribogaine HCl at 160 and then 320 mg/kg by gavage, with at least 7 days between doses and continuous bipolar-derivation EEG telemetry (C3-O1, C4-O2, Cz-Oz) beginning ≥24 h before dosing and continuing ≥24 h after. At both doses, EEG showed no seizure activity and no premonitory signs of seizure risk (no sharp waves, no unusual synchrony, no high-frequency pattern shifts). Clinical observations at 160 mg/kg in 3/6 animals included scratching, licking, chewing, emesis, and decreased activity/appetite; at 320 mg/kg the clinical signs were more pronounced, and one monkey showed brief myoclonic movements that two independent neurologists confirmed did not correlate with EEG abnormalities. Pentylenetetrazol (PTZ) administered as a positive control reliably produced paroxysmal EEG activity (mean onset 72:30 min) and generalized seizures (mean onset 81:24 min), verifying the sensitivity of the recording system. Pharmacokinetics at 320 mg/kg showed Cmax of approximately 1003 ng/mL (males) and 1133 ng/mL (females) with Tmax 2.5–9 h, and the male:female AUC ratios were close to unity. On this basis, 320 mg/kg PO was designated the EEG no-observed-adverse-effect level (NOAEL) for noribogaine in conscious freely-moving cynomolgus monkeys (Authier et al., 2016). This NOAEL, when compared with the noribogaine plasma exposures produced by clinical ibogaine doses in humans (where noribogaine Cmax is typically well below the primate NOAEL exposure), suggests a substantial safety margin for CNS excitatory effects of noribogaine.

The potential toxicity of ibogaine on neuropathology and nerve conduction velocity was examined in rabbits by the International Research and Development Corporation for the National Institute on Drug Abuse (Schaefer, 1995). The study conclusions were reported as follows:

Following preliminary dose range-finding studies, adult male New Zealand White rabbits (12/dose) were administered vehicle control (2% methylcellulose), 30, 60 or 100 mg/kg ibogaine intraperitoneally. Two

animals in the 100 mg/kg group died within one day following ibogaine administration. Seven days after the single drug/vehicle administration, blood samples were taken from the central ear artery of all surviving rabbits for clinical pathology studies. Dissected nerves and carcasses of six animals/group of 100 mg/kg rabbits were sent to EPL for light microscopic evaluation. For the remaining five or six animals per group, the sciatic nerves were removed after euthanasia and nerve conduction velocity studies were performed. None of the hematological or clinical biochemical values showed statistically significant changes from vehicle control. In the nerve conduction studies, neither the average conduction velocity nor the area under the stimulus amplitude control showed an ibogaine-treatment effect. Additionally, in the neuropathology studies no light microscopic lesions considered test article-related were noted in the neural tissues examined. These studies demonstrated that deaths occurred at 100 mg/kg ibogaine, but that dosages below this produced no toxicity (Schaefer, 1995).

Two studies in female rats provide evidence of the highest safe single dose. Molinari and colleagues (Molinari et al., 1996) reported that from a single dose of 40 mg/kg i.p., ibogaine produced evidence of toxic changes in only one of 15 rats. This can be considered the Lowest Observed Adverse Effects Level (LOAEL) in rats. In a second study, summarized in Table 11 below, Xu and colleagues found that while 2 of 6 rats showed toxicity after a single dose of ibogaine at 50 mg/kg i.p., 25 mg/kg i.p. produced no detectible neurotoxicity in another 6 rats, indicating that 25 mg/kg may be considered a No Observed Adverse Effects Level (NOAEL) (Xu et al., 2000).

Table 12: Relationship between Dose and Purkinje Cell Toxicity in Female Rats (Xu et al., 2000)

Ibogaine Dose (i.p.)	Result
100 mg/kg	All rats showed the same pattern of cerebellar damage with multiple bands of degenerating Purkinje neurons.
75 mg/kg	All rats showed neurodegeneration similar to the 100-mg/kg group, but the bands appeared to be narrower.
50 mg/kg	Only 2 of 6 rats were affected; despite few degenerating neuronal perikarya, cerebella from these rats did contain patches of astrocytosis similar to those observed with 75 or 100 mg/kg ibogaine.
25 mg/kg	All rats were indistinguishable from saline controls, indicating that this dose level may be considered as a no-observable-adverse-effect level (NOAEL)

With regard to repeated exposures, administration of 10 mg/kg i.p. ibogaine every other day for 60 days to male rats did not result in any damage to Purkinje cells (Helsley, Dlugos, et al., 1997).

Acute neurotoxicity from single oral doses of ibogaine in capsules was investigated for the National Institute on Drug Abuse using a dose of 100 mg/kg in eight female beagle dogs, with two of the dogs serving as controls not administered ibogaine (Page, Rogers, O'Callaghan, et al., 1994). Significant findings were summarized as follows:

The objective of this study was to determine the time course effect of ibogaine (100 mg/kg) on glial fibrillary acidic protein (GFAP) in the dog brain at 3, 5, and 7 days after dosing. Clinical observations of ibogaine-treated dogs included ataxia, tremors, convulsions, aggressiveness, hypoactivity, slight dehydration, injected sclera, and mydriasis. Ibogaine-treated dogs that were sacrificed on Day 3 or 5 after dosing exhibited a slight (< 10 percent) weight loss. Levels of GFAP appeared to be increased as a result of ibogaine treatment in a region- and time-dependent manner. The brain stem showed substantial increases in GFAP by Day 3 of the study compared to both the control animals and the ibogaine-treated animals sacrificed on Day 5 or 7. Modest increases were also seen in the cortical areas, the cerebellum (including vermis), the olfactory bulb and tract, and the hippocampus. These data suggest that exposure of

female dogs to ibogaine results in reactive gliosis, a characteristic feature of underlying brain damage (Page, Rogers, O'Callaghan, et al., 1994).

Despite an increase in GFAP of 209% on Day 7 and 155% on Day 3 compared to the controls, the increases were comparable or more than those in experimental animals following doses of various "known neurotoxicants at dosages that do not result in overt CNS cytopathology, that is, a corresponding morphological change could not be established at these dose levels." MDMA (3,4-methylenedioxymethamphetamine), for example, increased GFAP in the anterior cortex of rats by 200% after twice daily injections (150 mg/kg s.c.) for 2 days compared to controls. In discussing the results, the authors concluded in part as follows:

The present quantitative data for GFAP suggest that exposure of female dogs to ibogaine results in reactive gliosis. On the basis of the results obtained herein, it is reasonable to concluded that ibogaine caused some morphological change in areas of the brain. However, the dogs showed no signs of irreversible neurobehavioral changes. The extent of the morphological changes induced by ibogaine, the specific cells involved, and long-term sequelae that potentially result were not established in this study (Page, Rogers, O'Callaghan, et al., 1994).

Evidence Against Neurotoxicity at Therapeutic Doses

Data presented at National Institute on Drug Abuse hearings on ibogaine demonstrated no evidence of neurotoxicity in monkeys treated for five days with either repeated oral doses of ibogaine ranging from 5 to 25 mg/kg or repeated subcutaneous doses of 100 mg/kg. Similarly, no neurotoxic changes were observed in male mice following intraperitoneal administration of ibogaine (100 mg/kg), despite confirmed toxic changes in male rats receiving the same dose (Scallet et al., 1996). Of particular significance, postmortem examination of an individual who died of natural causes approximately 25 days following the last of four ibogaine exposures—at doses ranging from 10 to 30 mg/kg (p.o.) administered across approximately 15 months—revealed no evidence of cerebellar abnormality (Mash et al., 1998).

Histopathological Features of Ibogaine-Induced Neurotoxicity in Rats

The mechanisms of ibogaine-induced neurotoxicity in rats have been characterized in detail. Neurotoxic regimens of ibogaine induce a glial reaction within the cerebellum, characterized by activated astrocytes and microglia aligned in parasagittal stripes within the cerebellar vermis (O'Hearn et al., 1995). This response is accompanied by loss of the neuronal proteins microtubule-associated protein 2 and calbindin, co-extensive with loss of Nissl-stained Purkinje cell bodies (O'Hearn & Molliver, 1993). Argyrophilic staining of Purkinje cell bodies, dendrites, and axons using the Gallyas reduced silver method for degenerating neurons has demonstrated that degenerating cells are confined to narrow parasagittal stripes within the vermis.

Proposed Mechanisms

A primary mechanistic hypothesis proposes that ibogaine produces sustained glutamate release at climbing fiber synapses on cerebellar Purkinje cells, with consequent excitotoxic degeneration (O'Hearn & Molliver, 1997). This hypothesis has been supported by evidence that neurotoxicity is dependent upon a functioning inferior olive, with ablation of the inferior olive using 3-acetylpyridine producing neuroprotection against subsequent ibogaine administration.

Nitric oxide has been implicated in ibogaine-induced neurotoxicity. Ibogaine induces certain Purkinje cells to express nicotinamide adenine dinucleotide phosphate (NADPH)-diaphorase and neuronal nitric oxide synthase (nNOS), neither of which is normally present in these cells. Induction of nitric oxide synthase is dose-related, delayed in onset, and detected within neurons adjacent to degenerated Purkinje cells. Although this nNOS induction follows excitotoxic neuronal injury, nitric oxide is unlikely to

participate in the initial phase of Purkinje cell damage. Both the delayed induction of nNOS and the spatial relationship between damaged and nNOS-expressing Purkinje cells are consistent with a role for nitric oxide in either neuronal recovery or delayed cell death following excitotoxic injury (O'Hearn et al., 1995).

An additional mechanistic hypothesis proposes that ibogaine-induced σ_2 receptor stimulation contributes to the neurotoxic phenomenon. (Repke et al., 1994; Mash et al., 1998; O'Hearn et al., 1995). Ibogaine functions as a high-affinity σ_2 receptor agonist and excessive σ_2 agonist activity may damage Purkinje cells within the olivocerebellar projection.

In rats, non-NMDA receptor antagonists have been shown to increase neurotoxicity to Purkinje cells; clinicians should accordingly exercise caution before co-administering glutamate antagonists with ibogaine (O'Hearn & Molliver, 2004).

Behavioral Correlates of Cerebellar Neurotoxicity

Given the role of the cerebellum in motor coordination and timing, manifestations of ibogaine-induced neurotoxicity in rats might reasonably be predicted to involve psychomotor or movement-related phenomena. A form of audiogenic myoclonus has been identified that results from administration of ibogaine at neurotoxic doses. Ibogaine-induced myoclonus is behaviorally characterized by reduced capacity to habituate to a startle stimulus, resembling the myoclonic jerks observed in rats during recovery from prolonged global cerebral ischemia. A closely analogous syndrome can be produced by cerebral ischemia, which similarly produces Purkinje cell loss within the posterior cerebellar lobe and deafferentation of the lateral aspect of the fastigial nucleus from the cerebellar cortex (Welsh et al., 2002).

Species Differences

Research has identified species-specific differences between rats and mice that may partially account for differential vulnerability to ibogaine-induced neurotoxicity. Comparative investigation of ibogaine effects on [^{3}H]glutamate release and uptake in cortical and cerebellar synaptosomes, as well as in cortical astrocyte cultures, has been conducted in tissues from both rats and mice. In rat synaptosomes, ibogaine (2 to 1000 μM) produced no effects on glutamate uptake or release. In mouse synaptosomes, however, ibogaine (500 to 1000 μM) significantly inhibited glutamate uptake and stimulated glutamate release—effects observed in cortical, but not cerebellar, mouse synaptosomes. Ibogaine (1000 μM) nearly abolished glutamate uptake in cortical astrocyte cultures from both rats and mice. Given the substantially supraphysiological concentrations employed in these investigations, the findings are likely more relevant to mechanisms of toxicity than to therapeutic effects (Leal et al., 2001).

Sex Differences

Female animals demonstrate greater sensitivity to ibogaine than males, and female rats are correspondingly more sensitive to ibogaine-induced neurotoxicity than male rats. When ibogaine is administered to female rats during the preovulatory phase of the reproductive cycle—characterized by elevated circulating estrogen—concentrations of ibogaine within blood and brain tissue substantially exceed those observed in similarly treated males (Baumann, Pablo, et al., 2001). Additional evidence has confirmed greater sensitivity of female rats to ibogaine-induced neurotoxicity, with findings suggesting that high doses of ibogaine produce damage extending beyond the cerebellum to additional regions including the hippocampus, olfactory bulb, brain stem, and striatum (O'Callaghan et al., 1996).

Abuse Potential

Preclinical investigations of the abuse potential of ibogaine have employed drug discrimination and conditioned place preference paradigms to compare ibogaine with compounds whose abuse potential is

more thoroughly characterized. The available evidence indicates that ibogaine possesses low abuse potential.

Drug discrimination studies support a determination of low abuse potential. Rats trained to discriminate the hallucinogens LSD (lysergic acid diethylamide) or DOM (2,5-dimethoxy-4-methylamphetamine) from placebo demonstrated intermediate levels of generalization to ibogaine (Helsley et al., 1998). Additional drug discrimination investigations have shown that ibogaine produces partial generalization from fenfluramine (Schechter, 1997) and from imidazoline I_2-site ligands such as 2-BFI (MacInnes & Handley, 2002).

Within the conditioned place preference paradigm, which represents a standard measure of abuse liability, ibogaine has been shown to induce neither preference nor aversion in rats (Parker et al., 1995).

The preponderance of preclinical evidence indicates that ibogaine exerts therapeutic effects in models of substance use disorder, including reductions in withdrawal symptomatology, drug craving, and tolerance. A meta-analysis of 27 animal investigations of the therapeutic activity of ibogaine concluded that oral, low-dose administration of ibogaine merits investigation in human studies, conducted only under close medical monitoring and following thorough medical screening (Belgers et al., 2016).

Epidemiological and Naturalistic Evidence Summary

Physiological Effects in Epidemiological Settings

The substantial volume of anthropological literature on the Bwiti Cult in both English and French attests that Africans who use iboga for religious purposes tend to value monogamy, sobriety, and wholesome lifestyles. However, there have not been any scientific or medical studies on the physiological effects of iboga among West African religious practitioners, or at least none that have been published in English. The majority of non-clinical epidemiological studies deal with Westerners, most of whom used ibogaine or iboga to detoxify from addictive drugs within an "ibogaine medical subculture." In addition to people seeking detoxification from substance use disorders, a miniscule percentage of Westerners have used ibogaine or iboga primarily for spiritual purposes or personal growth.

Reports of Serious Incidents, Mortality, and Morbidity

While many thousands of individuals have used ibogaine without serious adverse outcomes, multiple serious incidents—including fatalities—have been documented in humans following ibogaine administration across a variety of settings.

Epidemiological data provide documentation of high-dose exposures to ibogaine in human populations. As of 2019, the highest survived dose of ibogaine recorded in the medical literature was an estimated 65 to 70 mg/kg (p.o.) (Steinberg & Deyell, 2018). The 61-year-old male patient survived following prolonged hospitalization, having sustained myocardial infarction and a week-long episode of QT prolongation. The patient was admitted with atrial flutter and a heart rate of 270 bpm; following defibrillation, prolonged QT was documented (714 ms) and persisted for seven days.

Multiple published case reports have documented neurological adverse effects following ibogaine administration, including ataxia, muscular spasms, and tonic-clonic seizures (Breuer et al., 2015; Cloutier-Gill et al., 2016; Hoelen et al., 2009; Marta et al., 2015; O'Connell et al., 2015). In additional cases, elevations in blood pressure and reductions in heart rate were observed in patients receiving 10 to 25 mg/kg (p.o.) of ibogaine (Lotsof & Alexander, 2001). A reported fatality following ibogaine administration involved an individual with a history of myocardial infarction, with autopsy findings

suggesting an interaction between the cardiovascular effects of ibogaine and pre-existing cardiac pathology (K. R. Alper et al., 2001). A review of 27 deaths associated with iboga or ibogaine use reached comparable conclusions, identifying pre-existing cardiac conditions as relevant contributing factors in the majority of fatalities, with concurrent administration of additional substances implicated in the remaining cases (K. R. Alper et al., 2012). Of 19 lethal cases reviewed in detail, nine were attributable to cardiotoxicity, with adverse events including cardiomyopathy, myocardial infarction, arrhythmia, and cardiac hypertrophy. In the majority of cases, patients had documented pre-existing cardiac disease. Notably, several of these deaths occurred several days following ibogaine administration—a temporal pattern that supports a substantive cardiotoxic role for noribogaine or, less plausibly, suggests that the fatalities were not directly attributable to the cardiotoxic effects of iboga or ibogaine.

A Dutch case report also offers information about the cardiotoxicity of ibogaine (Hoelen et al., 2009). An American patient went to the Netherlands to take ibogaine as an alternative treatment for severe alcoholism. After consuming "3.5 g of ibogaine 15%" (a description implying ingestion of an extract), the patient had a seizure-like attack and was taken to the emergency room. The patient displayed a significant QT prolongation (616 ms) and ventricular tachyarrhythmia, yet had no personal or family history of cardiac issues. QT prolongation normalized after 42 hours of hospitalization. The authors of this case report recommended that "future trials of the drug should be permitted only under strict medical observation and continuous electrocardiacographic monitoring" (Hoelen et al., 2009). In three additional case reports (Hildyard et al., 2016; Pleskovic et al., 2012; Vlaanderen et al., 2014), adverse events related to cardiac activity occurred in people who had no personal or familial history of cardiac issues.

More recent case reports continue to document life-threatening cardiac events associated with ibogaine, including in patients receiving very low test doses. A reported case of a 47-year-old male with longstanding heroin dependence who was admitted to a Portuguese alternative detoxification center (Mestre et al., 2024). One hour after ingesting a 200 mg pre-treatment test dose of ibogaine, corresponding to only 2.6 mg/kg, well below the typical therapeutic range of 8–25 mg/kg, the patient developed polymorphic ventricular tachycardia with cardiac arrest, which required defibrillation with return of spontaneous circulation. He subsequently experienced two further episodes of polymorphic ventricular tachycardia with cardiac arrest in the emergency department and a fourth episode in the intensive care unit, all requiring defibrillation. The QTc interval (Bazett) was 636 ms, and serum troponin remained normal. He was on chronic buprenorphine patches at the time of ibogaine ingestion. Lidocaine infusion was administered, the QTc normalized by day 8, and the patient was discharged on day 9. This case is particularly notable because it demonstrates that life-threatening cardiac arrhythmias can occur even at very low ibogaine doses intended only as pre-treatment safety tests, and underscores the potential contribution of concomitant buprenorphine to QT prolongation risk.

There have also been deaths in epidemiological settings. For example, a man who used ibogaine for symptoms of heroin withdrawal suffered a fatal cardiac arrest. The patient had taken 4 grams of ibogaine and 2 grams of an "uncharacterized booster." Their doctors stated, "While it is possible that their cardiac arrest could have been secondary to vomiting, aspiration, and hypoxemia, their suffering a cardiac arrest less than 8 hours after ibogaine use is consistent with previous case reports linking ibogaine and cardiac toxicity" (Meisner et al., 2016).

Beyond cardiac and neurological adverse events, atypical presentations have also been reported. (Ramanathan & R Pradhan, 2022) described the first reported case of severe rhabdomyolysis and acute liver injury following iboga ingestion in a 27-year-old woman who consumed iboga powder obtained from an "African shaman" for spiritual purposes. The patient presented with palpitations, dark urine, and progressive muscle weakness. Laboratory findings showed creatine phosphokinase (CPK) of 179,120 U/L, AST 7,056 U/L, ALT 2,640 U/L, troponin 6.04 ng/mL, INR 1.5, and a mixed anion-gap and non-anion-gap metabolic acidosis (pH 7.18). Notably, the electrocardiogram showed a normal QTc interval. Comprehensive infectious and autoimmune workup was negative. The patient was managed

conservatively in the intensive care unit with intravenous fluids, bicarbonate infusion, and N-acetylcysteine, and made a full recovery (Ramanathan & R Pradhan, 2022). The authors hypothesized that "either there was a responsible unknown co-ingestion with the iboga powder, or more likely, ibogaine may have direct muscle toxic effects, with the liver injury secondary to the severe rhabdomyolysis." Confounders include the unknown ibogaine content of the iboga powder, prior use of ayahuasca and "sacred tobacco" one month earlier in Mexico, and the lack of analytical confirmation of the ingested material.

The most comprehensive synthesis of ibogaine adverse events covering the period 2015–2020 is the PRISMA systematic review by (Ona et al., 2023). The review identified 18 eligible studies through searches of PubMed, Scopus, Web of Science, Scielo, Google Scholar, and Core.ac.uk: 15 case reports or case series (Barsuglia et al., 2018; Breuer et al., 2015; Cloutier-Gill et al., 2016; Grogan et al., 2019; Henstra et al., 2017; Hildyard et al., 2016; Knuijver et al., 2018; Marta et al., 2015; Mash et al., 2018; Matamoros-Castillo et al., 2019; Meisner et al., 2016; O'Connell et al., 2015; Steinberg & Deyell, 2018; Wilkins et al., 2017; Wilson et al., 2021), two randomized double-blind clinical trials (Glue, Winter, et al., 2015; Glue et al., 2016), and one observational study (T. K. Brown & Alper, 2017).

Adverse events were classified into acute effects (<24 hours) and prolonged effects (>24 hours). Among acute events, the most consistently reported was QTc prolongation, with values across the included case reports ranging from 512 ms (Wilson et al., 2021) and 516 ms (Knuijver et al., 2018) to 730 ms (Hildyard et al., 2016; Meisner et al., 2016) and 788 ms (Grogan et al., 2019). Other reported acute cardiac alterations included tachycardia, hypotension, wide QRS complex tachycardia with alternating QRS morphologies, and Torsades de Pointes (Grogan et al., 2019; Henstra et al., 2017; Hildyard et al., 2016; Meisner et al., 2016; Steinberg & Deyell, 2018). Gastrointestinal symptoms, predominantly nausea and vomiting, were reported across multiple cases (Barsuglia et al., 2018; Breuer et al., 2015; Mash et al., 2018; Meisner et al., 2016; O'Connell et al., 2015; Steinberg & Deyell, 2018; Wilkins et al., 2017). Visions, hallucinations, and space/time disorientation were also commonly reported (Breuer et al., 2015; Grogan et al., 2019; Knuijver et al., 2018; Matamoros-Castillo et al., 2019), as were physical symptoms including ataxia, muscle tension, weakness, diaphoresis, akathisia, and tremor. Neurological adverse events of particular concern included generalized tonic-clonic seizures in three cases (Breuer et al., 2015; Grogan et al., 2019; Hildyard et al., 2016), dysmetria (O'Connell et al., 2015), anoxic brain injury (Meisner et al., 2016), and unconsciousness (Henstra et al., 2017). (Ona et al., 2023) suggested that ibogaine-induced seizures may reflect 5-HT2A agonist-mediated increases in glutamatergic tone, with the antagonistic effect of ibogaine on NMDA receptors apparently insufficient to prevent seizures at high doses.

Prolonged adverse events (>24 hours) were primarily psychiatric, neurological, and cardiac in nature. The mean hospitalization duration across cases reporting this information was 7.8 days (range 3–13 days). Prominent psychiatric features included insomnia persisting 5–14 days, alterations in speech, delusions, aggressiveness, irritability, dissociation, and hallucinations (Grogan et al., 2019; Marta et al., 2015; Matamoros-Castillo et al., 2019). Persistent neurological features included psychomotor slowness, bilateral ptosis, dysarthria, psychomotor agitation, and amnesia (Breuer et al., 2015; Marta et al., 2015; Matamoros-Castillo et al., 2019). QTc prolongation persisting for up to 7 days was reported in some cases (Hildyard et al., 2016; Steinberg & Deyell, 2018), consistent with the long elimination half-life of noribogaine. Notably, the controlled administration of pure ibogaine (Glue, Winter, et al., 2015) and noribogaine (Glue et al., 2016) under hospital supervision and cardiac monitoring did not produce serious or prolonged adverse events.

Three case reports documented intensive care unit admission (Breuer et al., 2015; Grogan et al., 2019; Steinberg & Deyell, 2018), and one fatality occurred despite hospital intervention (Meisner et al., 2016), a case in which naloxone was administered in the field followed by morphine and unspecified vasopressors at hospital, an emergency-department management approach that (Ona et al., 2023) noted "would not be

indicated from a pharmacological point of view" given the QT-prolongation context. Interventions used to manage adverse events across the reviewed cases included benzodiazepines, antipsychotics, anticonvulsants, atropine, isoproterenol, magnesium and saline infusions, electrical cardioversion, defibrillation, pacemaker placement, and intubation.

Several cross-cutting findings from the are particularly relevant to clinical safety. First, only two of the 15 case-report subjects had no history of drug abuse or medical/psychiatric disorders (Breuer et al., 2015; Marta et al., 2015). Others (Mash et al., 2018) reported that 52.9% of their 191-patient cohort met clinical criteria for major depressive disorder or depression at baseline, with bipolar disorder also present, underscoring the high baseline psychiatric morbidity in populations seeking ibogaine treatment. Second, the doses of ibogaine differed widely between cases, ranging from 725 mg of ibogaine HCl (Wilson et al., 2021) to 38 g of dried *T. iboga* root bark (Breuer et al., 2015), with most cases lacking any analytical confirmation of the ingested material. The authors specifically referenced a GC/MS analysis of 16 vendor samples (Bouso et al., 2020), which found ibogaine concentrations ranging from 0% to 73.4% in products labelled as ibogaine HCl, with unidentified substances present in almost all samples, as illustrative of the uncertainty surrounding iboga products used in unregulated settings. Third, with respect to drug interactions, some have noted (Ona et al., 2023) that the combination of methadone and diazepam (both QT-prolonging) had been associated with synergistic repolarization prolongation in vitro (Kuryshev et al., 2010) and increased mortality in clinical practice (Ernst et al., 2002), supporting the interpretation of ibogaine as a contributing, rather than sole, cause in fatalities involving these co-ingestibles. The authors additionally drew attention to the finding that ibogaine inhibits P-glycoprotein (Tournier et al., 2010), suggesting that P-gp substrates should be avoided or used with caution alongside ibogaine. Fourth, the review confirmed that hERG potassium channel blockade is the principal molecular basis of ibogaine cardiotoxicity, citing IC50 values of 4.09 ± 0.69 μM for ibogaine semi-synthesized from voacangine, 3.53 ± 0.16 μM for ibogaine extracted directly from *T. iboga*, and 2.86 ± 0.68 μM for noribogaine (K. Alper et al., 2016), consistent with the clinically observed pattern of delayed and persistent QTc prolongation driven by the longer-half-life metabolite.

Delayed Cardiotoxicity and the Role of Noribogaine

The plasma half-life of noribogaine in humans has been reported as 24 to 30 hours (Glue et al., 2016). Cardiac complications developing many hours following ibogaine administration are therefore likely attributable to the metabolite noribogaine, which persists in circulation for at least one day—substantially longer than the parent compound (Baumann, Pablo, et al., 2001). Ibogaine is additionally sequestered within adipose tissue and released gradually, a pharmacokinetic feature that may contribute to prolonged therapeutic effects and potentially to delayed toxicity as well (Glick & Maisonneuve, 1998).

Eight cases of fatalities occurring days following ibogaine ingestion have been examined in detail. These fatalities occurred predominantly several days following administration or after intake of small doses, with no definitive explanation currently established. One proposed mechanism attributes these deaths to cardiac arrhythmias produced by dysregulation of the autonomic nervous system. Ibogaine influences autonomic function through effects on multiple neurotransmitter systems and on the fastigial nucleus. The cerebellar nucleus responds to small doses with sympathetic stimulation producing a fight-or-flight response, whereas higher doses produce vagal dominance approximating a feigned-death state. The risk of cardiac arrhythmias is elevated under conditions of sympathetic stimulation or in the coincidence of high parasympathetic tone with left-sided sympathetic stimulation—conditions that may arise both under the influence of small doses of ibogaine and during periods of exhaustion accompanied by high vagal tone, when acute fear responses could precipitate critical left-sided sympathetic stimulation (Maas & Strubelt, 2006).

Experimental evidence has subsequently demonstrated that therapeutic concentrations of ibogaine and its long-lived active metabolite noribogaine significantly delay action potential repolarization in human cardiomyocytes. These findings represent the first experimental confirmation that ibogaine administration

entails a cardiac arrhythmia risk in humans, and provide a mechanistic explanation for the clinically observed delayed incidence of cardiac adverse events occurring several days following ibogaine intake. The retardation of action potential repolarization at therapeutic concentrations may produce QT prolongation on the electrocardiogram and consequent cardiac arrhythmias (Rubi et al., 2017).

Illustrative Case Report

A representative case of severe ibogaine-induced cardiac toxicity has been documented in a 33-year-old male who self-administered a single 600 mg dose of ibogaine following two days of abstinence from cocaine, heroin, and methadone (Pleskovic et al., 2012). The administered dose was relatively modest; assuming a body weight of approximately 70 kg, the dose would correspond to approximately 9 mg/kg—below the 12 mg/kg dose representing the lower end of doses typically administered for detoxification.

Thirty minutes following administration, the patient lost consciousness due to ventricular fibrillation and required hospitalization for nine days. Clinical evaluation associated ibogaine administration with ventricular fibrillation, ventricular tachycardia, and QTc interval prolongation, providing a potential explanation for sudden death following ibogaine. The mechanism underlying ventricular fibrillation remains uncharacterized, although subsequent episodes of ventricular tachycardia were attributed to QTc prolongation. Autonomic nervous system involvement in the observed ventricular tachyarrhythmias was implicated by the temporal pattern of events: two of five fibrillation episodes and all three tachycardia episodes occurred during micturition or defecation, both of which represent vagal maneuvers that prolong the QTc interval.

The QTc interval remained prolonged for nine days, with both ibogaine and noribogaine detectable in blood across the same interval. The contribution of residual methadone in the systemic circulation was determined to be negligible, and both genetic predisposition to long QT syndrome and structural heart disease were excluded. This patient experienced a major life-threatening adverse reaction to a modest dose of ibogaine that could not be attributed to any identified cardiac defect, although CYP2D6 metabolizer status was not characterized through genotyping or phenotyping. In the management of this case, amiodarone did not demonstrate efficacy in the treatment of ventricular fibrillation or ventricular tachycardia, and direct-current cardioversion has been recommended as the preferred first-line intervention.

Metabolism and Nutrition Disorders

No specific cases of ibogaine-induced primary metabolic or nutritional disorders have been identified in the published literature. Indirect metabolic disturbances, most notably hypokalaemia and hypomagnesaemia secondary to treatment-related vomiting, reduced oral intake, and pre-existing alcohol use, have been documented as contributing factors in fatal cases (K. R. Alper et al., 2012; Koenig & Hilber, 2015). Severe metabolic acidosis (pH 7.18, mixed anion-gap and non-anion-gap) was reported in the (Ramanathan & R Pradhan, 2022) rhabdomyolysis case, but this was secondary to massive muscle breakdown rather than a primary metabolic effect of ibogaine.

Hepatobiliary Disorders

Ibogaine undergoes hepatic metabolism via the CYP2D6 enzyme, and severe pre-existing hepatic dysfunction can therefore be expected to increase the risk of toxicity. A documented fatality involved a male patient who died suddenly within 12 to 24 hours of ibogaine administration undertaken for the purpose of alcohol detoxification (Papadodima et al., 2013). Autopsy findings included hepatic cirrhosis and pronounced fatty infiltration, with a postmortem ibogaine concentration of 2 mg/L.

Blood and Lymphatic System Disorders

No specific cases of ibogaine-induced primary hematological or lymphatic disorders have been identified within the published literature. Across an inpatient detoxification cohort of 191 participants, no changes were observed on physical examination or laboratory safety assessments across the administered dose range, indicating an absence of consistent hematological abnormalities at therapeutic doses (8–12 mg/kg, oral) (Mash et al., 2018).

Injuries, Poisonings, and Procedural Complications

Reports of ibogaine-related injuries and poisonings have been documented primarily within the context of unregulated ibogaine administration, where product quality control, dosing accuracy, and medical supervision vary substantially. The fatal and non-fatal cardiac cases described elsewhere in this document represent the predominant category of ibogaine-related procedural complications, typically occurring in alternative or non-medical detoxification settings. A particularly instructive cautionary case has been described in which molecular networking based on liquid chromatography–tandem mass spectrometry (LC-MS/MS) was applied to a fatal intoxication initially attributed to *Tabernanthe iboga* ingestion (Allard et al., 2020).

The analysis revealed that the powder ingested by the deceased—labeled as *T. iboga*—did not contain ibogaine or ibogamine, but instead contained ajmaline, reserpine, and yohimbine: alkaloids characteristic of the genus *Rauwolfia*. Neither ibogaine nor ibogamine was detected within the product or within biological specimens obtained from the deceased. This case underscores the substantial risk of product adulteration, mislabeling, and species substitution within the unregulated ibogaine supply chain, and demonstrates the value of analytical confirmation of ingested material in any forensic investigation of suspected iboga-related poisoning. From a pharmacovigilance perspective, this finding additionally indicates that a subset of adverse outcomes attributed to ibogaine within the grey literature and online sources may in fact reflect exposure to unrelated alkaloids, with implications for both clinical risk assessment and the interpretation of the existing case-report database.

Gastrointestinal Disorders

Nausea and vomiting are among the most commonly reported acute adverse effects of ibogaine across both clinical and naturalistic settings. No cases of severe primary gastrointestinal pathology — such as gastrointestinal hemorrhage, perforation, or bowel obstruction — have been attributed to ibogaine in the published literature. However, the indirect consequences of severe vomiting (volume depletion, electrolyte loss, aspiration risk) are clinically significant in the context of the prolonged sleep-like dosing state and contribute to the cardiac risk profile.

Respiratory, Thoracic, and Mediastinal Disorders

Respiratory difficulties documented in fatal case reports have typically arisen secondary to cardiac events, vomiting and aspiration, or the depressant effects of co-ingested substances, rather than as a primary respiratory toxicity of ibogaine itself (Koenig & Hilber, 2015; Meisner et al., 2016). Patients with pre-existing obstructive sleep apnea, chronic obstructive pulmonary disease, asthma, or heavy smoking histories may nonetheless be at increased risk during the prolonged sleep-like dosing state, and oxygen saturation monitoring is recommended in clinical settings.

Psychiatric Disorders

Psychiatric adverse events have been documented across the published ibogaine literature, although systematic characterization remains limited by the predominance of case reports and uncontrolled observational data. A case of hallucinogen-persisting perception disorder (HPPD) has been described in a patient following ibogaine administration for the treatment of opioid dependence (Knuijver et al., 2018).

Human data show a double profile: ibogaine can acutely induce intense psychedelic states and, in rare cases, mania (Marta et al., 2015) or other persistent psychiatric problems, yet it may also produce marked short-term improvements in PTSD, depression, anxiety, and craving.

Four cases of psychotic symptomatology have additionally been documented in association with ibogaine ingestion. A practitioner of African spiritual traditions in France developed psychotic symptoms during a period of daily iboga consumption, characterized by dream-like experiences featuring threatening imagery (Houenou et al., 2011). Three additional cases of manic episodes associated with ibogaine administration have been reported (Marta et al., 2015).

Nervous System Disorders

Although a long history of traditional use is not an infallible indicator that a plant is safe for human consumption, it can provide useful preliminary evidence. It can therefore be helpful to estimate typical doses of ibogaine taken during traditional use as well as to evaluate any evidence of neurotoxicity from these exposures. The extensive anthropological literature about the Bwiti and other West African religious cults describes initiates consuming large servings of rasped iboga root bark for the purpose of having a transcendental epiphany that they refer to as "breaking open the head." During Bwiti initiations, the initiate typically consumes up to one kilo of fresh iboga root bark or 67 g of dry root bark, the ibogaine content of which is estimated to be as high as 1.675 grams. For a small person weighing 50 kilos, that works out to be an ibogaine dose of 33.5 mg/kg. Bwiti practitioners also frequently attend weekly services in which they consume only one or two teaspoons of root bark containing perhaps 60 to 240 mg of ibogaine.

Ethnographic accounts do not mention adverse side effects that would be indicative of neurotoxicity, although there is documentation of rare deaths, which may have occurred at doses of iboga root bark with ibogaine contents exceeding 40 mg/kg (Fernandez & Fernandez, 2001). Neurotoxic impairments can, of course, be subtle and might not have been detected. Nonetheless, as noted previously, animal data suggest that neurotoxic impairments would manifest as changes in motor functioning, which would seem most likely to be detectable without professional neurocognitive assessment. There does not seem to be mention of motor-skill impairment among African practitioners. This is notable because these individuals are known to ingest 33.5 mg/kg servings of ibogaine during their religious initiation and smaller doses of under 3.4 mg/kg during subsequent weekly church services. Nevertheless, monitoring for subtle subclinical signs of potential ibogaine-induced neurotoxicity may be valuable (Vocci & London, 1997).

To determine what dose is safe in humans, we can find some evidence by extrapolating from rat studies. Because rats are more sensitive to ibogaine-induced neurotoxicity than mice or primates, it seems reasonable to conclude that 25 mg/kg (the i.p. NOAEL determined in rats) would generally be a non-neurotoxic dose. Additionally, even if therapeutic doses of ibogaine do produce measurable neurotoxicity to Purkinje cells in humans (and there is no indication that this is so), this damage must be weighed against the damage that could be caused by continued substance use disorder, particularly with potentially neurotoxic drugs like ethanol, which can also damage Purkinje cells (Cavanagh et al., 1997).

Cognitive Function and Performance

Beyond acute and persistent perceptual disturbances, formal cognitive testing in clinical populations has not identified consistent ibogaine-induced cognitive impairment at therapeutic doses. In the controlled placebo-controlled study by Forsyth et al., low-dose ibogaine (20 mg) had no detectable effects on basic visuomotor function, inhibitory function, switching ability, or selective attention in healthy male volunteers (Forsyth et al., 2016). In contrast, the magnesium–ibogaine MISTIC protocol study by (Cherian et al., 2024) reported significant improvements in processing speed, executive function (including inhibition, cognitive flexibility, problem-solving, phonemic fluency, and working memory), learning and memory, and sustained attention in 30 Special Operations veterans with traumatic brain

injury at 1 month after treatment (Cherian et al., 2024). These data, together with the recent follow-up (Lissemore et al., 2025) demonstrating measurable changes in cortical oscillations and neural complexity in the same cohort, suggest that ibogaine may improve rather than impair cognitive function in clinical populations with pre-existing neuropsychiatric impairment.

Effects in Humans in Clinical Settings

Few randomized, blinded controlled trials exist in which ibogaine or noribogaine was administered to humans; however, many case and open-label studies have been conducted. Despite their limitations, they are discussed in this section in order to synthesize as much information as possible on the use of ibogaine. Formal trials are summarized in Table 12, while additional observational studies are discussed in the text of this section. Together these studies support the efficacy of ibogaine while pointing to a need for careful monitoring for potential toxicity.

Table 13: Randomized Controlled Trials and Open-Label Studies with Ibogaine

Reference	Objective	Design	Population	Dose
(Mash et al., 1998)	Assess the safety of the clinical administration of ibogaine	Open-label, single-dose	32 opioid-dependent patients (31% women)	500, 600, 800 mg
A single dose of ibogaine facilitated "cold turkey" (i.e., without a gradual taper of opiate) detoxification with an apparent reduction in physician-rated withdrawal signs and patient-rated withdrawal symptoms compared to before ibogaine administration. No recurrence of withdrawal syndrome occurred in the week during which patients were still observed. "Many" (exact number not given) patients maintained their abstinence from opiates in the months following discharge. (Note: the authors published almost the same data with slightly different sample sizes in different publications (Mash et al., 1998).				
(K. R. Alper et al., 1999)	Assess effectiveness at heroin and methadone detoxification	Open-label	33 opioid dependent patients (33% women)	6 to 29 mg/kg
Sustained resolution of withdrawal signs and drug-seeking behavior throughout the 72-hour post-treatment observation period was experienced by 76% of the patients; 12% sought drugs despite lack of withdrawal signs; 6% had attenuated withdrawal without drug seeking; 3% (one patient) sought drugs and displayed withdrawal; and 3% (one patient) died, possibly involving surreptitious heroin use concurrent with ibogaine.				
(Glue, Winter, et al., 2015)	Assess the influence of CYP2D6 on PK and PD of a low dose of ibogaine	Randomized, placebo-controlled	21 healthy volunteers (100% men)	20 mg
Volunteers were administered paroxetine for 7 days to inhibit CYP2D6. Ibogaine was rapidly metabolized – primarily by CYP2D6 – into noribogaine, with peak concentrations at 4 hours. This low dose of ibogaine was well-tolerated by all subjects. Inhibition of CYP2D6 approximately doubled exposure to ibogaine. The researchers advised using CYP2D6 genotyping to identify poor metabolizers among patients awaiting treatment.				
(Glue, Lockhart, et al., 2015; Glue, Winter, et al., 2015)	Assess the safety, PK, and PD of increasing doses of noribogaine	Randomized, placebo-controlled	36 healthy volunteers (100% men)	3 mg, 10 mg, 30 mg, and 60 mg

Noribogaine was rapidly absorbed with peak concentrations at 2 to 3 hours. Noribogaine was eliminated with an estimated mean half-life of 28 to 49 hours. No safety issues were identified. Single, oral doses of up to 60 mg noribogaine were well-tolerated.				
(Glue et al., 2016)	Assess the safety of increasing doses of noribogaine	Randomized, double-blind, placebo-controlled, between-subjects	27 morphine-stabilized opioid-dependent patients (22% women)	60 mg, 120 mg, and 180 mg
Study design allowed patients to request resumption of opioid substitution therapy (OST), which all patients did. No dose of noribogaine produced significant differences in the withdrawal syndrome or in the length of time it took patients to ask for OST resumption. The most common adverse events were headache, visual impairment (such as lights brighter), and nausea. Three adverse events were rated severe (headache, nausea, and vomiting). Noribogaine caused dose- and concentration-dependent QTc prolongation, which were considered to reach clinically concerning levels in the two higher-dose groups.				
(Forsyth et al., 2016)	Evaluate mood and cognitive function after ibogaine	double-blind, placebo-controlled	21 healthy volunteers (100% men)	20 mg
No effects of low-dose ibogaine were seen on mood and cognitive measures of basic visuomotor function, inhibitory function, switching ability, and selective attention, administered before and 2 hours after ibogaine. This study is a sub-study of Glue et al.'s 2015 PK/PD CYP2D6 study.				
(Mash et al., 2018)	Assess the safety and efficacy of ibogaine for detoxification from opioids and cocaine	Open-label	191 drug-dependent patients (25% women)	8–12 mg/kg
A single oral dose of ibogaine diminished withdrawal syndrome, depressive symptoms, and drug craving. There were no serious adverse events. Headache was reported by 7%. Orthostatic hypotension occurred in 5% and was associated with cocaine- but not opioid-dependent patients. Among the AEs, approximately 2% were judged to be of moderate severity. This sample likely includes patients from the study in the first row of this table.				

Available case-series and observational data support a therapeutic role for ibogaine in the treatment of withdrawal syndromes across multiple substance classes. In an early case series, withdrawal syndromes resolved without subsequent drug-seeking behavior in 25 of 33 opiate-dependent patients across the 72-hour observation period following ibogaine administration (K. R. Alper et al., 1999). Patients received oral ibogaine doses ranging from 6 to 29 mg/kg. One fatality was reported and was attributed to possible concomitant undisclosed heroin use.

A subsequent observational study employed a repeated-dose ibogaine protocol consisting of an initial 200 mg dose, followed 1 to 4 hours later by an additional dose ranging from 400 to 600 mg, with subsequent administration of multiple 200 mg doses (Noller et al., 2018). The mean total treatment duration was 57 hours. Repeated-dose protocols offer the advantage of permitting assessment of individual patient response to an initial test dose prior to escalation; the principal limitation lies in the accumulation of noribogaine within the systemic circulation across the treatment period, which may produce adverse events if not anticipated within the protocol design. Of the 15 patients initially enrolled, 14 completed treatment; one withdrew from the study, two were lost to follow-up, and one died during the treatment course. Six of the 11 patients who underwent urine testing for opioid use at 12 months following

treatment produced negative results, corresponding to a 40% success rate among originally enrolled patients and a 75% success rate among the 11 patients who remained in the study at one-year follow-up.

A further observational investigation conducted long-term follow-up in 30 heroin- or oxycodone-dependent patients treated with high-dose ibogaine (a total of at least 1540 ± 920 mg administered across at least three doses (T. K. Brown & Alper, 2017). The proportion of patients reporting 30-day opioid abstinence was 50% at one month, 33% at three months, 20% at six months, 37% at nine months, and 23% at 12 months.

A survey of 73 long-term opioid users (30% female) who had received ibogaine treatment within an inpatient facility in Mexico documented substantial subjective treatment effects. The majority of respondents (80%) indicated that ibogaine had eliminated or substantially reduced withdrawal symptomatology, with 50% reporting reductions in opioid craving and 25% reporting that craving reductions persisted for at least three months. Thirty percent reported uninterrupted abstinence from opioids following ibogaine treatment; among this subgroup, more than half (54%) had maintained abstinence for over one year and 31% for over two years. Respondents reporting cessation or reduction of opioid use also reported lower rates of depressive and anxiety symptoms, higher levels of subjective well-being, and greater perceived spiritual meaningfulness of the ibogaine treatment relative to other respondents (Davis et al., 2017).

Among cocaine- and opiate-dependent patients treated with ibogaine at 8 to 12 mg/kg, reductions in craving, withdrawal symptomatology, and depressive symptoms have been documented (Mash, 2018). A Brazilian retrospective analysis of 75 individuals with prior alcohol, cannabis, or cocaine use—72% of whom reported polysubstance use—identified no serious adverse reactions or fatalities following ibogaine administration (Schenberg et al., 2014). In 61% of cases, patients treated once with ibogaine maintained abstinence for a median of 5.5 months, while those receiving multiple treatments maintained abstinence for a median of 8.4 months. The available evidence supports the proposition that physician-supervised ibogaine administration accompanied by psychotherapeutic support may facilitate prolonged periods of abstinence without serious complications, and indicates that ibogaine may represent a candidate therapeutic for dependence on stimulants and other non-opioid substances.

History of Use in Clinical Settings

Iboga extracts and ibogaine have been incorporated into various medicinal preparations, none of which achieved widespread use. In 1905, ibogaine (10 to 30 mg) was reportedly employed for the treatment of influenza, convalescence following infectious disease, neurasthenia, and selected cardiac disorders (Pope, 1969). The compound was observed to improve appetite, muscle tone, and overall recovery, producing a mild euphoria in nearly all patients that resembled the effects of other stimulants. During the early twentieth century, ibogaine was recommended for the treatment of asthenia at doses ranging from 10 to 30 mg daily. From 1939 until 1970, ibogaine was commercially marketed in France under the trade name *Lambarène* as a neuromuscular stimulant, formulated as 8 mg tablets intended to alleviate fatigue, depression, and the residual effects of infectious diseases (Goutarel et al., 1993). A related preparation marketed as *Iperton* was also available in this period; each capsule contained 40 mg iboga extract combined with 10 mg belladonna extract (Naranjo, 1969; Popik & Wrobel, 2001). This preparation was apparently different from another modern drug with the same name that is still available in some countries outside the United States.

In 1955, ibogaine was administered to patients with morphine dependence at the United States Addiction Research Center in Lexington, Kentucky (K. R. Alper et al., 2001). The therapeutic recognition of ibogaine's effects on substance dependence at this time is uncertain, and this research was conducted within the broader context of investigations into hallucinogens undertaken on behalf of the Central Intelligence Agency. In 1957, prior to the recognition of ibogaine's potential utility in the treatment of

established substance use disorder, Ciba Pharmaceutical Products, Inc. (now Novartis) registered a patent for ibogaine intended to reduce opioid tolerance and thereby diminish the risk of developing opioid dependence (J. A. Schneider & Sigg, 1957).

The contemporary recognition of ibogaine's potential therapeutic effects in substance use disorder is attributed to Howard Lotsof (K. R. Alper et al., 2001; K. R. Alper & Lotsof, 2007; Lotsof & Alexander, 2001; Mash, 2010); a heroin user who participated in informal gatherings in New York in 1962 and 1963 at which a group of at least 20 individuals explored the subjective and therapeutic effects of psychoactive compounds, including hallucinogens and stimulants. In a session employing ibogaine at doses of 14 to 19 mg/kg, the seven participants who were heroin users reported that ibogaine alleviated drug craving and withdrawal symptomatology. Five of these participants reportedly maintained abstinence from heroin for at least six months following their ibogaine session (K. R. Alper et al., 2001).

The putative antiaddictive properties of ibogaine were popularized by Howard Lotsof, who reported that administration of 6–9 mg/kg induced an active phase of visualizations characterized as a "waking dream state," followed by an intense period of "deep introspection" (K. R. Alper et al., 2001; Mash et al., 2018). Drug-dependent individuals frequently report that these dream-like visions revisit early childhood memories, traumatic experiences, or other significant life events. Many patients describe the experience as providing meaningful insight into their addictive and self-destructive behavioral patterns (D. Q. Chen et al., 2025). Notably, opioid- and cocaine-dependent individuals have reported substantial attenuation, and in some cases complete cessation, of drug craving for extended periods following a single dose of ibogaine, with some individuals remaining abstinent for several years thereafter (K. R. Alper et al., 2001; Davis et al., 2018; Mash et al., 2001).

Early Psychotherapeutic Applications

From the late 1950s through the 1960s, the Chilean psychiatrist Claudio Naranjo employed ibogaine within psychotherapeutic practice, observing that the compound exerted favorable effects on unresolved emotional content. Naranjo was central to a group of psychotherapists—predominantly based in Latin America—who used ibogaine in psychotherapy and convened clinical meetings at the University of Chile. Approximately 100 ibogaine sessions are documented in *The Healing Journey* (Naranjo, 1974). The protocol employed doses of 3 to 5 mg/kg, with 4 mg/kg administered as a standard initial dose, with patients reclining on a couch or bed during the session:

With such dosages taken orally in a gelatin capsule, the symptoms become manifest about forty-five minutes after ingestion. These may extend from eight to twelve hours, and some patients have reported subjective after-effects even twenty-four (20 per cent) thirty-six (15 per cent), or more (5 per cent) hours later. Yet even in such instances, the patient is usually able to function normally after six to eight hours from the beginning of the effects. In the majority of instances, I have ended the therapeutic session in seven hours or less, leaving the patient in congenial company (Naranjo, 1974).

At these comparatively low doses administered orally in gelatin capsules, symptom onset typically occurred approximately 45 minutes following ingestion, with effects persisting for 8 to 12 hours. Subjective after-effects were reported at 24 hours by approximately 20% of patients, at 36 hours by 15%, and at longer durations by 5%; however, patients were typically able to function normally within 6 to 8 hours of symptom onset. In the majority of sessions, the therapeutic encounter was concluded within seven hours or less, with the patient remaining in supportive company. In 1969, Naranjo received a French patent for the psychotherapeutic application of ibogaine at doses ranging from 4 to 5 mg/kg (K. R. Alper et al., 2001).

Development of the Modern Ibogaine Research Program

In 1982, more than a decade following the placement of ibogaine on Schedule I, Howard Lotsof founded the non-profit Dora Weiner Foundation with the objective of legitimizing the use of ibogaine in the treatment of substance dependence (T. K. Brown, 2013). In 1986, NDA International became active in funding and supporting preclinical research into the therapeutic effects of ibogaine in substance use disorder (K. R. Alper et al., 2001). Research conducted in Rotterdam produced the first peer-reviewed publication documenting the efficacy of ibogaine in attenuating opioid withdrawal syndrome (T. K. Brown, 2013). From 1989 to 1993, NDA International, Dutch Addict Self Help (DASH), and the International Coalition of Addict Self-Help (ICASH) collaborated in the development of ibogaine-based treatment for substance dependence in the Netherlands, with approximately 45 patients treated across this period (K. R. Alper et al., 2001).

During the same period, the Medication Development Division of the National Institute on Drug Abuse (NIDA) initiated support for preclinical research into ibogaine. In 1993, an FDA drug abuse advisory committee approved a Phase I dose-escalation study to be conducted by the research group of Deborah Mash at the University of Miami School of Medicine. In 1995, the FDA additionally authorized a protocol to extend this investigation to individuals with cocaine and opioid dependence (K. R. Alper & Lotsof, 2007). From 1993 to 1994, NIDA developed Phase 1 and Phase 2 draft protocols for the use of fixed 150 mg and 300 mg doses of ibogaine versus placebo for the treatment of cocaine dependence; these protocols were ultimately not implemented, in part due to criticism from the pharmaceutical industry (Mash, 2010). From 1993 to 1994, NIDA developed Phase 1 and Phase 2 draft protocols for the use of fixed 150 mg and 300 mg doses of ibogaine versus placebo for the treatment of cocaine dependence; these protocols were ultimately not implemented, in part due to criticism from the pharmaceutical industry (K. R. Alper et al., 2001).

Concurrently, Erasmus University in Rotterdam was preparing a clinical trial protocol for human investigation (K. R. Alper et al., 2001). However, in 1993, a fatality occurred in the Netherlands during clinical use of ibogaine. A female patient receiving ibogaine at a dose of 29 mg/kg died of respiratory failure. Dutch authorities identified evidence of undisclosed opioid use, although no postmortem analysis was conducted to confirm opioid presence (T. K. Brown, 2013). This event precipitated the cessation of NIDA-supported clinical research and substantially impaired the procurement of funding for subsequent human studies, despite the absence of an established causal relationship between ibogaine administration and the patient's death. NIDA withdrew funding for the planned Phase 1 and Phase 2 clinical trials but continued to support preclinical investigation of ibogaine (K. R. Alper et al., 2001, 2001).

Emergence of Alternative and Informal Treatment Settings

Following the cessation of NIDA-supported clinical development, the use of ibogaine became progressively restricted to alternative and informal settings. The network of ibogaine providers expanded internationally, and a distinct medical subculture surrounding ibogaine administration emerged. Ethnographic analysis has identified a typology of ibogaine treatment settings, including the medical model, the lay provider or treatment guide model, the activist or self-help model, and the religious or spiritual model (K. R. Alper et al., 2008). An estimated 3,414 individuals had received ibogaine as of February 2006, representing a four-fold increase over the preceding five years, with 68% of recipients having undertaken treatment for substance-related disorder and 53% specifically for opioid withdrawal.

Clinical Investigations of Substance Use Disorder

Many patients turn to this medical subculture looking for an alternative treatment for their substance use disorders (T. K. Brown, 2013). As an example of the kind of person who would seek ibogaine treatment, consider the case of a woman with a 19-year history of severe heroin use disorder. The subject had suffered near-fatal overdoses and had been refractory to all treatment until taking ibogaine in a Canadian clinic, after which the subject reported being abstinent from opiates for 18 months. Although the ibogaine treatment did not involve formal psychotherapy, during treatment the subject revisited past traumatic

incidents and attributed sustained recovery to a spiritual awakening induced by the ibogaine experience (Cloutier-Gill et al., 2016).

The contemporary character of this medical subculture has been further documented by recent qualitative and sociological work. Researchers conducted a thematic analysis of 40 threads (101 contributors) drawn from Reddit and Drugs Forum, identifying three dominant themes, DIY research, therapeutic interaction, and therapeutic mechanisms, and documenting that contemporary unregulated ibogaine use spans clinic settings (typically USD 3,000–5,000), home flood-dose self-administration, and microdosing protocols (Barber et al., 2020).
The authors observed that "online fora appear to have facilitated a sense of community where individuals are held to account for the success of ibogaine therapy" and that "neuroscientific explanations of substance use disorder and behavior have explanatory salience for people involved in ibogaine therapy" (Barber et al., 2020). Later work extended this sociological analysis into a global market case study of the ibogaine medical subculture, documenting how providers navigate regulatory gaps through informal credentialing, medical screening protocols, and peer networks in the absence of regulatory oversight (Söderberg & Lundgren, 2025).

Table 13 provides a comprehensive summary of the identifiable body of primary clinical evidence evaluating the therapeutic efficacy of ibogaine in opioid use disorder, encompassing early non-clinical observational case series conducted in the 1990s through to more recent medically supervised inpatient detoxification studies. Inclusion was restricted to investigations reporting original human data; secondary analyses, narrative reviews, and survey-based self-reports lacking clinical verification were excluded from consideration.

Collectively, the human evidence synthesized in Table 13 delineates a consistent yet methodologically constrained signal of clinical activity for ibogaine in the treatment of opioid use disorder. Across heterogeneous observational designs, the most reproducible outcome is the rapid attenuation of opioid withdrawal symptomatology following treatment exposure, a finding reported consistently from early non-clinical case series through to subsequent medically supervised inpatient detoxification studies. This convergence of results across independent cohorts suggests that ibogaine exerts a robust acute effect on withdrawal-related physiological and subjective domains that is temporally aligned with administration and independent of assumptions regarding long-term follow-up outcomes.

Beyond the acute suppression of withdrawal, several studies extended outcome assessment into post-detoxification domains and reported reductions in craving intensity along with improvements in mood state during short- and medium-term follow-up intervals. These effects, however, were variably sustained, frequently confined to subsets of participants, and strongly influenced by participant attrition, reliance on self-reported outcomes, and incomplete longitudinal verification. Notably, abstinence-related outcomes were inconsistently defined, heterogeneously measured, and only rarely corroborated through biological confirmation, thereby precluding reliable estimation of sustained remission rates at the population level.
A critical interpretive advance emerging from later investigations is the recognition that the clinical effects of ibogaine cannot be adequately characterized through dose-centric frameworks alone. Studies incorporating pharmacokinetic assessments have highlighted substantial interindividual variability driven by CYP2D6-dependent metabolism and prolonged systemic exposure to the active metabolite noribogaine, providing a biologically plausible substrate for the observed heterogeneity in clinical trajectories. This metabolic dimension introduces an additional layer of analytical complexity that constrains cross-study comparability and underscores the necessity of mechanistically informed interpretation of observational outcomes.

Despite the accumulation of human observational data spanning more than three decades, the current evidence base remains insufficient to establish efficacy in a formal regulatory or comparative framework. The absence of randomized, placebo-controlled clinical trials, standardized dosing regimens, harmonized

outcome measures, and systematic long-term follow-up represents a structural limitation that cannot be addressed through continued aggregation of naturalistic reports alone. Accordingly, the findings synthesized in this section should be interpreted strictly as descriptive mappings of reported human outcomes, rather than as confirmatory evidence of therapeutic effectiveness.

Table 14: Human Studies Evaluating Therapeutic Efficacy of Ibogaine in Substance Use Disorders (Esperança et al., 2026)**.**

Ref	Study Design	N	Exposure/Dosing	Main Efficacy Outcomes	Methodological Limitations
(Sheppard, 1994)	Open-label observational case series	7	Oral ibogaine HCl (verified purity > 98%) in capsule form (test dose: 100–200 mg; total dose: 700–1800 mg); acute psychoactive phase (≈24–38 h).	Clinically significant opioid withdrawal symptoms were fully suppressed in all participants (0/7) after the acute psychoactive phase. Follow-up showed dose-related variability: the participant who received 700 mg relapsed within 2 days; among those receiving ≥1000 mg (n = 6), two relapsed after several weeks, one reverted to intermittent opioid use, and three remained abstinent for ≥14 weeks.	Very small sample size; open-label design; absence of control group; non-standardized outcome assessment; reliance on self-report for follow-up drug use; non-clinical setting.
(K. R. Alper et al., 1999)	Open-label observational case series (non-clinical setting)	33	Oral ibogaine administration; non-standardized dosing; observation period up to 72 h post-treatment.	Resolution of opioid withdrawal signs within 24 h in 25/33 patients, sustained over 72 h without further drug-seeking behaviour	Open-label design; absence of control group; non-clinical setting; short observation window; non-standardized dosing and formulation
(Mash et al., 2000)	Open-label observational clinical study with pharmacokinetic analysis	27	Single oral dose of ibogaine HCl with pharmacokinetic monitoring	Significant reduction in cocaine and heroin craving and depressive symptoms during detoxification and sustained at 30-day follow-up	Open-label, non-randomized design; limited sample size; absence of a control group; self-reported outcomes
(Schenberg et al., 2014)	Retrospective observational study	75	Ibogaine is administered under medical supervision and combined with psychotherapy	61% self-reported abstinence at retrospective assessment; statistically significant prolongation of abstinence duration compared with pre-treatment periods (median 5.5 months after single treatment; 8.4 months after multiple treatments; $p < 0.001$)	Retrospective design; reliance on self-reported outcomes; absence of a control group; heterogeneous substance use
(T. K. Brown & Alper, 2017)	Observational study (naturalistic, non-randomized)	30	Mean total dose 1540 ± 920 mg ibogaine HCl (mean ~19 mg/kg);	Marked reduction in opioid withdrawal severity within 72 h (SOWS: −17 points; $p < 0.001$) and significant reductions in opioid use relative to	Observational design; absence of control group; attrition over long-term follow-up;

			administered in non-medical clinic settings with short inpatient stay (3–6 days)	pretreatment baseline, with maximal effect at 1 month and partial maintenance up to 12 months in a subset of subjects.	reliance on self-reported drug use; heterogeneity of sustained response.
(Noller et al., 2018)	Observational 12-month follow-up study	14 (8 completers at 12 months)	Single ibogaine treatment (25–55 mg/kg ibogaine HCl; staggered dosing over 24–96 h)	Significant acute reduction in opioid withdrawal symptoms (SOWS, n = 14); significant reduction in ASI-Lite drug use scores at 12 months among completers (n = 8, p = 0.002); sustained reduction in depressive symptoms (BDI-II, p < 0.001); opioid cessation or sustained reduced use over 12 months in a subset of participants	Small sample size; high attrition (12-month completers n = 8); partial reliance on self-report; incomplete biological verification of drug use; absence of a control group; one treatment-related fatality reported
(Mash et al., 2018)	Open-label observational case series (inpatient medically supervised detoxification)	191	Oral dose of ibogaine HCl (8–12 mg/kg) administered under medical supervision; pre-treatment opioid stabilization; continuous ECG and laboratory monitoring; pharmacokinetic assessment of ibogaine/noribogaine	Marked reduction in opioid withdrawal severity; significant reduction in opioid and cocaine craving during detoxification and at 1-month follow-up (where available); significant improvement in depressive symptoms; PK data demonstrating ibogaine–noribogaine conversion and prolonged noribogaine exposure	Open-label design; no control group; heterogeneous substance use (opioids and cocaine); short and incomplete follow-up; reliance partly on self-report; outcomes focused on detoxification and short-term transition rather than sustained abstinence
(Cloutier-Gill et al., 2016)	Case report	1	Four-day ibogaine treatment (oral administration; exact dose and formulation not reported)	37-year-old female with 19-year history of severe opioid use disorder achieved sustained opioid abstinence at 18-month follow-up after ibogaine treatment; previous longest continuous abstinence was two months while on methadone; no safety issues reported during or after treatment	Single-case design; absence of control or comparator; lack of dosing and pharmacokinetic details; outcomes not generalizable; abstinence outcome based on case description and clinical follow-up rather than systematic or blinded assessment

In summary, ibogaine has been used studied in recent decades for detoxification from opioids and other addictive drugs, with some evidence of success.

Phase 1 Studies

The first modern, regulatory-compliant Phase 1 investigation of ibogaine was conducted as part of the DemeRx/atai Life Sciences Phase 1/2a clinical trial program (NCT05029401), which received approval from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) in 2021. This landmark study represented the first Good Clinical Practice (GCP)–compliant trial of ibogaine hydrochloride (DMX-1002) and was designed as a two-stage investigation to assess safety, tolerability, pharmacokinetics, and preliminary efficacy. The Phase 1 segment was conducted at the MAC Clinical Research Early Phase Unit in Manchester, United Kingdom, and evaluated single oral doses of DMX-1002 in recreational drug users and healthy volunteers. Dosing of the first subjects commenced in September 2021. The trial was subsequently designed to pause following the Phase 1 portion to allow MHRA review of accumulated human safety data alongside nonclinical study results prior to initiating Stage 2 enrollment in opioid-dependent patients. The primary objectives of the Phase 1 component focused on characterizing the pharmacokinetic profile of ibogaine and its active metabolite noribogaine under controlled dosing conditions, with particular emphasis on cardiac safety monitoring given known concerns regarding hERG channel inhibition and QT interval prolongation. Overall trial enrollment was planned to include approximately 110 participants, comprising 30 healthy volunteers in Stage 1 and 80 opioid-dependent patients in Stage 2 (NCT05029401; (Luz & Mash, 2021)).

Additional mechanistic and translational investigations currently in progress include a neuroimaging study at the University of California, Irvine (NCT07226570) examining ibogaine's effects on resting-state functional connectivity and glutamatergic signaling in reward circuitry among adults with opioid use disorder.

Phase 2 Studies

The available Phase 2 evidence base for ibogaine remains limited but is expanding across multiple therapeutic indications. Schellekens and colleagues described the protocol and early findings of a Dutch clinical investigation in which 15 opioid-dependent patients were treated with ibogaine 10 mg/kg as an adjunct to treatment as usual. Treatment of the initial cohort confirmed pronounced effects of ibogaine on cardiac rhythm (QTc interval prolongation) and ataxia, while the observed opioid withdrawal symptomatology was comparatively mild. The same publication presented a meta-analysis of 30 animal studies (27 included in the quantitative synthesis) demonstrating that ibogaine most robustly reduces drug self-administration within the first 24 hours following administration, alongside motor impairment and cerebellar cell loss as the predominant preclinical adverse effects (Schellekens et al., 2022). The companion (Knuijver et al., 2022) safety study and the (Knuijver et al., 2024) pharmacokinetic/pharmacodynamic analysis from the same Dutch consortium are described in detail in Section 6.4.

Additional completed Phase 2 investigations have examined ibogaine across alternative indications. A Phase 2 open-label escalating-dose trial conducted at the University of São Paulo (NCT03380728) evaluated three sequential oral doses of ibogaine ranging from 20 to 400 mg in nine adults with alcohol use disorder, with time to alcohol use as the primary endpoint. Separately, a Phase 2 study sponsored by the International Center for Ethnobotanical Education, Research, and Service (ICEERS) at Hospital Universitari Sant Joan in Reus, Spain (NCT04003948) evaluated six doses of ibogaine administered under either fixed or ascending dosing regimens in 20 adults maintained on methadone, with methadone dose reduction over six months as the primary endpoint. Both studies were completed in 2024, and formal results are awaited.

Beyond substance use disorders, ibogaine is also being investigated for neuropsychiatric indications associated with traumatic brain injury. The Trifecta Research Study (NCT06810765), a Phase 2 multi-treatment protocol incorporating ibogaine for the management of PTSD and brain injury in Special

Operations Veterans, was initiated at Johns Hopkins University but was subsequently withdrawn prior to enrollment.

Phase 3 Studies

To date, no Phase 3 clinical studies of ibogaine have been completed. DemeRx Inc., in partnership with atai Life Sciences, is currently conducting a combined Phase 2/3 trial program for its proprietary ibogaine hydrochloride formulation (DMX-1002), building upon the Phase 1 safety and pharmacokinetic data generated through the MHRA-approved trial at MAC Clinical Research (NCT05029401).

Pharmacology in Humans

Pharmacokinetics and Product Metabolism in Humans

Ibogaine (12-methoxibogamine) is metabolized via *O*-demethylation primarily by the liver enzyme CYP2D6 to noribogaine (12-hydroxyibogamine) (Obach et al., 1998).

Glue et al. (Glue, Winter, et al., 2015) analyzed the pharmacokinetic properties of a single low oral dose (20 mg) of ibogaine in healthy volunteers. The sample was divided into two groups, one receiving a pre-treatment with paroxetine, a potent CYP2D6 inhibitor, and the other a pre-treatment of placebo. Paroxetine was administered to participants so that the influence of this isoform on the pharmacokinetic parameters of ibogaine could be observed. Subjects who received placebo as a pre-treatment showed very low plasma concentrations of ibogaine (Cmax=1.1 ng/mL). Ibogaine became undetectable in all subjects by 4 hours post-dose because it was rapidly converted to noribogaine. Noribogaine concentrations were substantially higher (Cmax=18.7 ng/mL), showing median peak concentrations at 4 hours, with a half-life of 13 hours. Among subjects who received paroxetine as a pre-treatment, much greater plasma concentrations of ibogaine were found (Cmax=29.5 ng/mL), with a half-life of 10.2 hours. Ibogaine was detectable for up to 72 hours. In this group, noribogaine concentrations were lower (Cmax=12.7 ng/mL), and the half-life was 20 hours (Glue, Winter, et al., 2015).

The results of Glue et al. (Glue, Winter, et al., 2015) corroborate those observed by Mash et al. (Mash et al., 2001). Subjects were genotyped for CYP2D6, and pharmacokinetic comparisons were made between those with extensive 2D6 activity and poor metabolizers with low activity. Significant effects of CYP2D6 status were observed, such that extensive metabolizers converted more ibogaine into noribogaine compared to poor metabolizers. As a result, the blood of extensive metabolizers had a higher proportion of noribogaine and a lower proportion of ibogaine (Mash et al., 2001).

The most rigorous and recent characterization of ibogaine PK/PD in opioid use disorder patients is the study by (Knuijver et al., 2024), which provides definitive data on the CYP2D6–exposure–QTc–ataxia relationship. In 14 OUD patients on opioid maintenance (11 on methadone, 3 on buprenorphine) who received a single 10 mg/kg oral dose of GMP-grade ibogaine HCl (Phytostan, 98% purity), median ibogaine Cmax was 4.77 μM/L (IQR 4.12–6.14) at Tmax 0.622 h, while noribogaine Cmax was 1.33 μM/L (IQR 1.09–1.46) at Tmax 7.57 h (IQR 5.93–10.4). AUC values were 49.12 μM·h/L for ibogaine and 60.4 μM·h/L for noribogaine. Critically, the basic clearance of ibogaine at a CYP2D6 activity score of 0 was 0.82 L/h and increased by 30.7 L/h per activity score point, the activity score therefore having a highly significant effect on ibogaine clearance and exposure ($p < 0.0001$). The authors fitted a sigmoid Emax model relating ibogaine plasma concentration to QTc prolongation, estimating a maximum QTc prolongation of 67.9 ms (RSE 10.9%) with EC50 = 0.195 μM (RSE 64.1%). QTc prolongation correlated significantly with ibogaine plasma concentration (Spearman $r = 0.109$, $p < 0.03$) but not with noribogaine concentration ($p = 0.668$). Cerebellar ataxia (SARA) scores correlated with ibogaine concentration ($r = 0.668$, $p < 0.01$) but not with metabolites. No correlation was observed between PK parameters and withdrawal severity (OOWS/SOWS). Across the 14 participants, CYP2D6 genotyping identified 2 poor metabolizers, 5 intermediate, 5 extensive, and 2 ultra-rapid metabolizers (Knuijver et al., 2024). These

data establish a quantitative concentration-effect framework for ibogaine cardiac safety and cerebellar adverse effects, and they provide the empirical basis for considering CYP2D6 genotype-guided dosing in future clinical trials.
Table 15 shows the Pharmacokinetic Parameters of Ibogaine (10 mg/kg) and its metabolite Noribogaine in Human Extensive and Poor Metabolizers of CYP2D6, based on a study by Mash et al. (Mash et al., 2001).

Table 15: Pharmacokinetic Parameters of Ibogaine (10 mg/kg) and Noribogaine (Mash et al., 2001)

	Extensive Metabolizers (16 males, 8 females)	**Poor (Slow) Metabolizers (3 males)**
Ibogaine 10 mg/kg		
Tmax, hour	1.70 ± 0.15	2.50 ± 1.04
Cmax, ng/mL	737 ± 76	896 ± 166
AUC0-24 hr, ng * hr/mL	3936 ± 556	11471 ± 414
t1/2, hr	7.45 ± 0.81	NQ
Noribogaine		
Tmax, hour	6.17 ± 0.85	3.17 ± 1.36
Cmax, ng/mL	949 ± 67	105 ± 30
AUC0-24 hr, ng * hr/mL	14705 ± 1024	3648 ± 435
t1/2, hr	NQ	NQ

Glue et al. (Glue, Lockhart, et al., 2015) assessed pharmacokinetics, pharmacodynamics, and the safety of four doses of noribogaine (3, 10, 30, and 60 mg) among healthy volunteers. The half-life was greater at low doses (3 and 10 mg), reaching 49 hours, while the half-life of larger doses (30 and 60 mg) did not go above 29 hours. The AUC and Cmax showed a dose-dependent behavior. Noribogaine is quickly absorbed, has a large volume of distribution, and is slowly eliminated due to various properties: enterohepatic circulation, the lipophilic profile, and slow metabolic processes (Glue, Lockhart, et al., 2015).

Absorption

Following oral administration, ibogaine is rapidly absorbed with peak plasma concentrations typically observed within 1–2 hours (Knuijver et al., 2024; Mash et al., 2001). Bioavailability is influenced by first-pass CYP2D6 metabolism in the gut wall and liver. Plasma protein binding has been reported in the range of 65–70% (Luz & Mash, 2021), and ibogaine accumulates in adipose tissue consistent with its lipophilic nature.

Distribution

Postmortem distribution analysis of ibogaine in a single individual has been characterized (Kontrimaviciute et al., 2006). Ibogaine and noribogaine were identified across all investigated tissue matrices with the exception of cardiac tissue, with the highest concentrations measured in the spleen, liver, brain, and lung. The tissue-to-subclavian blood concentration ratios averaged 1.78, 3.75, 1.16, and 4.64 for ibogaine and 0.83, 2.43, 0.90, and 2.69 for noribogaine in spleen, liver, brain, and lung, respectively. Very low concentrations of both compounds were detected within prostatic tissue. Both ibogaine and noribogaine are secreted within bile and cross the blood–brain barrier.

Metabolism

Ibogaine (12-methoxibogamine) is metabolized primarily by the liver enzyme CYP2D6, which converts the drug into its metabolite noribogaine (12-hydroxyibogamine) via *O*-demethylation (Obach et al., 1998). The (Knuijver et al., 2024) PK/PD study described above provides the most rigorous in-clinic characterization of CYP2D6-mediated ibogaine clearance to date, demonstrating that clearance increases by 30.7 L/h per CYP2D6 activity score point, a more than ten-fold range across the activity score spectrum (Knuijver et al., 2024).

Tolerance

Certain clinical providers have employed repeated ibogaine dosing protocols administered across several days. Preclinical evidence indicates that repeated administration can produce tolerance to ibogaine; however, the parameters governing ibogaine tolerance in human recipients have not been characterized (Mash, 2023).

Elimination

Ibogaine itself has a relatively short plasma half-life in humans, estimated at 2–7 hours depending on CYP2D6 status (Luz & Mash, 2021; Mash et al., 2001). Noribogaine has a substantially longer plasma half-life of 24–49 hours (Glue et al., 2016; Glue, Lockhart, et al., 2015), contributing to the persistence of pharmacological effects beyond the parent compound's elimination.

Pharmacogenomics

CYP2D6 polymorphisms are the dominant pharmacogenomic determinant of ibogaine pharmacokinetics and cardiac safety. CYP2D6 activity score has a more than ten-fold effect on ibogaine clearance (Knuijver et al., 2024), and poor metabolizers are at substantially higher risk of prolonged ibogaine exposure and consequent QTc prolongation. CYP2D6 genotyping is therefore widely advocated as a pre-treatment screening tool in any future regulatory clinical use (Glue, Winter, et al., 2015; Mash, 2023; Yockey, 2025).

Pharmacokinetic Drug Interactions

Patients undergoing ibogaine treatment should accordingly avoid grapefruit juice and other foods or beverages containing significant quantities of furanocoumarins, as these compounds inhibit CYP2D6 and CYP3A4 activity and may impair ibogaine metabolism (Litjens & Brunt, 2016). Concurrent administration of pharmaceutical CYP2D6 inhibitors, including selective serotonin reuptake inhibitors such as fluoxetine and paroxetine, bupropion, and a range of additional agents, should be discontinued in advance of ibogaine administration, with washout intervals adjusted to account for the half-lives of the inhibitor and any active metabolites. The extended elimination half-life of fluoxetine and its active metabolite norfluoxetine, in particular, may warrant washout periods of several weeks prior to ibogaine treatment.

Pharmacodynamics

Primary Pharmacodynamics

An open-label case series of ibogaine administration in substance-dependent patients has been documented across multiple publications spanning 1998 through 2018, ultimately encompassing 191 patients (Mash et al., 1998). Patients received ibogaine in doses of 8–12 mg/kg in an inpatient setting (Mash et al., 2018).

Ibogaine administration was well tolerated, with no serious adverse events recorded across the cohort. The most common adverse effects observed shortly following administration included nausea, vomiting, and gait ataxia. Physical examination findings remained unremarkable, and laboratory safety parameters were unaltered from baseline. The majority of patients reported perceptual changes during the absorption phase, which typically resolved within 4 to 6 hours of ibogaine administration. Headache was reported by 7% of patients, although a substantial proportion of these complaints may have reflected concurrent opioid discontinuation (Mash et al., 2018).

Orthostatic hypotension was observed in 5% of patients, with approximately 2% of all adverse events characterized as moderate in severity. Orthostatic hypotension and bradycardia were observed in the early post-administration period in cocaine-dependent patients, but were not consistently observed in opioid-dependent patients. Administration of intravenous fluids produced rapid normalization of both symptomatic bradycardia and hypotension, suggesting that the underlying mechanism involved volume depletion. On the basis of this observation, prophylactic intravenous fluid administration one hour prior to ibogaine dosing was subsequently incorporated into routine protocol for all patients (Mash et al., 2018).

There were no ocular or visual side effects noted in post-dose physician examinations and no patients had complaints of pronounced dry eye, ocular pain, eye redness or eye discomfort. Clinical laboratory test results were in the normal range for white blood cell counts, neurotrophic levels, and sodium and potassium levels. Liver function (ALT, AST, ALP and GGT) was unchanged from baseline measures following ibogaine administration (Mash et al., 2018).

No alterations in vital signs were associated with low-dose oral ibogaine administration (20 mg) in healthy volunteers (Glue, Winter, et al., 2015). The single 20 mg dose was well tolerated and considered safe, with no psychoactive effects recorded. Minor adverse effects, including nausea and gastrointestinal symptoms, occurred without requiring medical intervention. Noribogaine administered to healthy volunteers produced dose- and concentration-dependent QTc prolongation, with an otherwise favorable safety profile (Glue, Lockhart, et al., 2015). Dizziness and headache were observed at lower doses, while no adverse events were recorded at the highest dose examined (60 mg).

Physiological Effects

Central Nervous System

There has been a single SPECT (Single-Photon Emission Computerized Tomography) study of the sub-acute effects (before and 3 days after) of ibogaine, although interpretation is complicated because the subject used both ibogaine and the serotonergic psychedelic 5-MeO-DMT. Barsuglia et al. (Barsuglia et al., 2018) presented the case of a man with moderate alcohol-use disorder who experienced short-term therapeutic benefits from attending an inpatient treatment program in Mexico that administered ibogaine in a dose of 17.9 mg/kg followed 2 days later by vaporized toad venom containing 5-MeO-DMT.

The patient received SPECT neuroimaging that included a resting-state protocol before, and 3 days after completion of the program. During the patient's ibogaine treatment, he experienced dream-like visions that included content pertaining to their alcohol use and resolution of past developmental traumas. He described their treatment with 5-MeO-DMT as a peak transformational and spiritual breakthrough. On post-treatment SPECT neuroimaging, increases in brain perfusion were noted in bilateral caudate nuclei, left putamen, right insula, as well as temporal, occipital, and cerebellar regions compared to the patient's Baseline scan. The patient reported improvement in mood, cessation of alcohol use, and reduced cravings at 5 days post-treatment, effects which were sustained at 1 month, with a partial return to mild alcohol use

at 2 months. In this case, serial administration of ibogaine and 5-MeO-DMT resulted in increased perfusion in multiple brain regions broadly associated with alcohol use disorders and known pharmacology of both compounds, which coincided with a short-term therapeutic outcome (Barsuglia et al., 2018).

In contrast to the classic hallucinogens, which induce pupillary mydriasis (dilation), ibogaine causes miosis. Glue et al. (Glue, Winter, et al., 2015) found that in 21 healthy volunteers given 20 mg oral ibogaine, "subjects had mean maximal decreases of 0.4–0.6 mm in pupil diameter at 4 hours post dosing, and a return toward baseline diameter by 12 hours." In contrast, noribogaine did not change pupil size (Glue, Winter, et al., 2015). Consequently, ibogaine-induced pupillary changes are probably unrelated to the "non-euphoric changes in light perception at 1 hour post dose" that some patients reported when administered noribogaine (Glue et al., 2016).

Functional EEG and structural MRI evidence from the MISTIC cohort

A series of recent studies of the same 30 Special Operations Forces veterans with traumatic brain injury who received magnesium–ibogaine therapy in the MISTIC trial (Cherian et al., 2024), has substantially expanded the human neurophysiological evidence base for ibogaine. A functional neuroimaging analysis of this cohort by (Lissemore et al., 2025), demonstrated that after magnesium–ibogaine treatment, slower oscillations (theta–alpha) increased in power, and power at higher frequencies (beta–gamma) decreased. Accordingly, the theta/beta ratio increased post-treatment, which correlated with improved cognitive inhibition. Peak alpha frequency and neural complexity were lower after treatment, with these changes persisting at 1-month follow-up. These neurophysiological markers correlated with improvements in executive function, PTSD, and anxiety, and represent the first reported in-human evidence that ibogaine alters cortical oscillations in a clinically meaningful manner (Lissemore et al., 2025).

Recently, the novel FREQ-NESS (FREQuency-resolved Network Estimation via Source Separation) framework to EEG data from the same cohort identified frequency-specific brain network reorganization following ibogaine treatment. Specifically, ibogaine significantly reduced the activation of frontal-left electrodes within high-beta (24–25 Hz) networks while elevating the activation of posterior electrodes — a posterior shift present at both 3–4 days and 1 month after treatment. Critically, this posterior shift correlated with improvements in PTSD symptoms on the CAPS-5 (24 Hz immediate-post $r = -0.66$, $p < 10^{-8}$; 1-month $r = -0.53$, $p < 10^{-4}$), particularly the Intrusion subscale, and replicated in an independent EEG dataset of OUD patients ($n = 11$) treated with ibogaine alone. Neural field modelling using the Robinson–Rennie–Wright framework attributed the shift to a ~15% reduction in cortico-cortical gain ($\beta = -0.0376$, $p = 0.04$ immediate-post; $\beta = -0.0581$, $p = 0.003$ at 1 month), with cortico-thalamic gain unchanged. The authors propose high-beta network reconfiguration as a robust biomarker for ibogaine's therapeutic effects (Shinozuka et al., 2026).

Recently, the first morphometric MRI evidence of brain structural changes following ibogaine treatment in humans was reported. Among 30 SOF veterans receiving 12.1 ± 1.2 mg/kg oral ibogaine plus IV magnesium, cortical thickness increased significantly in 11 of 13 regions of interest at approximately 7 days post-treatment relative to baseline visits, with no significant changes between immediate-post and 1-month visits, suggesting a sustained increase in cortical thickness across the study period. Right ventral diencephalon volume also changed. Critically, predicted brain age decreased by 1.60 years at 1 month (Cohen's $d = 1.035$, $p = 0.0082$) (Adamson, 2025). These findings provide the first direct in-human evidence that ibogaine, at least in the context of magnesium co-administration, produces measurable structural brain changes consistent with its proposed neurotrophic mechanism.

Beyond the substance use disorder and trauma indications, the first published evidence that ibogaine may produce neurorestorative effects in multiple sclerosis (MS) was reported by (D. Q. Chen et al., 2025) in *Frontiers in Immunology*. Two MS patients treated at Ambio Life Sciences (Tijuana, Mexico) underwent

serial MRI evaluation. Patient A, a 41-year-old male with relapsing-remitting MS, demonstrated a 70% reduction in lesion volume (1,609.8 → 480.5 mm^3) and a decrease in apparent diffusion coefficient (ADC: 2,716.3 → 1,774.5 $\times 10^{-6}$ mm^2/s) at 3 months post-ibogaine, consistent with remyelination and reduced inflammation. Patient B, a 44-year-old woman with secondary progressive MS and complex PTSD, exhibited cortical and subcortical alterations particularly in regions associated with pain and emotional processing (D. Q. Chen et al., 2025). These case reports, though confined to two patients, single-clinic, and unblinded, represent the first ibogaine-MS neuroimaging data.

Cardiovascular System

Across a cohort of more than 150 substance-dependent patients receiving ibogaine at doses of 8, 10, or 12 mg/kg (p.o.), no systematic alterations were observed in heart rate, blood pressure, or respiratory rate, although a subset of cocaine-dependent patients exhibited a hypotensive response that was responsive to volume repletion (Mash et al., 2001).

In a controlled clinical investigation, noribogaine administered at three dose levels (60, 130, and 180 mg) to 27 opioid-dependent volunteers produced dose- and concentration-dependent QTc prolongation (Glue et al., 2016).

The pharmacokinetic-pharmacodynamic analysis described in Section 6.2.1 provides the most rigorous concentration–QTc characterization conducted to date in patients with opioid use disorder receiving 10 mg/kg oral ibogaine hydrochloride (Knuijver et al., 2024). Sigmoid E_max modeling estimated a maximum QTc prolongation of 67.9 ms with an EC_{50} of 0.195 μM, and demonstrated that QTc prolongation correlated with ibogaine, rather than noribogaine, plasma concentrations within this acute clinical setting.

Hepatic System and Other Laboratory Values

Large open-label clinical case series have not reported substantial hepatic enzyme abnormalities attributable to ibogaine at doses employed for opioid and cocaine detoxification. In a cohort of 191 inpatient detoxification participants receiving 8 to 12 mg/kg oral ibogaine hydrochloride in gelatin capsules, no changes were observed on physical examination or laboratory safety assessment across the administered dose range (Mash et al., 2018). Comparable findings have been documented in 30 opioid-dependent participants receiving a mean total dose of 1,540 ± 920 mg ibogaine hydrochloride, with no clinically significant hepatic abnormalities identified (T. K. Brown & Alper, 2017). A controlled safety investigation of 10 mg/kg oral ibogaine hydrochloride in 14 opioid-dependent patients similarly identified no significant hepatic transaminase elevations (Knuijver et al., 2022).

Although ibogaine itself does not appear to function as a primary hepatotoxin at therapeutic doses, pre-existing hepatic disease has been identified as a confounding factor in multiple fatal case reports. A documented fatality involved a patient with advanced hepatic cirrhosis and severe steatosis in whom ibogaine ingestion was temporally associated with sudden death (Papadodima et al., 2013). An additional case involved a 52-year-old male with a 20-year history of alcohol use disorder who died suddenly following ibogaine administration; postmortem examination identified hepatic cirrhosis and steatosis as concomitant pathologies, alongside coronary artery sclerosis (Koenig & Hilber, 2015). These cases do not implicate ibogaine as directly hepatotoxic, but rather indicate that pre-existing hepatic compromise represents a clinically significant risk factor through multiple mechanisms, including altered metabolism, prolonged systemic exposure, and increased vulnerability to electrolyte disturbance and cardiac complications. Pre-treatment hepatic function testing should accordingly be considered an essential component of clinical screening prior to ibogaine administration.

Reproductive System

No scientific data indicates ibogaine is either safe or unsafe with respect to reproduction and development.

Cognition and Performance

A single low-dose administration of ibogaine (20 mg) produced little or no measurable effect on mood or cognitive performance, including measures of basic visuomotor function, inhibitory control, task-switching ability, and selective attention, when participants were assessed before and two hours following administration (Forsyth et al., 2016).

In preclinical models, ibogaine has been characterized as promoting a waking state accompanied by robust and prolonged suppression of REM sleep, alongside dose-dependent atypical motor profiles and additional serotonin-related behavioral effects (Gonzalez et al., 2018). Given the rapid biotransformation of ibogaine to noribogaine, further investigation is required to determine the relative contributions of the parent compound and the metabolite to these behavioral observations.

In 30 U.S. Special Operations veterans with combat/blast exposure and TBI history undergoing the MISTIC magnesium–ibogaine protocol, repeated-measures ANOVA revealed significant post-treatment improvements across multiple cognitive domains, including processing speed (WAIS-IV PSI; $F(2,25) = 26.957$, $p < .001$), executive functions on D-KEFS Color-Word Conditions 3 and 4 ($p < .001$ and $p = .004$ respectively), verbal fluency (D-KEFS VF Condition 3; $p = .003$), and verbal learning (HVLT Total Recall; $p = .004$). No cognitive decline was observed on any measure at 1-month follow-up. The authors note that improvements may reflect a combination of ibogaine-induced neuroplastic effects, reductions in PTSD and mood symptoms, and practice effects, but emphasize the absence of detectable cognitive impairment up to 1 month post-treatment (Cherian et al., 2024)

Psychological Effects

An online survey of 27 ibogaine users has documented the subjective psychological experiences associated with ibogaine administration (Heink et al., 2017). All survey participants reported that the ibogaine experience produced insights relating to their personal past. The majority of respondents additionally reported insights regarding the meaning of life (92%), the nature of creation (88%), the evolution of humanity (85%), the evolution of the animal world (77%), the evolution of the universe (89%), and death and the afterlife (85%). Following the ibogaine experience, 85% of participants reported subjective relief from guilt.

These findings have been interpreted to suggest that ibogaine induces altered states of consciousness that support an individual's capacity for adaptive personal change. The role of the altered state itself in mediating therapeutic outcomes remains incompletely characterized; comparison of ibogaine with non-psychedelic structural derivatives has been proposed as a methodological approach for elucidating whether the psychedelic phenomenology contributes meaningfully to treatment efficacy.

Perceptual Effects

A subset of individuals receiving ibogaine experience perceptual effects ranging from mild distortions of spatial and temporal perception to closed-eye visual phenomena. These effects do not constitute significant safety concerns within a controlled clinical setting.

While these visual phenomena are sometimes experienced as meaningless or fragmentary, they are at other times reported as carrying substantial symbolic and psychological significance. In one online survey

of ibogaine users, participants described rapid visual sequences, with some respondents likening the experience to viewing a film at accelerated speed or to a sequential slideshow (Heink et al., 2017). The visual altered states associated with ibogaine have been characterized as vivid, personal, and meaningful, with anecdotal reports suggesting that the visions themselves may function as a vehicle for psychological insight into current or past concerns.

In the same survey, participants reported alterations in multiple sensory and perceptual modalities. Heightened perception was endorsed by 88% of respondents, with specific alterations reported in the perception of light (89%), sound (85%), body (82%), time (93%), and space (78%). The majority (97%) experienced hallucinations, with 63% indicating that hallucinations or visions occupied "quite a bit" or "almost all" of the ibogaine experience. Common visual content included living persons (77%) and deceased persons (38%), animals (62%), and television-screen-like imagery (46%). Auditory phenomena included drumming sounds (54%) and buzzing sounds (96%); communication with deceased individuals was reported by 27% of respondents. Most participants indicated that their visions conveyed a coherent narrative (70%) and contained symbolic content (74%); 74% reported that the visions carried obvious personal significance, and 77% experienced visions drawn from their own childhood.

Participants demonstrated variable capacity to modulate the visionary experience. Most (78%) reported the ability to exit a vision by opening the eyes at least intermittently, and most (78%) returned to the same visionary content upon closing the eyes again. Approximately half (52%) reported a complete inability to exert voluntary control over the content of their visions.

The subjective character of the ibogaine experience has been described in patient accounts that emphasize autobiographical content and emotional processing. Representative descriptions reference visions of past relationships, family, and pivotal life events, accompanied by intense emotional content including grief, remorse, and the contemplation of alternative life trajectories (T. K. Brown & Alper, 2017).

The most pronounced visual effects generally occur within the first four hours following administration (Lotsof & Alexander, 2001) corresponding to peak plasma ibogaine concentrations. It has been proposed that the therapeutic activity of ibogaine may depend in part upon facilitated access to autobiographical memory content, potentially relevant to the initiation of substance use disorder (Popik, 1996). Preclinical investigation employing the Morris maze spatial navigation task demonstrated that ibogaine at 0.25 or 2.5 mg/kg administered immediately prior to test trials facilitated spatial memory retrieval in rats compared with placebo-treated controls. Although low-dose ibogaine has been shown to enhance short-term spatial memory in rodent models, this phenomenon is distinct from the autobiographical, emotionally charged, and thematically rich subjective content reported by human ibogaine recipients.

An observational study of 44 opioid-dependent individuals undergoing ibogaine treatment determined that 43% of participants met criteria for a complete mystical experience as measured by the Altered States of Consciousness Questionnaire (T. K. Brown et al., 2019). The experiences described included cyclic visual content leading to confronting realizations involving remorse and regret for prior actions toward others, alongside subjective release from feelings of guilt and worthlessness. Many participants reported the experience as carrying significance comparable to spiritual transformation.

Efficacy of Ibogaine Across Populations

There are no data demonstrating that the efficacy of ibogaine varies systematically across patient populations. However, evidence exists for sex differences in pharmacokinetics and therefore in pharmacodynamic response, and the activity of the CYP2D6 enzyme is known to vary across racial and ethnic groups.

Female animals demonstrate greater sensitivity to ibogaine than males, with the supporting evidence derived predominantly from rodent investigations (Baumann, Rothman, et al., 2001). Preovulatory female rats in the proestrus phase—when circulating estrogen concentrations are at their highest—exhibited plasma and brain ibogaine concentrations approximately twice those measured in males or in postovulatory females following intraperitoneal administration (Baumann, Pablo, et al., 2001). The available evidence suggests that estrogen enhances the bioavailability of ibogaine, an effect potentially mediated by increased absorption from the peritoneal cavity into systemic circulation. Whether this enhanced absorption effect extends to orally administered ibogaine remains uncharacterized.

These pharmacokinetic findings may indicate that women are more sensitive to ibogaine than men and could potentially benefit from lower average doses. Postmenopausal women may exhibit reduced sensitivity relative to preovulatory females while remaining potentially more sensitive than men. Further investigation is required to characterize sex differences in human response to ibogaine.

CYP2D6 Variation Across Racial and Ethnic Groups

No formal studies have characterized population-level differences in human response to ibogaine. However, the activity of CYP2D6 varies substantially across racial and ethnic groups (Bernard et al., 2006). Within the United States population, individuals of Caucasian ancestry exhibit the highest reported frequency of the poor metabolizer phenotype, characterized by reduced enzymatic capacity and consequently elevated sensitivity to CYP2D6 substrate medications. Asian and Hispanic populations exhibit comparatively lower frequencies of the poor metabolizer phenotype. Reported frequencies of CYP2D6 polymorphisms among African American populations vary substantially across investigations. Notably, the magnitude of genetic diversity within these broad racial and ethnic categories renders such categories of limited utility in predicting individual CYP2D6 phenotype; pharmacogenetic testing of individual patients is therefore considered more clinically informative than population-level inference.

Although ibogaine is not currently approved as a medical treatment for substance use disorders (SUDs), a substantial body of uncontrolled and anecdotal case studies has been accumulated through private clinics in the Netherlands (K. R. Alper et al., 1999; Sheppard, 1994), New Zealand (Noller et al., 2018), Mexico (T. K. Brown & Alper, 2017; Camlin et al., 2018; Davis et al., 2017; Malcolm et al., 2018), Panama (Luciano, 1998), and the West Indies (Mash et al., 2000). The general consensus emerging from these observational studies is that ibogaine may be clinically useful in the management of opioid and other SUDs. The published case series collectively suggest the effectiveness of single high-dose ibogaine administration in attenuating opioid withdrawal symptoms, post-withdrawal drug cravings, and the compulsion to continue substance use (Mash et al., 2001); Dos (K. R. Alper et al., 1999; Bastiaans, n.d.; T. K. Brown & Alper, 2017; Camlin et al., 2018; Davis et al., 2017; Dos Santos et al., 2017; Luciano, 1998; Malcolm et al., 2018; Noller et al., 2018; Sheppard, 1994). Table 2 summarizes representative case series characterizing the human clinical experience with ibogaine. While claims of high abstinence rates following ibogaine detoxification have been advanced in several studies (T. K. Brown & Alper, 2017; Davis et al., 2018; Noller et al., 2018), verification of relapse prevention through random urine screening following treatment is currently lacking, and the study cohorts and clinical methodologies are not directly comparable.

When administered for the treatment of SUDs, ibogaine is most commonly delivered orally as the hydrochloride salt. Reported doses vary widely, ranging from 6 to 55 mg/kg, although typical therapeutic doses fall between 8 and 25 mg/kg (Mash et al., 2018); Dos (K. R. Alper et al., 1999; T. K. Brown & Alper, 2017; Davis et al., 2017; Dos Santos et al., 2017; Malcolm et al., 2018; Noller et al., 2018; Sheppard, 1994). Patients frequently report sustained resolution of withdrawal symptoms within 12 to 18 hours of administration, accompanied by reductions in drug craving and improvements in mood that persist for weeks to months. The prolonged beneficial aftereffects associated with ibogaine for relapse

prevention appear to extend well beyond the clearance of ibogaine and noribogaine from systemic circulation (Mash et al., 2018).

To date, no controlled clinical efficacy trials of ibogaine have been published. The largest body of observational clinical data supporting open-label efficacy and safety derives from the St. Kitts ibogaine study (Mash et al., 2018). This investigation reported outcomes from patients enrolled in a 12-day inpatient protocol designed to evaluate the safety and efficacy of ibogaine as a pharmacological intervention for drug detoxification. The study cohort comprised self-referred, treatment-seeking opioid- and cocaine-dependent patients (N = 191; 24.6% female). All opioid-dependent patients (N = 102) were transitioned at program entry to oral morphine for stabilization prior to ibogaine administration. Opioid withdrawal symptoms were assessed at baseline, approximately 12 hours following the last dose of oral morphine, and 24 hours after ibogaine administration (i.e., 36 hours after the final morphine dose). All patients received oral ibogaine hydrochloride at doses of 8 to 12 mg/kg.

Opioid-dependent patients demonstrated statistically significant reductions in withdrawal symptoms and drug cravings across all Heroin Craving Questionnaire (HCQ) subscales following ibogaine administration, with sustained effects observed at 1-month follow-up where available. Comparable improvements were reported in mood state assessments, with significant reductions in depressive symptomatology from baseline to post-dose and 1-month follow-up time points ($p \leq 0.01$). Pharmacokinetic parameters, including Cmax values, and opioid withdrawal ratings stratified by CYP2D6 genotype were reported for a subset of patients. Physician-rated opioid withdrawal scores (scale range 0–13) indicated that objective withdrawal signs at 24 hours were mild (0–2), with no exacerbation observed at subsequent time points (Mash et al., 2018). These findings are consistent with previously published case reports demonstrating the effectiveness of ibogaine for opioid detoxification based on both physician-rated and subjective assessments (T. K. Brown & Alper, 2017; Davis et al., 2017; Malcolm et al., 2018; Mash et al., 2001; Noller et al., 2018). The rapid management of opioid withdrawal symptoms and drug cravings represents a potentially important therapeutic advantage relative to lofexidine and methadone, the two FDA-approved agents currently employed to alleviate acute somatic withdrawal from heroin and prescription opioids.

In the St. Kitts study, patient volunteers were administered an open-ended elicitation narrative to characterize their subjective interpretation of the therapeutic benefit derived from the ibogaine experience. Approximately 92% of participants reported perceiving benefit from the oneiric experience and endorsed ibogaine as a useful treatment for substance dependence (Mash et al., 2018). Participants described gaining insight into their self-destructive behaviors and reported becoming "mindful" of the need to pursue sobriety and abstinence. These observations suggest that ibogaine's oneiric effects may engage frontal lobe function to facilitate reasoning, decision-making, and adaptive behavioral regulation following detoxification from opioids and other substances of abuse.

The multitarget pharmacological actions of ibogaine and noribogaine identify molecular mechanisms that operate in concert to modulate circuit-level processes within brain regions implicated in drug and alcohol dependence. Through its actions at NMDA receptors, ibogaine may promote neuroplasticity and enhance receptor functionality through mechanisms analogous to those reported following single oral doses of psilocybin (Vollenweider & Kometer, 2010), intravenous allopregnanolone administration (Schverer et al., 2018), and repeated intravenous ketamine treatment (Fava et al., 2020). Numerous studies have demonstrated that drugs of abuse may induce permissive adaptations that subsequently influence synaptic plasticity through a process termed "plasticity of synaptic plasticity," or metaplasticity (Abraham & Bear, 1996). The metaplasticity associated with compulsive drug-taking behavior has been characterized as a maladaptive process that renders neural circuits more rigidly configured and less responsive to normal patterns of synaptic remodeling (Chiamulera et al., 2021). Analogous to other classical psychedelics, NMDA receptor antagonism combined with serotonergic circuit modulation may account for ibogaine's dose-dependent oneiric effects in humans. It has been hypothesized that noribogaine may contribute to the

beneficial aftereffects of ibogaine therapy through dynorphin–kappa opioid and serotonergic mechanisms (Maillet et al., 2015; Mash et al., 2016).

Classical psychedelics have been shown to promote glutamate-dependent increases in pyramidal neuron activity within the prefrontal cortex, as recently demonstrated through in vivo proton magnetic resonance spectroscopy assessment of glutamate levels (Mason et al., 2020). The action of psychedelic medicines on 5-HT2A receptor-mediated glutamate release represents a putative final common pathway underlying both the acute alterations in thought and perception and the potential mechanisms of therapeutic efficacy (Nutt et al., 2020). Ibogaine has been described by patients as a "substance use disorder interrupter" in the context of opioid and other substance use disorder treatment. Ibogaine and its active metabolite are classified as "psychoplastogens" that exert specific effects on dopaminergic circuitry through activation of GDNF and other downstream second-messenger signaling cascades (Carnicella et al., 2010; He et al., 2005; Olson, 2018). Reward hyposensitivity and anhedonia are well-characterized features of substance use disorders, with particularly pronounced severity in SUDs comorbid with depression (Destoop et al., 2019). The polypharmacological profile of ibogaine and its active metabolite may mitigate withdrawal-associated anhedonia and restore dysregulated reward circuitry by re-engaging or reversing the state-dependent glutamatergic tone that becomes pathologically altered through chronic use of opioids, psychostimulants, and alcohol. Elucidating the mechanisms by which ibogaine may produce a "reset" of brain reward circuitry represents an area of active investigation, particularly within the broader context of clinical development of psychedelic compounds and ketamine for the treatment of various mental health disorders.

There is no data exploring possible age differences in how people respond to ibogaine.

Safety of Ibogaine in Humans

The principal risk associated with ibogaine is cardiotoxicity resulting from blockade of repolarizing potassium channels and slowed repolarization of the ventricular action potential simultaneous with QT interval prolongation. This may lead to life-threatening *Torsades de Pointes* (TdP) arrhythmias and sudden death in rare instances (Noller et al., 2018).

The risks of ibogaine can be reduced but not eliminated by proper screening of patients, by CYP2D6 phenotyping or genotyping to determine an appropriate dose, and by providing an appropriate setting with careful supervision (particularly monitoring the heart) before and after the session.

A calculated initial dose of approximately 0.87 mg/kg body weight has been proposed on the basis of pharmacological modeling, a value substantially lower than doses currently employed in clinical practice (Schep et al., 2016). This calculated dose may be unduly conservative and is likely insufficient to produce the therapeutic effects in substance use disorder for which ibogaine is administered. Through systematic exclusion of patients with significant cardiac or hepatic compromise, combined with CYP2D6 phenotyping or genotyping to identify poor metabolizers, the safe administration of higher therapeutic doses capable of attenuating withdrawal symptomatology and drug craving may be achievable.

Adverse Events

While many thousands of individuals have used ibogaine without serious adverse outcomes, ibogaine can produce significant medical complications, particularly in patients with pre-existing cardiac conditions or those concurrently exposed to other substances capable of producing adverse interactions.

The medical literature contains several adverse psychiatric events associated with ibogaine consumption.

At 48 hours after ibogaine treatment (10 mg/kg) for opioid use disorder, a patient began hallucinating scenes from their past that brought up emotions of rejection, shame, and guilt. These memories included maternal abandonment and finding the body of a friend who had a fatal overdose from heroin that the patient had supplied. The unbidden images recurred for 5 weeks, and subsided after the patient received Eye Movement Desensitization and Reprocessing Therapy. The report about this patient described it as a case of Hallucinogen-Persisting Perceptual Disorder (HPPD) (Knuijver et al., 2018). In contrast, this case involved a patient who suffered from unpleasant memories of traumatic events. Despite apparently being misdiagnosed, this case is a rare example of a prolonged reaction to the psychedelic effects of ibogaine.

Four cases of psychotic symptomatology have additionally been documented in association with ibogaine ingestion. A practitioner of African spiritual traditions in France developed psychotic symptoms during a period of daily iboga consumption, characterized by dream-like experiences featuring threatening imagery (Houenou et al., 2011). Three additional cases of manic episodes associated with ibogaine administration have been reported.

Table 16 summarizes human studies reporting on adverse events and notes methodological limitations; Table 17 summarizes details of individual non-fatal cases; Table 18 summarizes fatal cases.

Table 16: Human Studies Reporting Safety, Toxicity, and Adverse Events Associated with Ibogaine. (Esperança et al., 2026)

Ref	Study Type	N	Exposure/Dosing	Main Safety Findings	Methodological Limitations
(Hoelen et al., 2009)	Case report	1	Oral exposure to a non-standardized ibogaine preparation (15% ibogaine; total dose 3.5 g), administered in a non-regulated alternative medicine setting	Severe QTc prolongation (QTc up to 616 ms) with documented ventricular tachyarrhythmias temporally associated with ibogaine exposure; QT interval normalized approximately 42 h after cessation despite correction of electrolyte abnormalities, indicating a strong temporal association between ibogaine exposure and malignant cardiac electrophysiological disturbances	Single-case design; absence of standardized or purified formulation; high-dose, imprecisely characterized exposure; concomitant electrolyte disturbances; no pharmacokinetic or genetic assessment; limited causal inference despite strong temporal relationship
(K. R. Alper et al., 2012)	Systematic retrospective forensic review of fatality cases	19	Ibogaine ingestion in medical and nonmedical settings; heterogeneous preparations and doses, including ethnopharmacological forms; exposure-to-death interval 1.5–76 h; dosing and formulation frequently undocumented or imprecise	19 deaths temporally associated with ibogaine ingestion. No consistent neurotoxic syndrome identified. Postmortem and clinical evidence indicated that preexisting cardiovascular disease and/or concomitant use of other substances explained or contributed	Retrospective design; reliance on medico-legal reports; heterogeneous and incomplete exposure data; frequent absence of standardized dosing, formulation, pharmacokinetic, or genetic information; multiple confounding

				to death in most cases, with adequate data. Additional risk factors included alcohol or benzodiazepine withdrawal–related seizures and uninformed use of non-standardized ibogaine preparations.	factors; temporal association without definitive causal attribution.
(Steinberg & Deyell, 2018)	Case report	1	Oral ingestion of ibogaine capsules obtained in a non-medical, non-regulated setting; estimated total dose of 65–70 mg/kg (highest survived dose reported); non-standardized preparation with uncertain alkaloid content; no serum ibogaine quantification performed	Extreme QTc prolongation (QTc up to 714 ms) mimicking acquired long-QT syndrome type 2, complicated by ventricular flutter/ventricular tachyarrhythmia at 270 bpm and near-fatal cardiac arrest requiring emergent defibrillation. Delayed QT recovery required approximately 7 days despite electrolyte correction, consistent with prolonged exposure to the active metabolite noribogaine. Strong temporal association between ibogaine ingestion and malignant ventricular arrhythmia.	Single-case design; estimated rather than measured dose; non-standardized ibogaine formulation; absence of serum ibogaine/noribogaine concentrations; presence of secondary hypokalemia as a proarrhythmic facilitating factor; findings not generalizable despite strong mechanistic and temporal coherence.
(Pleskovic et al., 2012)	Case report	1	Oral ibogaine exposure (600 mg); non-regulated setting; objective confirmation of ibogaine and noribogaine in blood by LC-MS/MS; no co-ingested substances detected except low-level methadone.	Recurrent malignant ventricular arrhythmias (≥5 episodes of ventricular fibrillation and multiple ventricular tachycardias) associated with marked and persistent QTc prolongation (up to 593 ms), lasting up to 9 days post-exposure; arrhythmic events temporally aligned with ibogaine/noribogaine plasma levels and frequently triggered by vagal maneuvers (micturition/defecation); exclusion of congenital	Single-case design; non-standardized product; prior opioid and cocaine abstinence; partial contribution of low-level methadone and amiodarone effects cannot be fully excluded; absence of controlled conditions limits generalizability despite strong temporal, toxicological, and electrophysiological evidence.

				long-QT syndrome and structural heart disease supports drug-induced cardiotoxicity.	
(Mazoyer et al., 2013)	Fatal case report (forensic toxicology)	1	Ingestion of powdered T. iboga root containing 7.2% ibogaine; non-standardized ethnopharmacological preparation; quantified ibogaine and ibogamine in ingested material and postmortem biological samples by GC-MS/MS; co-ingestion of methadone and diazepam at therapeutic concentrations.	Death occurring approximately 12 h after ingestion of powdered iboga root; postmortem toxicological analyses demonstrated significant systemic exposure to ibogaine (blood concentrations up to 1.27 μg/mL) and ibogamine, with extremely high gastric concentrations (53.5 μg/mL); death attributed to iboga ingestion in the context of concomitant methadone and diazepam use, indicating a fatal toxicological interaction rather than isolated ibogaine exposure.	Single fatal case; polysubstance exposure confounds attribution of causality to ibogaine alone; non-standardized plant preparation with variable alkaloid content; absence of premortem ECG or clinical monitoring; limited generalizability despite robust analytical confirmation of exposure and cause-of-death attribution.
(Papadodima et al., 2013)	Fatal case report (forensic pathology and toxicology)	1	Ibogaine use in a non-medical, unregulated setting; formulation and exact administered dose not reported; postmortem blood concentration of ibogaine measured at 2.0 mg/L; no standardized pharmaceutical preparation; exposure confirmed by toxicological analysis.	Sudden death occurring approximately 12–24 h after ibogaine exposure; autopsy revealed advanced liver cirrhosis with severe fatty infiltration; death temporally associated with ibogaine use in the context of significant pre-existing hepatic pathology, raising concern for impaired metabolism and increased systemic exposure; cardiac arrhythmia considered a plausible mechanism given the known electrophysiological effect of ibogaine.	Single fatal case; absence of premortem ECG or cardiac monitoring; lack of precise dosing and formulation details; significant pre-existing liver disease represents a major confounder; causality cannot be attributed exclusively to ibogaine despite high blood concentration and close temporal relationship; limited generalizability.
(Henstra et al., 2017)	Case report with toxicokinetic analysis (LC-MS/MS)	1	Repeated oral ingestion of internet-purchased ibogaine capsules over approximately 12 h (total dose ≈ 1400 mg);	Marked QTc prolongation (maximum QTc 647 ms) associated with multiple clinically significant cardiac	Single-case design; non-standardized and unregulated ibogaine product; absence of CYP2D6

			non-regulated, non-medical setting; plasma ibogaine and noribogaine concentrations quantified by validated LC-MS/MS; maximum ibogaine concentration 1.45 mg/L; noribogaine peak concentration 0.569 mg/L with prolonged persistence.	arrhythmias, including atrial tachycardia, ventricular tachycardia, and torsades de pointes; QTc prolongation and arrhythmic risk persisted for up to 12 days after ingestion, extending well beyond clearance of parent ibogaine; toxicokinetic modelling demonstrated that prolonged cardiotoxic effects were temporally and quantitatively aligned with sustained noribogaine exposure rather than ibogaine itself, supporting a metabolite-driven mechanism of delayed cardiotoxicity.	genotyping; potential contribution of transient hypokalemia and hypomagnesaemia as pro-arrhythmic cofactors; lack of controlled dosing conditions limits generalizability despite robust temporal, electrophysiological, and toxicokinetic evidence.
(Kontrimavic iute et al., 2006)	Forensic post-mortem toxicology study (case-based tissue distribution analysis)	1	Fatal ingestion of T. iboga root bark (non-standardized ethnopharmacological preparation); exact dose unknown; post-mortem quantification of ibogaine and noribogaine in blood, bile, and multiple tissues using validated LC–ESI–MS/MS.	Extensive systemic and tissue distribution of ibogaine and noribogaine was demonstrated post-mortem, with highest concentrations in spleen, liver, brain, and lung; both compounds shown to cross the blood–brain barrier and to be excreted via bile; high tissue-to-blood concentration ratios indicate marked lipophilicity and tissue sequestration, supporting prolonged biological persistence and mechanistic plausibility for delayed and systemic toxicity following iboga ingestion.	Single fatal case; absence of controlled dosing or timing data; polysubstance exposure not fully characterizable; post-mortem design precludes causal attribution of death mechanism but provides robust toxicokinetic and distributional evidence relevant to human safety risk.
(Chèze et al., 2008)	Forensic post-mortem case report with comprehensive toxicological and tissue	1	Fatal ingestion of T. iboga root (non-standardized ethnopharmacological preparation); recent exposure confirmed by	Systemic detection of ibogaine and noribogaine across all post-mortem biological matrices, including incorporation into hair,	Single fatal case; death attributed primarily to drowning rather than a defined cardiotoxic event; absence of

	distribution analysis		LC–MS/MS detection of ibogaine and noribogaine in blood, urine, bile, gastric contents, liver, lungs, vitreous humor, spleen, and hair; no co-ingested licit or illicit drugs or alcohol detected.	consistent with recent high-level exposure; autopsy established drowning as the immediate cause of death, with a concomitant myocardial abnormality (myocardial bridging); the widespread presence of iboga alkaloids supports acute intoxication preceding death and underscores the potential for central nervous system impairment and loss of situational awareness contributing indirectly to fatal outcomes.	quantitative dose reconstruction; potential contribution of pre-existing myocardial abnormality; post-mortem design limits causal attribution while providing robust forensic confirmation of exposure and distribution.
(Mestre et al., 2024)	Clinical case report (life-threatening cardiotoxicity)	1	Oral ibogaine exposure, 200 mg, administered in an alternative detoxification setting; no co-ingestion of other QT-prolonging drugs; normal baseline electrolytes; no structural heart disease identified.	Acquired long-QT syndrome (QTc up to 636 ms) associated with polymorphic ventricular tachycardia (torsade de pointes) and multiple episodes of cardiac arrest shortly after exposure; recurrent malignant arrhythmias requiring repeated defibrillation and intensive care admission; gradual QTc normalization over 8 days following supportive management; findings demonstrate severe cardiotoxicity occurring at a low ibogaine dose, independent of electrolyte imbalance or underlying structural cardiac disease.	Single-case design; absence of pharmacokinetic measurements (ibogaine/noribogaine plasma levels not quantified); lack of genetic testing for congenital long-QT syndrome; exposure occurred in a non-regulated clinical context, limiting dose verification and generalizability despite strong temporal and clinical association.

Commonly Reported Reactions

Oral doses of ibogaine from 5 to 25 mg/kg can cause minor side effects such as dizziness, nausea, vomiting, and motor incoordination that can last for hours (Baumann, Rothman, et al., 2001). One online survey of 27 ibogaine users reported:

Participants indicated that they felt at least "some" of the following physical symptoms: lightheadedness/dizziness (56%), decreased control of movements in any body parts (70%), buzzing in ears (89%), nausea (52%), vomiting (30%), diarrhea (19%), feeling physically heavy (77%), difficulty trying to move (81%), emotional distress (46%), and feeling hesitant to take the next dose of ibogaine (35%) (Heink et al., 2017).

A Brazilian ibogaine clinic reduces potential nausea from ibogaine by administering a 20-mg dose of domperidone (a dopamine D2/D3 receptor antagonist) 30 to 45 minutes beforehand (Schenberg et al., 2014). The use of domperiodone is based on advice from *Manual for Ibogaine Therapy Screening, Safety, Monitoring, and Aftercare* (2003) by Howard Lotsof and Boaz Watchel (Lotsof & Wachtel, 2003). Also see S.L. Costache's thesis: Pharmacological Attenuation of the Tremorigenic Effect of Ibogaine (Costache, 1995).

Mash and colleagues found that ataxia was frequently accompanied by nausea and, in some cases, vomiting; dry mouth was also reported. Ibogaine has additionally been associated with visual hallucinations, typically occurring with eyes closed, along with perceptual disturbances. Consistent with these clinical observations, the most frequently reported adverse events using MedDRA terminology were visual hallucination, ataxia, nausea, feeling hot, and headache, with frequencies ranging from 18% to 48% of patients. Adverse events observed in the St. Kitts cohort were transient in nature and resolved without sequelae (Mash et al., 2018).

Serious Adverse Reactions

As of 2019, the medical literature documents 46 cases of serious adverse events associated with ibogaine, most of them due to cardiac arrest following such symptoms as QT prolongation (long QT), ventricular fibrillation (VF), *Torsades des Pointes* (TdP), and other ventricular tachydysrhythmias (VT). There were 13 nonfatal cases and 33 fatal cases. Many of the non-fatal cases probably would have been fatal if not for hospitalization and medical intervention.

Table 17: Cases of Non-Fatal Serious Adverse Cardiac Events Induced by Ibogaine

Age, Sex, Year	**Diagnosis**	**Dosage ibogaine HCl mg/kg,**	**Ibogaine (blood, mg/L)**	**Electrolyte Levels**	**QTc (ms)**	**Reference**
Female, age 31, 2009	Long QT, VT?	3500	Not available	Low K, Mg	616	(Hoelen et al., 2009)
History, Pathology, Other Drugs: Alcoholism but no alcohol or other drugs						
Male, age 49, 2012	Long QT, VT, TdP	Not available	Not available	Low K	700	(Paling et al., 2012)
History, Pathology, Other Drugs: Heroin use disorder, hyperthyroidism and asthmatic symptoms, traces of opioids						
Female age 31, 2012	Long QT, TdP	8.75; estimated	Not available	Low K, Mg	616	(Paling et al., 2012)
History, Pathology, Other Drugs: Alcoholism; no other medication						

Female, age 43, 2012	Long QT	Not available	0.37	Low K	480	Paling, (Paling et al., 2012)
History, Pathology, Other Drugs: Heroin and benzodiazepine substance use disorder; on methadone						
Male, age 33, 2012	Long QT, VF	10; estimated	0.68	Not available	593	(Pleskovic et al., 2012)
History, Pathology, Other Drugs: No cocaine, heroin, or methadone for more than 48 hours						
Male, age 63, 2012	Long QT, VT, TdP	10.5 plus iboga extract	Not Available	Low K	498	(Shawn et al., 2012)
History, Pathology, Other Drugs: Heroin; short-acting opioids						
Male, young, 2013	Long QT, VT, TdP	17.5	Not Available	Not available	600	(Asua, 2013)
History, Pathology, Other Drugs: No alcohol, no heroin, and no methadone for more than 72 hours						
Male, age 26, 2014	Long QT, VT, VF	35	0.95	low K, Mg	663	(Vlaanderen et al., 2014)
History, Pathology, Other Drugs: Ibogaine taken for spiritual experience; healthy; no other drugs						
Male, age 39, circa 2014	Long QT, VT	7 grams total	Not available	<0.04, in normal range	730	(Hildyard et al., 2016)
History, Pathology, Other Drugs: No heroin within 2 days; no other drugs						
Female, age 46, circa 2016	Atrial tachy-cardia, long QT, VT, TdP	1400 mg total	1.45	Not available	647	(Henstra et al., 2017)
History, Pathology, Other Drugs: Opioid dependence; no other relevant history; no other drugs detected						
Male, age 33, 2015	Long QT		377			(O'Connell et al., 2015)
History, Pathology, Other Drugs: Opioid dependence; no other relevant history; no other drugs detected						
Male, age 61, 2018	Long QT, VF 270 beats per minute	60 to 70	Not available	Serum K was 2.4 mmol/L; serum Mg and Ca normal	714	(Steinberg & Deyell, 2018)
History, Pathology, Other Drugs: Opioid dependence; no other relevant history; no other drugs detected						

Female, age 43 2019	Long QT, TdP	2000	Not available	Serum K 3.4 mmol/L; serum Mg 2.7 mg/dL	788	(Grogan et al., 2019)
History, Pathology, Other Drugs: Opioid and cocaine dependence; urine drug screen showed presence of cannabinoids, cocaine, and opiates						
Long QT=a syndrome that impedes repolarization of the heart after heartbeat VF=ventricular fibrillation VT=ventricular tachycardia TdP=Torsades des Pointes						

The 43-year-old female in Table 17 who apparently took 3.5 g of iboga extract, which was said to contain 15% ibogaine, would have ingested 525 mg (approx. 7.5 mg/kg), which is a small dose. The subject's blood level was 0.37 mg/mL. Although this is lower than the blood levels of the other patients in this table for whom the blood level is known, the authors of the report described it as "potentially lethal" (Paling et al., 2012).

Noller et al. (Noller et al., 2018) discussed a death during their study of ibogaine-treatment providers in New Zealand:

Despite the study's evidence of positive outcomes, it remains that there are also specific risks associated with ibogaine. The most salient of these concerns is mortality temporally associated with treatment. Given the death during treatment of one subject pre-enrolled in the present study, this issue is of particular significance. As described above, the New Zealand death was the subject of two investigations, with a coronial inquiry supporting the earlier ruling of a failed duty of care by the treatment provider (Health & Disability, 2015). The coroner, however, also noted a lack of post-mortem and forensic evidence indicating any significant cardiac pathology or history, or other definable cause of death. Consequently, report suggests that the death was very likely "related to ibogaine ingestion and most probably related to a cardiac arrhythmia." Nonetheless, given the positive outcomes reported in this study and in a recent study of treatments in Mexico that both suggest that treatments are likely to continue (T. Brown, 2016), it is appropriate to discuss what is clearly a risk.

In Australia, the National Drugs and Poisons Schedule Committee noted in 2010 that the data suggested "the number of deaths due to ibogaine were lower than those associated with the use of methadone" (Committee, 2010). The medical literature has documented 34 fatalities following the ingestion of ibogaine, all but one of them by people outside of the traditional tribal rituals in West Africa. It is reasonable to estimate that at least 10,000 people outside of western Africa have used ibogaine or iboga root bark; if so, then almost 1 in 300 Westerners who have taken ibogaine have died. There were at least 19 deaths as of 2012 (K. R. Alper et al., 2012), 27 deaths as of 2016 (Litjens & Brunt, 2016), and 33 by 2018 (Corkery, 2018). (The 2018 article mistakenly reported 33 deaths due to double-counting one case). One of these fatalities was determined to be due to the non-pharmacological cause of a bleeding ulcer, and in another case the decedent had a congenital myocardial abnormality and drowned following iboga ingestion at a beach in Gabon (Chèze et al., 2008). A case not included in Table 15 below was a death that resulted from a woman ingesting another substance that was mislabeled as ibogaine by their internet supplier (Gicquel et al., 2016).

A substantial proportion of documented ibogaine-related fatalities have occurred in individuals self-administering ibogaine for the treatment of substance use disorder outside of clinical settings in which standard medical screening procedures would have been applied. Such procedures typically include exclusion of patients with significant cardiac compromise, enforcement of a defined abstinence period

from substances that could produce adverse pharmacological interactions, and clinical supervision during and following administration to enable management of any complications. The availability of ibogaine within regulated clinical settings would therefore be expected to provide safer environments for patient administration than the unregulated settings within which much existing administration occurs.

A review of 33 documented ibogaine-associated fatalities has characterized the demographic and clinical features of this case series (Corkery, 2018). The cohort included 25 male and 8 female decedents, with a mean age of 39.5 years (range 24–60 years). The therapeutic indication for ibogaine administration varied across cases: opioid detoxification in 26 cases, alcohol use disorder in 5 cases, methamphetamine use disorder in 2 cases, and religious or spiritual use in 3 cases. The form of ibogaine administered also varied: hydrochloride salt (n = 15), alkaloid extract (n = 5), root bark (n = 3), brown powder (n = 1), and unknown formulation (n = 9). Among the 16 cases for which postmortem blood concentrations were available, the mean ibogaine concentration was 2.11 mg/L (range 0.24–9.3 mg/L). Concomitant use of additional substances or medications was documented in at least 12 cases, and pre-existing medical comorbidities were identified in at least 18 cases. Among the 11 cases for which ethnicity was documented, 10 decedents were identified as white or of European descent, and one was identified as Black.

The geographic distribution of fatalities encompassed multiple countries: Mexico (n = 8), the United States (n = 7), the United Kingdom (n = 5), France (n = 4), the Netherlands (n = 2), and Cameroon, Costa Rica, Germany, Greece, New Zealand, South Africa, and Thailand (n = 1 each). The expanding geographic distribution of ibogaine-related fatalities has been observed to parallel the increasing international availability of ibogaine treatment services.

Table 18: Ibogaine-Induced Fatalities Reported in the Medical Literature

Case Number, Sex, Age, and Reference	**Official Cause of Death**	**Reason for Taking Ibogaine**	**Year of Death**	**Dose (ibogaine HCl unless otherwise indicated). Timing of death after last dose**
1. Female, age 44 (K. R. Alper et al., 2012)	Acute heart failure	Psychological-Spiritual	1990	Approximately 4.5 mg/kg, 300 mg Died 4 hours later.
Pre-existing conditions and background events: Hypertension; prior left-ventricular myocardial infarct, marked 3-vessel coronary artery atherosclerosis, and inverted T waves noted on EKG 3 months prior to death. Conditions contributing to death were atherosclerotic and hypertensive cardiovascular disease. Autopsy performed.				
2. Female, age 24 Alper et al., (K. R. Alper et al., 2012)	Official cause of death undetermined, but died of combined ibogaine and an opiate.	Opioid detoxification	1993	29 mg/kg Died in 19 hours after using ibogaine during treatment.
Pre-existing conditions and background events: Depression and adverse life events prior to treatment. Died from acute intoxication due to ibogaine possibly combined with surreptitious use of either morphine or heroin. Autopsy performed.				

3. Male, age 36 (K. R. Alper et al., 2012)	Acute intoxication due to combined effects of opiates, cocaine, and ibogaine.	Opioid detoxification and cocaine dependence	1999	Believed to be 16 to 20 mg/kg Died 8 to 9 hours later at home with a syringe near their body.
Pre-existing conditions and background events: Depression; adverse life events prior to treatment; decedent aware of dangers of use of cocaine or heroin concurrently with ibogaine. Benzoylecgonine: 0.6; Opiates: 0.1 (Morphine:<0.1). Autopsy performed.				
4. Male, age 40 (K. R. Alper et al., 2012) citing Kerr, (Kerr, 2001)	Fatal reaction to a Tabernanthe iboga extract. Contributing condition: hepatitis C.	Opioid detoxification	2000	6 g of Tabernanthe iboga extract administered over 6 hours. Died 40 hours later immediately after vomiting while at toilet.
Pre-existing conditions and background events: Hepatitis C with liver fibrosis; pulmonary and cerebral edema. This heroin user had hepatitis, which caused liver damage that facilitated the toxicity of the ibogaine. Blood toxicology results revealed ibogaine 0.38 µg/mL and positive for ibogamine. No prescription medications and no other substances were found in post-mortem toxicology results. This case resulted in restrictions on ibogaine in the U.K. Autopsy performed.				
5. Female age 35 (K. R. Alper et al., 2012)	Heart failure; intoxication	Psychological-Spiritual	2002	8 mg/kg (500 mg). Died 1.5 hours later.
Pre-existing conditions and background events: Acute ibogaine intoxication (unknown if other drugs involved). Contributing conditions: atherosclerotic cardiovascular disease. Autopsy performed.				
6. Male, age 32 (K. R. Alper et al., 2012)	Ibogaine intoxication. Contributing conditions: atherosclerotic cardiovascular disease, chronic cocaine use.	Self-administered detoxification for opiate	2003	Unknown quantity of brown powder that tested positive as ibogaine-alkaloid extract. Unknown how long until death.
Pre-existing conditions and background events: Moderate coronary artery atherosclerotic stenosis. History of opiate abuse, and had been in methadone maintenance treatment at time of death. Benzoylecgonine 0.1 Methadone:<0.1 Nordiazepam:<0.1. Autopsy performed.				
7. Male, age 54 (K. R. Alper et al., 2012)	Pulmonary thromboembolism	Opioid detoxification and alcoholism.	2003	13 mg/kg Died 60 hours later at Mexican ibogaine treatment facility.
Pre-existing conditions and background events: Obesity, chronic alcoholism, smoker (unclear if autopsy was performed; report unavailable)				

8. Male, age 45 (K. R. Alper et al., 2012)	Acute hemorrhagic pancreatitis. Contributing conditions: chronic alcoholism, obesity, and opiate pain-medication dependency.	Opioid detoxificiation and alcoholism	2004	15 mg/kg Died 20 hours later at ibogaine treatment facility.
Pre-existing conditions and background events: cardiac pacemaker. Autopsy performed.				
9. Female, age 48 (K. R. Alper et al., 2012)	Sudden cardiac death due to acute myocardial infarct due to acute coronary syndrome. Contributing conditions: Fibromyalgia, chronic pain-medication dependency.	Opioid detoxification	2005	14 mg/kg Died 2 days later in a Mexican ibogaine treatment facility.
Pre-existing conditions and background events: Prior gastric bypass surgery with 135 lb weight loss in 8 months preceding death. Fibromyalgia, benzodiazepine dependence that was not disclosed to treatment providers. Autopsy performed.				
10. Male, age 43 (K. R. Alper et al., 2012)	Valvular heart disease. Contributing conditions: Dilated cardiomyopathy.	Opioid detoxification and alcohol dependence	2005	Unknown quantity of ibogaine HCl. Had seizure 17 hours later and died 27 hours after last ingestion of ibogaine.
Pre-existing conditions and background events: Acute ibogaine intoxication. Contributing conditions: Mitral insufficiency with dilated cardiomyopathy. Dilated cardiomyopathy, coronary artery atherosclerosis, pulmonary edema, and hepatitis B. Diazepam: 0.03 [?]; trimethobenzamide: 0.85 [?]; benzoylecgonine: detected; ibogamine, ibogaline: detected. Autopsy performed.				
11. Male, age 51 (K. R. Alper et al., 2012)	Cardiorespiratory arrest due to acute myocardial infarction.	Dependence on opioids, meth-amphetamine, and alcohol	2005	12 mg/kg Died 24 hours later
Pre-existing conditions and background events: Cause of death determined by attending physician				

12. Male, age 36 (Corkery, 2018)	Ibogaine and opiate intoxication.	Detoxification from heroin	2005	Unknown dosage. Subject then used opiates while briefly unsupervised during ibogaine treatment. Died at an unofficial clinic in London 18 hours after taking ibogaine.
Pre-existing conditions and background events: Post-mortem toxicology: blood: ibogaine, 0.8 mg/mL; noribogaine not measurable but likely to be three times that of the parent drug; morphine (free), 0.04 µg/mL (11% present as unchanged morphine); diazepam, 0.04 µg/mL; nordiazepam, 0.07 µg/mL; temazepam, 0.001 µg/mL; zopiclone, low therapeutic level; desipramine (low therapeutic level); urine: alcohol, 2 mg/dL; ibogaine positive; THC (positive); stomach: nordiazepam (positive); ibogaine, <0.01 mg (probably back-absorption); zopiclone (positive; probably back-absorption); washing-up bowl containing vomit: ibogaine, 35 mg (total). Examined by the coroner.				
13. Male, age 38 (K. R. Alper et al., 2012)	Pulmonary thromboembolism	Opioid detoxification	2006,	13 mg/kg Died at Mexican clinic 12 hours later.
Pre-existing conditions and background events: Insufficient information due to inadequate autopsy				
14. Male, age 48 (K. R. Alper et al., 2012)	Acute ibogaine intoxication; unknown if other drugs were involved.	Unknown	2006	18 spoonfuls of powdered iboga root bark mixed with condensed milk Died 56 hours later in meditation room.
Pre-existing conditions and background events: History of substance abuse; pulmonary edema; buprenorphine tablets found at site of death. Autopsy performed.				
15. Male, age 28 (K. R. Alper et al., 2012)	Hemorrhagic complications of duodenal ulcer. Low levels of ibogaine and Cannabis found in system, so toxicological cause of death was determined to be unlikely.	Opioid detoxification	2006	Unknown dosage Died 76 hours later.
Pre-existing conditions and background events: Choroid plexus papilloma involving hippocampus with hypoxic damage to hippocampus; large duodenal ulcer with accumulation of blood in duodenum. Possible causal or contributing factors were hemorrhagic complications of duodenal ulcer, increased intracranial pressure resulting from obstruction of third ventricle, and partial seizures originating from the temporal lobe. Autopsy stated: ‘‘Toxicological cause not likely”.				
16. Male, age 30 (K. R. Alper et al., 2012)	Cardio-respiratory collapse secondary to drug-related illness.	Opioid detoxification	2006	Single dose of 17 mg⁄kg (1.75 g) Died 8 hours later en route to hospital.
Pre-existing conditions and background events: Autopsy not performed.				

17. Male, age 27 Alper et al., 2012 (K. R. Alper et al., 2012) and Corkery, 2018 (Corkery, 2018) citing: (Mazoyer et al., 2012), 2013 (Mazoyer et al., 2013)	Drug overdose due to ibogaine and therapeutic levels of methadone and diazepam. Temazepam also found in autopsy.	Unknown	2006	19.5 g iboga root bark (estimated) Died 12 hours after ingesting iboga in treatment program.
Pre-existing conditions and background events: History of polydrug abuse. Autopsy 8 days after death.				
18. Male, age 45 (K. R. Alper et al., 2012)	Acute intoxication due to ibogaine, fentanyl, and diazepam.	Opioid detoxification	2006	22 mg/kg Died 8 to 12 hours later.
Pre-existing conditions and background events: Hepatic steatosis; diazepam, 77 ng⁄mL; fentanyl, 1.2 ng⁄mL; norfentanyl, 1.5 ng⁄mL. Qualitative urine screen detected oxycodone, alphahydroxyalprazolam, oxazepam, temazepam, and ephedrine⁄pseudoephedrine.				
19. Male, age 33 (K. R. Alper et al., 2012)	Pulmonary thromboembolism (diagnosis may be inaccurate).	Detoxification from opioids and crack cocaine dependence.	2007	11 mg/kg Died in Mexican clinic 6.5 hours after last ibogaine ingestion.
Pre-existing conditions and background events: Caught using cocaine during a prior admission to the clinic where they died. Patient's father had pulmonary thromboembolism. The attending physician at the time of death wrote "pulmonary thromboembolism" on the death certificate but the autopsy was inadequate to determine the proximate cause of death.				
20. Male, age 41 (K. R. Alper et al., 2012)	Fatal arrhythmia with cardiac hypertrophy.	Detoxification from opioids and cocaine dependence.	2007	13 mg/kg; 1080 mg total Died at Mexican clinic 6 hours after last ibogaine ingestion.
Pre-existing conditions and background events: Cardiac hypertrophy. Autopsied in the U.S.				
21. Male, age 37. (Chèze et al., 2008)	Drowning and myocardial bridging.	Unknown	Case published in 2008	Decedent was assumed to have been under the influence of an unknown dosage of iboga root when he drowned.
Toxicology results: ibogaine: m/z 311.4 □ 122.1, 174.1 and 188.1; noribogaine: m/z 297.4 □ 122.1, 159.1 and 160.1; clonazepam-d(4): m/z 319.9-->218.1, 245.1 and 274.1.				
22. Male in early 50s (Corkery, 2018)	Acute and chronic toxic effects of drugs (including iboga, heroin, and alcohol).	Cure long-term substance use disorder to alcohol, heroin, and diazepam.	2009	Dosage unknown. Perished at an unofficial self-help treatment center.

Pre-existing conditions and background events: Post-mortem toxicology was positive for ibogaine, noribogaine, unspecified tryptamine, oxycodone and mirtazapine. Had formerly used methadone but was not known to be on prescription medications.				
23. Female, age 60 Corkery, 2018 (Corkery, 2018) citing: (Myeboga, 2018)	Cause of death not released.	Methadone substance use disorder	2009	Unknown dose. Died in a Mexican ibogaine facility.
Pre-existing conditions and background events: 15-year history of methadone use, a history of hepatitis B managed with interferon, and a thyroid condition				
24. Female, age 32 Corkery, 2018 (Corkery, 2018) citing: (Black, 2011; Newenham, 2011)	Likely cardiac arrest associated with iboga consumption.	Consumed iboga at a shamanic ritual in Africa.	2010	Unknown quantity of iboga root.
Pre-existing conditions and background events: Healthy athlete with no history of drug use other than one previous experience with iboga. A post-mortem found fluid in the lungs, soft tissue hematomas, and an iboga blood level of 0.4 mg/L.				
25. Male, age 25 (Warrick & Baltarowich, 2012)	Cardiac arrest from ventricular tachycardia and ventricular fibrillation.	Self-administered detoxification from heroin.	Case published in 2012.	Ingested 2 g of ibogaine. After ingestion, subject developed seizures, hypotension, and hyperthermia. Died in hospital.
Pre-existing conditions and background events: A history of cardiac dysrhythmias and heroin abuse.				
26. Male, age 25 Corkery, (Corkery, 2018) citing: Jalal et al., (Jalal et al., 2013) and Bronstein et al., (Bronstein et al., 2012)	Cardiac arrest and multi-organ failure.	Self-administered detoxification from heroin.	Case published in 2012 and 2013.	Exact dose is unknown, but may have been 2.5 g of pure ibogaine. After ingestion, subject had a heart attack, problems breathing, and seizure activity. Died in hospital the next day.
Pre-existing conditions and background events: A history of supraventricular tachycardia.				
27. Male, age 52 Corkery, (Corkery, 2018) citing Papadodima et al., (Papadodima et al., 2013)	Ibogaine-related cardiac fatality in conjunction with liver disease.	Detoxification from alcoholism.	Case published in 2013.	Decedent consumed botanical preparation containing ibogaine. Died 16.45 hours after leaving "therapist".
Pre-existing conditions and background events: 20-year history of alcoholism. An autopsy revealed: (a) cerebrospinal fluid shunt; (b) slightly increased weight of the heart with coronary lesions causing occlusion of the left and right coronary arteries; (c) pulmonary edema; and (d) a small yellowish nodular and firm liver indicating cirrhosis and heavy fatty infiltration. Histopathology also revealed recent ischemia of the myocardium and an extremely fatty (more than 90%) liver.				

28. Female, age 45 Corkery, 2018 (Corkery, 2018) citing; (Chilton-Towle, 2014; Roden, 2015; Stewart, 2015; Tan, 2015)	Suspected heart Attack.	Detoxification from polydrug abuse including morphine.	2013	Four doses of unknown quantity; between 25 and 55 mg/kg. Died 23 hours later at a New Zealand iboga clinic.
Pre-existing conditions and background events: Patient left unsupervised by their incompetent physician.				
29. Male, age 33 Corkery, (Corkery, 2018) citing: (Cheer, 2015; Drummond, 2015a), 2015b (Drummond, 2015b)	Ibogaine and diazepam, and an undiagnosed heart problem.	Cure for methamphetamine use disorder.	2014	Patient was given two doses of ibogaine. Two hours later patient received two tablets of diazepam and stopped breathing 20 minutes later. Died at the treatment center in Thailand.
Pre-existing conditions and background events: Clinic owners denied administering ibogaine, but it was found in autopsy.				
30. Female, age 42 Corkery, 2018 (Corkery, 2018) citing (Amundsen, 2015; Amundsen et al., 2015; Delgado & Bran, 2015), and (Lopez, 2015)	Use of ibogaine and myocardial infarction.	Detoxification from Methadone.	2014	Unspecified amount of ibogaine. Found dead the next day at treatment clinic in Costa Rica.
Pre-existing conditions and background events: History of polydrug abuse and heroin use disorder; an EKG the month before death did not show any abnormality.				
31. Male, age 53 Corkery, 2018 (Corkery, 2018) citing: (Proctor, 2015)	Acetone and ibogaine overdose.	Self-detoxification from heroin and methadone.	2014	Unknown quantity of white ibogaine powder purchased on the internet. Found dead the next day.
Pre-existing conditions and background events: An autopsy revealed that, with regard to the heart, the myocardium showed mild dilation of the left ventricle, the thickness here being 14 mm compared to 4 mm for the right ventricle. The lungs were deeply congested, with mild to moderate edema, and areas of fresh hemorrhage. Some steatosis was present in the liver. Post-mortem toxicology: Acetone: blood, 3 mg/dL; urine, 95 mg/dL (indicating extreme ketosis); ibogaine: blood, 3.33 μg/mL; free morphine: blood, 0.01 μg/mL; urine, positive; cocaine: urine positive. The coroner concluded that the deceased suffered a drug-related death. It is believed the subject previously used ibogaine in 2004.				
32. Male, age 36 Corkery, 2018 (Corkery, 2018) citing: (Carr, 2017; Coats-Ledden, 2017)	Combined effects of ibogaine and morphine or heroin intoxication.	Detoxification from heroin.	2015	Dose not stated. Died at an unregistered ibogaine clinic in U.K. after a seizure and cardiac arrest. Subject appears to have used heroin during treatment.

Pre-existing conditions and background events: An autopsy revealed no evidence of natural diseases that caused or contributed to death: there was severe congestion of the lungs, with patchy alveolar hemorrhage and edema; the liver showed signs of congestion and mild fatty change; the kidney was severely congested; the brain showed early changes of hypoxiaischemia in the cerebellum and hippocampi. Post-mortem toxicology indicated the ingestion of morphine/heroin in the hours prior to death with a free morphine level of 0.048 mg/L. Ibogaine was detected in the urine.				
33. Male, age 40 Corkery, 2018 (Corkery, 2018) citing: (Meisner et al., 2016)	Ibogaine-induced cardiac arrest.	Self-detoxification from heroin.	Case published in 2016.	4 g ibogaine followed by 2 g of uncharacterized booster; 8 hours later subject was found covered in vomit and having a cardiac arrest.
Pre-existing conditions and background events: The patient received morphine for unknown reasons upon arrival at the hospital. Corkery's report did not mention if this contributed to an adverse drug interaction. Laboratory tests showed leukocytosis, anion gap metabolic acidosis, and an elevated creatinine level. Head computerized tomography suggested anoxic brain injury. On arrival, the patient had signs of severe anoxic brain damage; however, an electroencephalogram (EKG) displayed no activity of definite cerebral origin. EKG recordings showed a significant lengthening of the QT interval, later returning to a level similar to that on admission. A clinical examination was consistent with brain death, confirmed by the patient failing an apnea test and a brain perfusion scan. Artificial respiration was disconnected following brain death, and this led to the fatal cardiopulmonary death.				
34. Male, age 26 Corkery, 2018 (Corkery, 2018) citing: (Gummin et al., 2017)	Brain death following ibogaine-induced cardiac arrest.	Detoxification from oxycodone.	2016	Dosage unknown. 48 hours later, patient possibly had a seizure; hospitalized and died 14 days later after a second cardiac arrest.
Pre-existing conditions and background events: History of polydrug abuse and previous ibogaine use. Medical responders administered midazolam, naloxone, and epinephrine, which do not compete for CYP2D6. No autopsy was performed.				

In the review article of 27 fatalities reported in the medical literature by 2016, Litjens and Brunt (Litjens & Brunt, 2016) stated there were eight cases that "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" (Litjens & Brunt, 2016). The authors note that in most case reports of cardiotoxicity, the dose of ibogaine was over 2 grams and it was not clear whether the drug was pure or not. The authors stated that open-label trials used lower doses, and [that?] this is probably why ibogaine was well-tolerated in those studies. Yet, the 191 participants in Mash's open-label study took doses of 8 to 12 mg/kg (Mash et al., 2018), which were only slightly lower than the doses (11 to 17 mg/kg) used by people who died with no apparent risk factors.

In the earlier study of 19 fatalities, 14 had autopsies among which for 12 cases death could be attributed to a co-morbidity (six of them cardiac co-morbidity) or concurrent use of other substances. In 11 of the 14 cases, other drugs were found in the bodies, indicating the possibility of adverse drug interactions contributing to the deaths. In two cases there were seizures. A generalized tonic-clonic seizure (GTCS, a.k.a. "grand mal seizure") in one case might have been due to alcohol or benzodiazepine withdrawal. In another death, a brain neoplasm might have caused the seizures (K. R. Alper et al., 2012).
A more recent analysis substantially expanded the evidence base on ibogaine-associated mortality and, importantly, examined whether risk is uniform across treatment indications or concentrated in specific populations (Arns et al., 2026). This work combined a retrospective multisite inventory of 19,071 patients

treated under established safety guidelines at 11 international clinics with an updated systematic review of reported fatalities. In the clinical cohort, six deaths occurred within 72 hours of administration (0.03%; 0.3 per 1,000), all in patients treated for opioid use disorder (6 of 10,382; 0.06%) and none among the 8,689 patients treated for non–substance-use-disorder (non-SUD) indications (Fisher's exact P = 0.026). All deaths occurred in males aged 45–49 at doses of 14–15 mg/kg, and the reported causes were consistent with cardiotoxicity; the implicated opioids were fentanyl (n = 3), heroin (n = 1), methadone and oxycodone (n = 1), and an unspecified opioid (n = 1).

The accompanying systematic review updated prior inventories to 48 reported deaths between 1990 and 2026 across 15 countries. In the combined dataset, 41 of 44 fatalities with a known indication (93.2%) occurred in individuals treated for SUD—predominantly opioid detoxification—a distribution highly inconsistent with chance (binomial $P = 1.6 \times 10^{-9}$); all three non-SUD deaths predated the 2016 safety guidelines and occurred in non-clinical or ceremonial settings. Mean annual fatality counts were lower in the post-guideline period (2017–2026) than before (1.1 vs. 2.15; P = 0.04). The authors emphasised that the observed absolute rate should be interpreted as a lower bound, given voluntary clinic participation and self-reported, non-adjudicated deaths; a sensitivity analysis indicated that overturning the finding of low contemporary mortality would require an implausible number of unobserved deaths (roughly 42–52 across the non-participating sites). Taken together, these data indicate that ibogaine-associated mortality under contemporary, guideline-concordant care is low and clusters in the opioid-detoxification population, reinforcing the importance of cardiac screening, electrolyte management, and careful patient selection—particularly the exclusion or extended washout of patients with recent fentanyl exposure—in forthcoming trials.

As shown in the preceding chart of 34 Ibogaine-Induced Fatalities Reported in the Medical Literature, pre-existing cardiac abnormalities were involved in 12 cases (numbers 1, 5, 6, 8, 10, 20, 21, 25, 26, 27, 29, and 31), and pre-existing liver disease was involved in three cases (numbers 4, 23, and 27). Other drugs producing adverse interactions with ibogaine were involved in 10 cases (numbers 2, 3, 12, 17, 18, 22, 29, 31, 32, 33], although it is unclear how often these other drugs were present at levels high enough to contribute to toxicity. There were 21 cases involving one or more of these risk factors. The fatality in case #15 was due to an ulcer apparently unrelated to ibogaine consumption.

The literature suggests that a significant factor in the cardiac ibogaine-induced fatalities is an interaction of prolonged QT interval or a pre-existing cardiac condition exacerbated by a bradycardia induced by ibogaine. The QT interval prolongation may be congenital, which would be picked up by an EKG, or due to other medications which can affect QT, or due to the participant being a poor metabolizer of CYP2D6 which converts ibogaine to noribogaine. Glue et al. (Glue, Winter, et al., 2015) reported that the overall exposure to ibogaine and noribogaine were increased in healthy volunteers pre-treated with the CYP2D6 inhibitor paroxetine (Glue, Winter, et al., 2015). This suggests that poor CYP2D6 metabolism is a significant risk and warrants screening to avoid potentially fatal outcomes.

In 11 cases (numbers 7, 9, 11, 13, 14, 16, 19, 24, 28, 30, and 33) the decedent had no known heart disease and no other drugs are known to have contributed to the death. Nine decedents were people attempting detoxification from substance use disorders, case #13 had a history of substance abuse but may have been using iboga root bark for meditation, and case #24 was a drug-free athlete. These cases are outlined below:

- Case #7: 13 mg/kg caused death from pulmonary thromboembolism. It is unclear if an autopsy was performed; if not, then no report is available. The individual was an obese smoker and alcoholic.
- Case #9: 14 mg/kg caused death from acute myocardial infarct. The subject had fibromyalgia in addition to gastric bypass surgery 8 months prior to death.
- Case #11: 12 mg/kg caused death from acute myocardial infarction.

- Case #13: 13 mg/kg caused death from pulmonary thromboembolism. An inadequate autopsy was performed.
- Case #14: Iboga root bark caused death from "acute ibogaine intoxication."
- Case #16: 17 mg/kg caused death from cardio-respiratory collapse. No autopsy.
- Case #19: 11 mg/kg caused death from pulmonary thromboembolism (this diagnosis may be inaccurate). An inadequate autopsy was performed.
- Case #24: The decedent was the well-known Irish tennis and squash player Laura Thornton. This healthy 32-year-old athlete died from ingesting an unknown quantity of iboga in an African religious ceremony and a nurse was unable to revive the decedent. The subject had no drug history other than having taken iboga on one previous occasion for spiritual purposes. News reports referred to the ritual as an initiation, so the dose of root bark may have been high.
- Case #28: An unknown quantity of ibogaine caused a suspected heart attack.
- Case #30: An unspecified dose of ibogaine caused myocardial infarction.
- Case #22: An unknown dose of ibogaine caused a seizure, cardiac arrests, and death.

Brunt and Litjens (Brunt & Litjens, 2016) cautioned that cardiotoxic effects and fatalities have been associated with modest concentrations "as in some therapeutic sessions a few mg/kg ibogaine HCl was used or 2-6 g of only a 15% extract, amounting to no more than 10 mg/kg ibogaine" (Brunt & Litjens, 2016). Indeed, in all of the six aforementioned cases for which the dose was known (numbers 7, 9, 11, 13, 16, and 19), the dosage ranged from 11 to 17 mg/kg, which is within a conservative therapeutic range. In at least four of these six cases (numbers 7, 13, 16, and 19), there was no autopsy or an inadequate autopsy, so it is possible that there were pre-existing cardiac problems or drug interactions that were not reported.

This leaves two cases that deserve particular attention. The death in case #9 occurred at a Mexican ibogaine clinic 2 days after the patient took 14 mg/kg, and there was an autopsy. The death in case #11 occurred 12 hours after the patient took 12 mg/kg. This patient did not have an autopsy, but the death occurred in a Mexican ibogaine clinic so presumably the patient was screened for contraindications upon intake. It is conceivable that if these two patients had been given a CYP2D6 genotype test, then that might have revealed them to be poor metabolizers who either should have been given even smaller doses than what they took or who should have been screened out entirely.

In summary, reviews of the existing literature indicate that a majority of fatalities reported to be related to ibogaine were cardiac in nature, and likely due to pre-existing cardiac conditions or prolonged QT complicated by interactions with other drugs. The compounded effect of cardiac complications added to bradycardia secondary to an increased pharmacokinetic duration of ibogaine resulting from poor CYP2D6 metabolism may constitute a significant mechanism in accounting for recorded fatalities. These factors can be screened for in a controlled medical environment, potentially reducing the risks significantly. However, these findings suggest that for a very small number of people who have no known or identifiable cardiac risk factors, therapeutic doses of ibogaine in clinical settings can be fatal.

Suicidal Ideation and Behavior

The Global Ibogaine Therapy Alliance includes suicidal ideation and/or attempts as a risk factor requiring "proper therapeutic support" before treatment with ibogaine (Dickinson, 2015). Notably, the MISTIC trial (Cherian et al., 2024) reported that suicidal ideation in 30 SOF veterans with TBI dropped from 47% at baseline to 0% immediately post-treatment and 7% at 1-month follow-up ($p < 0.001$) with these reductions sustained at 12-month follow-up (Cherian et al., 2024);(Lissemore et al., 2025), suggesting that with appropriate screening and a controlled clinical context, ibogaine therapy may produce rapid and sustained reductions in suicidal ideation alongside its other antidepressant and anxiolytic effects in some populations. However, these conclusions should be interpreted with caution, and further research would be needed to come to move substantive conclusions.

Cardiovascular System

There are several case reports of ibogaine causing non-fatal heart problems (Henstra et al., 2017; O'Connell et al., 2015; Paling et al., 2012; Steinberg & Deyell, 2018). Henstra et al. (Henstra et al., 2017) reported:

Our patient developed markedly prolonged QTc interval of 647 ms maximum, several multiple cardiac arrhythmias (i.e., atrial tachycardia and ventricular tachycardia and Torsades des Pointes). QTc-prolongation remained present until 12 days after ingestion, several days after ibogaine plasma-levels were low, implicating clinically relevant noribogaine concentrations long after ibogaine had been cleared from the plasma. The ratio k12/k21 for noribogaine was 21.5 and 4.28 for ibogaine, implicating a lower distribution of noribogaine from the peripheral compartment into the central compartment compared to ibogaine (Henstra et al., 2017).

Hepatic Effects

There is no evidence that ibogaine has clinically meaningful hepatic effects in standard clinical case series; however, a liver with low levels of the enzyme CYP2D6 can be expected to lead to altered pharmacokinetics. The (Ramanathan & R Pradhan, 2022) case of severe rhabdomyolysis with secondary acute liver injury in a patient who consumed unanalyzed iboga powder (described in Section 5.1.3) is the principal exception in the published literature, but is heavily confounded by the unknown alkaloid content of the ingested material. Pre-treatment hepatic function evaluation is recommended as standard practice. See Sections 4.1.7 and 5.1.3 for further detail.

Cognition and Performance

Given the varying thresholds for neurotoxicity observed across animal species, preclinical data cannot conclusively determine the ibogaine exposure levels associated with neurotoxic risk in humans. A review of 19 ibogaine-associated fatalities documented as of 2012 identified no clinical or postmortem evidence supporting the occurrence of neurotoxicity in humans (K. R. Alper et al., 2012). For example, neuropathological examination of a woman who died in 1994 of causes unrelated to ibogaine—following four prior ibogaine exposures at doses ranging from 10 to 30 mg/kg, with the first administration 15 months prior to death and the final administration 25 days prior to death—revealed no evidence of cytopathological or neurodegenerative changes within the cerebellum or any other brain region, nor evidence of astrocytosis or microglial activation (K. R. Alper et al., 2001).

Ibogaine administration can produce acute, though non-persistent, impairments in cognitive function. These effects do not represent significant safety concerns within a controlled clinical setting. Consistent with the cognitive profile of other psychedelic compounds, cognitive function during the acute phase may be characterized either by transient disorganization or by the integration of disparate concepts into novel synthetic insights. Cognitive processing during the acute ibogaine experience has been characterized as more visual than verbal, more symbolic than literal, and more holistic than linearly sequential in nature. The visionary content associated with ibogaine has been described as more dream-like than the perceptual phenomena typically associated with classical hallucinogens, with some individuals reporting the recall of repressed or traumatic memories (Heink et al., 2017).

Abuse Potential

Ibogaine is not characterized by habit-forming or dependence-producing properties. The compound has been assessed as carrying low abuse potential among individuals who use substances recreationally,

owing both to the psychoactive effects not being subjectively pleasurable in a manner that promotes repeated administration, and to physical adverse effects, including nausea and ataxia, that range from disagreeable to substantially uncomfortable (K. R. Alper et al., 2006).

The psychologically and physically challenging character of the ibogaine experience renders it unappealing as a recreational substance. The experience of ibogaine is often described as unpleasant or even harrowing (T. K. Brown et al., 2019). In a qualitative study of 10 individuals who underwent ibogaine treatment at a medical facility in Mexico, 80% described their ibogaine experiences as physically draining, with one participant saying the experience felt as though he "survived cancer" (Camlin et al., 2018).

Although recognition of the therapeutic potential of ibogaine in the treatment of substance use disorder is increasing, ibogaine remains legally unavailable within numerous countries, including the United States. Consequently, individuals seeking to attenuate drug craving or withdrawal symptomatology through ibogaine administration frequently obtain treatment through herbalists or other alternative practitioners. The expanded availability of ibogaine within regulated clinical settings would be expected to reduce the public health burden associated with administration in unregulated contexts.

Summary of Data and Guidance for the Investigator

Ibogaine is currently being investigated for its therapeutic potential in treating drug-dependence disorders, with a rapidly expanding evidence base also supporting its potential utility in traumatic brain injury and post-traumatic stress disorder, treatment-resistant depression, neuropathic pain, and several emerging neurological indications. Data collected from open-label studies, the recent magnesium-ibogaine MISTIC trial (Cherian et al., 2024), and an extensive body of case reports suggest that ibogaine can be used to great effect to assist in detoxification from opioid dependency, among other types of drug dependencies.

The ibogaine doses administered in clinical trials and informal settings vary considerably. The highest oral ibogaine dose regarded to be safe in healthy volunteers and which shows a good tolerability profile is 20 mg (Forsyth et al., 2016; Glue, Winter, et al., 2015), while much larger doses (typically 8–14 mg/kg) have been safely administered in many cases under cardiac monitoring (Cherian et al., 2024; Knuijver et al., 2022; Mash et al., 2018).

The contemporary regulatory landscape for ibogaine is changing rapidly. (Yockey, 2025) summarized the key recent developments, including Texas's $50 million public-private partnership for FDA-regulated ibogaine clinical trials in opioid use disorder, PTSD, and TBI; Colorado's Natural Medicine Health Act creating licensed "healing centers"; and similar ibogaine-specific legislation in New York, Washington, and Kentucky. (Söderberg & Lundgren, 2025) additionally documented a $42 million state investment in ibogaine research in Kentucky. The UK Medicines and Healthcare products Regulatory Agency (MHRA) has granted approval for subject enrollment in a Phase 1/2a clinical trial of ibogaine HCl for opioid use disorder (Mash, 2023). (Swieczkowski et al., 2025), in a cross-sectional analysis of nine ibogaine clinical trials registered across ClinicalTrials.gov, EU registries, and the WHO ICTRP, found that early-phase trials currently dominate, with no large-scale late-phase trials yet underway. This Investigator's Brochure is intended to support the design and conduct of such trials.

The use of ibogaine for detoxification should be conducted in conjunction with some form of counseling such one-on-one discussions and possibly peer-group sessions, along with referral to post-treatment aftercare programs and community support groups such as 12-step meetings.

Best Practices for Clinical Use

The following highlights some best practices for the clinical use of ibogaine drawn from the existing literature.

Outcome Measures

Clinicians can gather data to record the effectiveness of ibogaine in treating substance abuse. This data may lead to a more effective way to conduct ibogaine detoxification, and it may also enable clinicians to more accurately predict which type of patients are most likely to benefit and which are not likely to benefit. For example, (Mash et al., 2001) used two instruments to evaluate withdrawal and drug craving during opiate detoxification. They developed the Opiate-Symptom Checklist to assess withdrawal symptoms using 13 items taken from the Hopkins Symptom Checklist-90. They also used the Beck Depression Inventory and E.G. Singleton's Heroin Craving Questionnaire, which is available from the Clinical Pharmacology and Therapeutics Branch, Intramural Research Program, NIDA (Mash et al., 2001).

Standardized outcome measures recommended for use in contemporary trials include COWS (Clinical Opioid Withdrawal Scale), SOWS (Subjective Opioid Withdrawal Scale), and BSCS (Brief Substance Craving Scale) for opioid withdrawal and craving (Malcolm et al., 2018); CAPS-5 and PCL-5 for PTSD; MADRS for depression; HAM-A for anxiety; and WHODAS for functional disability (Cherian et al., 2024). For characterizing the subjective ibogaine experience, the validated 70-item, seven-factor Ibogaine Experience Scale (IES) (González Espejito et al., 2025) provides the first ibogaine-specific multidimensional instrument and is recommended for adoption in future clinical trials. The Mystical Experiences Questionnaire (MEQ30) has also been used in the MISTIC trial and demonstrated significant predictive value for PTSD outcomes, paralleling its role in psilocybin trials ((Lissemore et al., 2025)).

Investigational Supply

Sigma-Aldrich supplies ibogaine HCl under the catalog number 17003. GMP-grade ibogaine HCl is available from Phytostan Enterprises (South Africa, 98% purity) and has been used in the most recent controlled clinical studies including the Knuijver et al. (2022, 2024) Dutch trials. DemeRx Inc. is developing DMX-1002 as a GMP oral noribogaine product, and atai Life Sciences is developing IBX-210 as a GMP intravenous ibogaine formulation. Because *Tabernanthe iboga* is being depleted in the wild by overharvesting and poaching, ibogaine should ideally be sustainably sourced from plantation-grown iboga or produced semi-synthetically from voacangine, found extractable at 0.5% in *Voacanga africana*, or derived from *Tabernaemontana* species. The molecular networking case (Allard et al., 2020), in which a powder labelled as *T. iboga* was found by LC-MS/MS to contain only *Rauwolfia* alkaloids (ajmaline, reserpine, yohimbine), highlights the critical importance of analytical confirmation of any non-pharmaceutical-grade material; and it was documented (Edwards et al., 2025) in the UK National Poisons Information Service case series that the contemporary unregulated supply chain includes online vendors, dealers, and shamans of variable reliability. Analytical confirmation of identity, alkaloid content, and purity should be considered a baseline requirement for any clinical study.

Reducing Risks/Maximizing Benefits

The subjective experiences of veterans receiving the magnesium–ibogaine protocol have been characterized as representing a compressed form of therapeutic processing within a single intensive session, encompassing trauma-related content, alterations in self-experience, emotional resolution, and reports of perceived neurobiological change (Olash et al., 2026). Complementary phenomenological taxonomies derived from observational studies of ibogaine treatment have provided frameworks for anticipating, normalizing, and integrating the subjective content reported by patients (Kohek et al., 2020). Recognizing the heterogeneity of various longstanding cultural and traditional uses, contemporary ibogaine clinical practice, Brazilian clinics, Mexican clinics (Ozmat et al., 2024), Vancouver underground providers (Wilson et al., 2021), and the broader international medical subculture (Söderberg & Lundgren,

2025), clinicians designing new programs should seek to actively engage and consult with those currently experienced with the safe administration of ibogaine-assisted therapies and practices, and consider and adopt the elements of practice that the literature has identified as protective and explicitly avoid the elements that have been associated with adverse outcomes.

Aftercare

In a retrospective study, approximately 23% of 73 opioid-substance use disorder patients mentioned having difficulty integrating their ibogaine experience into their daily lives, which emphasizes the need for a structured program of recovery following detoxification (Davis et al., 2018). The conditions to which patients return following ibogaine administration are likely to influence treatment outcomes (T. K. Brown, 2013). Effective aftercare typically requires a multimodal approach incorporating elements that may include continued engagement with the patient's social support network, structured residential or outpatient treatment programs, participation in mutual support groups, ongoing psychotherapeutic support for integration of the subjective experience, and, where clinically appropriate, maintenance medication for substance use disorder using evidence-based pharmacotherapies.

The acute therapeutic effects of ibogaine may attenuate over time, and ibogaine should not be conceptualized as a comprehensive standalone treatment for substance use disorder. Ethnographic observation has noted that the maintenance dose used by Bwiti practitioners during routine ceremonial participation is well below one-tenth of the dose administered during initiation, and is similarly lower than doses employed within contemporary self-help networks for personal growth applications (Fernandez & Fernandez, 2001).

Drug craving following detoxification typically recurs in cyclical patterns, with greater frequency during the early recovery period and progressively longer intervals between episodes as recovery continues. A hypothetical aftercare protocol incorporating low-dose ibogaine administration has been proposed as a potential pharmacological strategy for attenuating the periodic recurrence of craving, even at doses producing minimal psychoactive effects. Such adjunctive pharmacological support would be expected to be most effective when administered in conjunction with concurrent participation in mutual support groups or other recovery-focused psychosocial interventions.

For patients receiving low-dose ibogaine following detoxification, periodic toxicological screening may be clinically appropriate. The principal rationales for such screening include verification of continued abstinence and identification of relapse, particularly given the elevated overdose risk associated with the post-detoxification reduction in opioid tolerance, a pharmacological state in which the reintroduction of opioid use carries substantially increased risk of respiratory depression and fatal overdose.

A case report has documented the use of multiple low ibogaine doses administered across a six-week period in the treatment of methadone use disorder in a 17-year-old female patient, with reductions in withdrawal symptomatology observed following each administration (Wilkins et al., 2017). This case provides preliminary support for the consideration of multiple-dose protocols extended across protracted treatment periods. Given the cyclical character of post-detoxification craving—with episodes occurring more frequently during early recovery and progressively dissipating across weeks, months, and years—further investigation of low-dose ibogaine maintenance protocols, whether administered under direct clinical supervision or through carefully structured self-administration frameworks, may be warranted to evaluate their utility in attenuating the recurrent craving that persists beyond acute detoxification.

Contraindications

Absolute contraindications to treatment with ibogaine are:

- Concomitant use of medication or drugs that prolong the QT interval (including but not limited to: ketoconazole, erythromycin, loratadine, ebastine, lithium, imipramine, cocaine, methadone, buprenorphine, ondansetron, quetiapine, and many others). The case of multiple cardiac arrests at 2.6 mg/kg ibogaine in a buprenorphine-maintained patient (Mestre et al., 2024), and the Client 2 case of QTc 512 ms following self-administered quetiapine during an iboga ceremony (Wilson et al., 2021).
- Pre-existing cardiac conditions and medical risk factors for developing Torsade de Pointes or prolongation of the QT interval, including congenital long-QT syndrome, structural heart disease, prior myocardial infarction, dilated cardiomyopathy, and significant coronary artery disease.
- Concomitant use of drugs, foods, and supplements that inhibit the CYP2D6 enzyme (including but not limited to: bupropion, fluoxetine, paroxetine, cinacalcet, quinidine, grapefruit juice, St. John's Wort). The PK/PD analysis demonstrated more than ten-fold variation in ibogaine clearance across CYP2D6 activity score, supporting CYP2D6 genotyping or phenotyping as standard pre-treatment screening (Knuijver et al., 2024).
- Significantly impaired renal or liver function.
- Positive test results for identified drugs of abuse on day of ibogaine administration.

Additionally, treatment providers should make a risk-benefit assessment regarding the following additional potential contraindications:

- Pregnancy or breastfeeding;
- Active psychiatric disorders, particularly active psychosis or mania;
- Previous prolonged or highly adverse reaction to hallucinogens, including prior hallucinogen-persisting perception disorder (HPPD) — see the HPPD case report (Knuijver et al., 2018);
- Personal history of epilepsy or unprovoked seizures;
- Eating disorders or significantly malnourished state;

Obstructive sleep apnea, severe COPD, or asthma poorly controlled, relevant given the prolonged sleep-like state during the dosing session and the absence of plethysmography data establishing a primary respiratory liability of ibogaine

This assessment should entail a holistic evaluation of the patient's entire presentation, viewed in the context of the particular provider's ability to manage the possible complications that might arise.

Pharmacology

The pharmacology of ibogaine is complex because it interacts with multiple neurotransmitters, some of which then affect other neurotransmitters.

Effects on opioid systems: Ibogaine binds to kappa-opioid receptors and shows weak affinity at mu and delta sites. More recent multi-laboratory work has characterised ibogaine, noribogaine, and 18-MC as functional μ-opioid receptor antagonists rather than agonists in standard cAMP and arrestin assays (Antonio et al., 2013), and the broader indole-alkaloid biased-agonism framework articulated by Grundmann and Henderson (2026, preprint) proposes that any residual opioid receptor activity is selectively G-protein-biased and therefore relatively spared of β-arrestin-mediated respiratory depression. (Maillet et al., 2015) characterised noribogaine specifically as a biased κ-opioid receptor agonist.

Effects on serotonergic systems: Ibogaine is a reversible inhibitor of the active transport of serotonin in platelets and produces a release of serotonin in its terminal fields. Ibogaine modulates the influence of serotonergic transmission on dopaminergic terminals in a complex manner. Ibogaine inhibits the enzymatic oxidation of peripheral serotonin. More recent biophysical work has shown that ibogaine inhibits the serotonin transporter (SERT) noncompetitively, in contrast to all other known SERT

inhibitors, which are competitive with substrate, and stabilises an inward-facing conformation of both SERT and the dopamine transporter (DAT) (Mash, 2023).

Effects on intracellular calcium regulation: Although the evidence from murine studies is equivocal, ibogaine might dose-dependently inhibit the binding of at least one kind of L-type calcium channel blocker. It was demonstrated (Koenig et al., 2013) that high concentrations of ibogaine reduce L-type Ca^{2+} currents in human ventricular cardiomyocytes, although this contributes only modestly to the overall cardiac action profile.

Effects on cholinergic systems: Ibogaine inhibits serum cholinesterase activity, and this might contribute to its effects in enhancing morphine-induced analgesia. The evidence is contradictory as to whether ibogaine inhibits binding to muscarinic receptors, and there is evidence that it inhibits binding to nicotinic receptors. Ibogaine, noribogaine, and 18-MC all act as functional antagonists at α3β4 nicotinic acetylcholine receptors (Glick et al., 2002; Maillet et al., 2015), and this α3β4 antagonism has been proposed as a primary mechanism underlying the anti-addictive effects across multiple drugs of abuse.

Effects on GABAergic systems: Some investigators presented evidence that ibogaine does not impact GABAergic systems, despite previous reports attributing this putative action as a cause of ibogaine-induced tremors.

Effects on voltage-dependent sodium channels: Ibogaine can block voltage-dependent sodium channels, an effect that might be related to its ability to induce tremors. (Koenig et al., 2013) confirmed that high concentrations of ibogaine reduce Nav1.5 sodium currents in human ventricular cardiomyocytes (Koenig et al., 2013).

Effects on glutamatergic systems: Ibogaine acts as a noncompetitive NMDA antagonist and can produce a voltage-dependent block of NMDA-evoked currents in hippocampal cultures. However, ibogaine is a competitive inhibitor of [^{3}H]MK-801 binding to NMDA receptor-coupled ion channels.

Effects on delta receptors: There is inconclusive evidence as to whether ibogaine inhibits binding to delta receptors. If it does, the significance of the action remains unclear.

Effects on sigma receptors and pharmacochaperoning: Ibogaine shows substantial affinity for the σ2 receptor (Ki = 0.10–0.30 μM;(Floresta et al., 2019; Helsley et al., 1998), and recent work has identified ibogaine as a pharmacological chaperone for SERT and DAT (Sucic et al., 2016; Sutton et al., 2022), with implications for both its anti-addictive mechanism and its potential role in neurorestorative indications such as Parkinson's disease (Fountaine et al., 2025).

Effects on cardiac hERG channels: Ibogaine, noribogaine, and voacangine all block the hERG (KV11.1) potassium channel with low-micromolar IC50 values (3.5–4.1 μM ibogaine, 2.9 μM noribogaine, 2.2 μM voacangine), which is the molecular basis of the QTc prolongation that constitutes the dominant clinical safety concern (K. Alper et al., 2016);(Kovar et al., 2011; Thurner et al., 2014).

Neurotrophic and neuroplastic effects: A growing body of preclinical and translational work has identified GDNF (glial cell line-derived neurotrophic factor) upregulation as a key mechanism underlying ibogaine's enduring anti-addictive action, particularly in alcohol use disorder (Carnicella et al., 2010; He et al., 2005). Noribogaine produces psychoplastogenic effects in vitro that are blocked by 5-HT2A antagonism, mTOR inhibition, and TrkB antagonism.

This polypharmacology has been more comprehensively tabulated in the (Mash, 2023) IUPHAR-invited review and the (Esperança et al., 2026) scoping review, both of which provide reference-quality binding-affinity tables across the principal CNS targets. The transdiagnostic reward-system framework recently

articulated by (Nicolas, 2025) proposes that ibogaine's GDNF induction, glutamatergic modulation, dopaminergic recalibration, and reopening of neuroplasticity together represent a unified mechanism for restoring reward-system fidelity across substance use disorder, PTSD, OCD, and eating disorders (Nicolas, 2025).

Toxicology

Ibogaine has two principal toxicological risks for patients undergoing substance use disorder treatment: cardiac problems and interactions with other drugs metabolized by or that inhibit CYP2D6. These are now well characterized at a quantitative level: the (Knuijver et al., 2024) sigmoid Emax model of QTc prolongation estimated a maximum QTc prolongation of 67.9 ms with an EC50 of 0.195 μM in opioid use disorder patients receiving 10 mg/kg oral ibogaine HCl (Knuijver et al., 2024). (Brunt, 2026) has noted that this EC50 is approximately ten-fold lower than the Cmax achieved at therapeutic doses, implying that clinically relevant QTc prolongation is "an inherent pharmacological effect of ibogaine at therapeutic doses", a structural problem that motivates the parallel development of safer analogues (18-MC, oxa-iboga compounds) and combination strategies such as magnesium-ibogaine (Brunt, 2026).

The cardiac risks can be minimized but not eliminated by:

1. Performing a 12-lead EKG at screening, and a careful review of medical history to screen out prospective patients who have heart problems.
2. Reviewing concomitant medications to identify medications which can cause QT prolongation or inhibit CYP2D6 activity (e.g., SSRIs or SNRIs, methadone, buprenorphine, ondansetron, quetiapine, and many others).
3. Urine drug screening and careful history to identify use of other non-opioid substances that can cause withdrawal such as benzodiazepines, barbiturates, or alcohol.
4. Using CYP2D6 genotyping or phenotyping to identify "poor metabolizers" who should be given a dose perhaps one-half that of fast metabolizers, or exclusion of these patients from ibogaine treatment. The (Knuijver et al., 2024) PK/PD analysis quantified the magnitude of this issue: ibogaine clearance increases by 30.7 L/h per CYP2D6 activity score point ($p < 0.0001$), creating a more than ten-fold range across the activity score spectrum (Knuijver et al., 2024).
5. Pre-treatment correction of any electrolyte deficiency (particularly hypokalaemia and hypomagnesaemia, which independently increase TdP risk;(Henstra et al., 2017)) and consideration of pre-treatment intravenous magnesium sulfate as employed in the MISTIC protocol (Cherian et al., 2024).
6. Continuous 12-lead Holter cardiac monitoring during the ibogaine session and for at least 24 hours afterward, and ideally for 2 to 3 days, since the prolonged half-life of noribogaine can produce delayed cardiac effects (Henstra et al., 2017; Rubi et al., 2017).
7. Use in sites which have access to medications, equipment, and a physician trained in advanced cardiac life support. The (Pleskovic et al., 2012) clinical observation that amiodarone was ineffective in ibogaine-induced VF/VT and that DC shock should be used first (Pleskovic et al., 2012) is an important practical consideration for ACLS protocols in the ibogaine setting.

Risks of drug interactions can be reduced by educating patients that the use of psychoactive substances during ibogaine detoxification can result in serious or even fatal interactions. Patients also have to be informed that after the session their drug tolerance will be reduced or eliminated, so if they relapse then they need to use a smaller dose to avoid overdosing. Some patients may try to sneak addictive drugs into the clinic, so the patient's possessions could be inspected upon intake. However, clinicians should be aware that a patient might hide drugs in clever ways, and so treatment providers should provide supervision to minimize the chance that a patient might use an opioid or stimulant during the ibogaine session.

There is no evidence that ibogaine is teratogenic, mutagenic, or carcinogenic. The absence of frank hepatotoxicity in the published clinical case series (T. K. Brown & Alper, 2017; Knuijver et al., 2022; Mash et al., 2018) supports the view that ibogaine is not a primary hepatotoxin at therapeutic doses, although mild dose- and sex-dependent histopathological changes have been documented in rat liver in the preclinical Belgrade group studies (Tatalović et al., 2019); (Tatalović et al., 2021); and the (Ramanathan & R Pradhan, 2022) atypical case of severe rhabdomyolysis with secondary acute liver injury in a patient who consumed unanalyzed iboga powder (Ramanathan & R Pradhan, 2022) represents a confounded but noteworthy case. A patient with a compromised liver might have trouble metabolizing ibogaine. While scientists have succeeded in inducing neurotoxicity in rats using high doses (≥75–100 mg/kg i.p., with NOAEL ~25 mg/kg i.p.), there is no clinical or postmortem evidence supporting the existence of neurotoxicity in humans (K. R. Alper et al., 2012); therapeutic doses up to about 25 mg/kg should therefore be safe from neurotoxicity. The (Cherian et al., 2024) prospective neuropsychological assessment in 30 SOF veterans receiving 12.1 ± 1.2 mg/kg ibogaine demonstrated no cognitive decline on any measure at 1-month follow-up, and indeed showed significant improvements in processing speed, executive function, verbal fluency, and verbal learning (Cherian et al., 2024). The (Adamson, 2025) MRI evidence of cortical thickness increases in 11 of 13 ROIs and a 1.6-year decrease in predicted brain age at 1 month following magnesium-ibogaine treatment (Adamson, 2025) further supports the absence of structural neurotoxicity in clinically dosed populations and is consistent with a neurotrophic rather than neurotoxic effect at therapeutic doses.

Physiological Effects

Clinicians should provide ongoing supervision of patients during and for a few days after the ibogaine session. In one case report of a patient who took only 600 mg of ibogaine, ventricular fibrillation (when the heart quivers instead of pumping) and ventricular tachyarrhythmia (fast heart activity due to improper electrical activity in the ventricles) appeared when the patient tried to urinate or defecate, which are vagal maneuvers that prolong the QTc interval. This suggests that a member of the clinical staff should wait outside the door while the patient uses the bathroom, just as they would for a patient who suffers from dizziness or mobility problems (Pleskovic et al., 2012). The (Mestre et al., 2024) case of four episodes of polymorphic ventricular tachycardia with cardiac arrest in a buprenorphine-maintained patient receiving only a 2.6 mg/kg pre-treatment test dose of ibogaine (Mestre et al., 2024) further reinforces the necessity of continuous bedside cardiac monitoring throughout the dosing period , including during what may appear to be a "low-risk" test dose.

Adverse Events

The (Ona et al., 2023) PRISMA systematic review of 18 studies covering ibogaine adverse events between 2015 and 2020, and the (Edwards et al., 2025) UK National Poisons Information Service case series of 7 patients between 2012 and 2022 (6 of 7 with cardiotoxicity, all 7 with neurological symptoms), provide the most recent population-level overviews of the adverse-event profile (Edwards et al., 2025; Ona et al., 2023).

Suicidal Ideation and Behavior

The Global Ibogaine Therapy Alliance advises that ibogaine may exacerbate or re-traumatize patients with suicidal ideation and/or attempts. Suicidal ideation is listed as a risk factor requiring "proper therapeutic support" before treatment (Dickinson, 2015). However, in appropriately selected and monitored populations the MISTIC trial reported that suicidal ideation in 30 SOF veterans with TBI dropped from 47% at baseline to 0% immediately post-treatment and 7% at 1-month follow-up ($p < 0.001$), with these reductions sustained at 12-month follow-up (Cherian et al., 2024; Lissemore et al., 2025). This signal suggests that, with appropriate screening and a controlled clinical context, ibogaine therapy may produce rapid and sustained reductions in suicidal ideation alongside its other antidepressant and anxiolytic effects.

Vitals

Vital sign monitoring should include continuous heart rhythm monitoring (12-lead Holter), continuous oxygen saturation (with awareness of the bradycardia and prolonged sleep-like state), regular blood pressure measurement (particularly given the documented orthostatic hypotension in cocaine-dependent (Mash et al., 2018), and core temperature monitoring during the dosing session. Monitoring should continue for at least 24 hours and ideally up to 72 hours given the prolonged half-life of noribogaine and the documented occurrence of cardiac events many hours after ibogaine ingestion.

Immunological Effects

Ibogaine has not been shown to impair the functioning of the immune system in vivo, nor is there any indication that it improves immune functions. The (D. Q. Chen et al., 2025) case reports of substantial reductions in MS lesion volume and apparent diffusion coefficient following ibogaine treatment (D. Q. Chen et al., 2025), described in Section 6.2.3.1, suggest the possibility of anti-inflammatory and remyelinating effects in central nervous system disease, but these are very preliminary findings from two patients and require independent replication.

Hepatic Effects and Other Laboratory Values

Ibogaine has never been shown to damage the liver in standard clinical case series at therapeutic doses (T. K. Brown & Alper, 2017; Knuijver et al., 2022; Mash et al., 2018); however, a patient with impaired liver function might have trouble metabolizing ibogaine, such that unusually high levels of ibogaine and noribogaine build up in the bloodstream.

Alcoholism can damage the liver, which in turn might impair the liver's ability to metabolize ibogaine ingested as a detoxification treatment for alcoholism. One alcoholic man, whose liver was afflicted by cirrhosis and heavy fatty infiltration, died while using ibogaine to detoxify from alcohol (Papadodima et al., 2013). This raises the possibility that patients with severe liver damage should either be screened out or be administered calculated lower doses on the logic that blood levels of ibogaine and its metabolite noribogaine will be unusually high.

The (Ramanathan & R Pradhan, 2022) atypical case of severe rhabdomyolysis with secondary acute liver injury in a patient who consumed unanalyzed iboga powder (CPK 179,120 U/L, AST 7,056 U/L, ALT 2,640 U/L, INR 1.5;(Ramanathan & R Pradhan, 2022)), described in Sections 5.1 and 5.1.3, represents the first documented instance of substantial hepatic transaminase elevation temporally associated with iboga exposure. The case is heavily confounded by the unknown alkaloid content of the ingested material and prior ayahuasca and "sacred tobacco" use, but should prompt vigilance for any signal of muscle or hepatic injury in clinical ibogaine programs, with baseline and post-dose creatine kinase and transaminase measurements considered as standard practice.

Risk Assessment and Mitigation

Study procedures and eligibility criteria have been developed based on historical clinical studies, observational data, case reports, and the contemporary controlled clinical literature (Cherian et al., 2024; Knuijver et al., 2022) to exclude potential participants with pre-existing medical conditions that would exacerbate risk. Additionally, protocols recommend that the therapy teams and site physicians are available via mobile phone throughout the study if any problem occurs when a participant is not at the site, and that in the event of a medical emergency or any other medical problem during an Experimental Session, the site physician will be immediately available by telephone, and based on assessment of the situation, will make the decision to either evaluate the participant at the site, or arrange for transfer of the participant to the Emergency Department. Risk mitigation procedures are described by risk category

below. Risk Categories were determined by review of possible risks within the Risk Assessment and Categorization Tool (RACT).

Recent sociological work on risk management within the global ibogaine medical subculture provides a useful comparative framework, documenting how providers in unregulated settings have developed parallel risk management strategies, medical screening protocols, peer-based credentialing systems, harm-reduction practices, in the absence of regulatory oversight (Söderberg & Lundgren, 2025). Contemporary regulatory pathways (Texas, Colorado, Kentucky (Yockey, 2025)) seek to formalize these practices within a clinical-trial framework.

High Level Risks

The largest known risks with ibogaine administration are cardiovascular and risks of administration to someone who has an impaired ability to metabolize the drug. During the intake exam, a physician should ascertain if the patient applying for ibogaine-assisted detoxification has heart problems or impaired liver or kidney function.

Low activity of CYP2D6 is a risk. The patient should be given a test for CYP2D6 to determine whether they are likely to need a low or high dose of ibogaine. The sigmoid Emax model relating ibogaine plasma concentration to QTc prolongation (EC50 = 0.195 μM, maximum QTc prolongation 67.9 ms; (Knuijver et al., 2024)) provides a quantitative basis for considering CYP2D6 genotype-guided dosing.

Some academics advise that "careful patient selection, genetic screening, and monitoring of vital parameters with professional equipment if ibogaine therapy is to be considered in the future" (Brunt & Litjens, 2016). A more recent update noted that the EC50 for QTc prolongation is approximately ten-fold lower than the Cmax achieved at therapeutic doses, and explicitly identifies the structural problem that therapeutic and cardiotoxic dose ranges overlap, making the safety margin for ibogaine inherently narrow, and motivating the parallel development of potentially safer analogues (18-MC, oxa-iboga compounds) and combination strategies such as the magnesium-ibogaine MISTIC protocol (Brunt, 2026).

Cardiovascular risk factors

It has been suggested that the risk of cardiac arrhythmias increases after the initial visionary phase of the ibogaine experience. They stated that African practitioners isolate people from daily life for a few days after ibogaine ingestion, and the healers induce a trance to minimize the risk of heart problems that might result from abrupt stimulation of the sympathetic nervous system. Substance use disorder treatment clinics might also keep the patient in a low-stimulus environment for a few days after detoxification with ibogaine, both to potentially protect the heart and to foster integration of the psychological content of the ibogaine experience (Maas & Strubelt, 2006).

Hypokalemia (low potassium levels) and hypomagnesemia (low magnesium levels) increase risk for Torsades des Pointes (Henstra et al., 2017). Pre-treatment correction of any electrolyte deficiency is therefore essential, and the MISTIC protocol's pre-treatment intravenous magnesium sulfate (1 g) is one approach to mitigating this risk (Cherian et al., 2024). Constant close monitoring of vital signs for at least 3 days after ibogaine administration is necessary since some patients have experienced fatalities up to 76 hours afterward, and the (Henstra et al., 2017) case demonstrated QTc prolongation persisting 12 days after ingestion driven by the long-half-life metabolite noribogaine (Henstra et al., 2017).

The (Mestre et al., 2024) case of multiple cardiac arrests at 2.6 mg/kg ibogaine in a patient on chronic buprenorphine (Mestre et al., 2024), and the (Wilson et al., 2021) Client 2 case of QTc 512 ms following self-administered quetiapine during an iboga ceremony (Wilson et al., 2021), specifically demonstrate that cardiac risk cannot be predicted from ibogaine dose alone, concomitant QT-prolonging medications

(including the opioid agonists used in maintenance therapy) substantially compound the risk and may produce life-threatening arrhythmia even at sub-therapeutic ibogaine exposure.

Acute Psychological Agitation

Because ibogaine has intense psychological effects, an issue that must be addressed is the patient's mental health when entering the treatment administration visit. Patients actively suffering from psychosis or mood disorders should be screened out unless the clinic can accommodate such a condition. Many patients suffering from substance use disorders have dual diagnoses, and self-medicate for psychiatric disorders that might come to the fore or worsen due to comorbid withdrawal once the use of the addictive substance is discontinued.

The phenomenological literature, including the (Olash et al., 2026) qualitative analysis of MISTIC veterans' experiences of "trauma processing with dialogic insight" and the (Schenberg, 2018) phenomenological identification of themes including "fear of dying" and "reliving childhood trauma", indicates that the ibogaine experience routinely involves intense engagement with traumatic material (Olash et al., 2026; Schenberg, 2018). Adequate psychological support during and after the experience is therefore essential, and clinicians should anticipate the possibility of acute distress requiring active intervention.

Drug Interactions

It has been noted that "In considering the potential patient population who might benefit from ibogaine, many of these patients may have taken other medications (prescription and/or illicit), increasing the potential for serious adverse drug interactions" (Mash et al., 2001). Ibogaine (12-methoxibogamine) is metabolized primarily by the liver enzyme CYP2D6, which uses *O*-demethylation to convert this drug into its metabolite noribogaine (12-hydroxyibogamine) (Obach et al., 1998). The patient should not drink grapefruit juice, and should not use other drugs that either significantly inhibit or compete for CYP2D6, since these may impair the metabolism of ibogaine; for example, a young man died 12 hours after ingesting a substantial quantity of iboga root while also being under the influence of methadone (which has adverse interaction with ibogaine) and diazepam (which does not have adverse interaction) (Mazoyer et al., 2013).

Even when patients suffering from substance use disorders are told that it is dangerous to mix ibogaine with other drugs, some will still try to do so because they are afraid of experiencing withdrawal symptoms if they go "cold turkey" under the influence of ibogaine. A urine test immediately prior to ibogaine administration can minimize the possibility that the patient may have ingested a psychoactive drug prior to the session; however, standard ELISA lab tests do not detect some synthetic drugs: oxycodone and fentanyl will not show up as opiates and neither will buprenorphine unless specifically requested. The Global Ibogaine Therapy Alliance recommends searching a patient's belongings upon intake into the clinic, although some hidden drugs may evade detection and this search may produce distrust that impedes therapeutic rapport (Dickinson, 2015). The clinicians overseeing ibogaine-mediated detoxification sessions should also be aware that they cannot administer certain prescription medications to the patient, lest there be an adverse drug interaction.

A procedure use by Lotsof's group was to administer ibogaine 8 to 10 hours after the patient's most recent use of heroin and 24 hours after the most recent use of methadone (Dickinson, 2015).

Due to the existence of genetic polymorphisms in CYP2D6 production, one researcher suggested that "it may be prudent to genotype patients awaiting ibogaine treatment, and to at least halve the intended dose of ibogaine in CYP2D6 poor metabolizers" (Glue, Winter, et al., 2015). A 2024 PK/PD analysis confirmed the more than ten-fold range of ibogaine clearance across the CYP2D6 activity score spectrum and provides the empirical basis for genotype-guided dosing (Knuijver et al., 2024). Additionally,

academics have explicitly emphasized CYP2D6 pharmacogenomics as "a critical research priority" for the field (Yockey, 2025).

Medium Level Risks

High doses (160 and 320 mg/kg p.o.) of noribogaine did not induce seizures in monkeys. However, there is a single report of a patient who experienced multiple generalized tonic-clonic seizures ("grand-mal seizures") while under the influence of root bark containing ibogaine at approximately 35 mg/kg. All other risk factors were ruled out, so the seizures do appear to have been induced by ibogaine, although this is the only such case report in the medical literature. The physicians speculated that although low doses of ibogaine seem to have anticonvulsive action via NMDA receptor antagonism, it is possible that higher doses stimulate a release of glucocorticoids that increases susceptibility to seizures (Breuer et al., 2015). This is contradicted by a mouse study in which ibogaine (a noncompetitive NMDA receptor antagonist) at a dose of 80 mg/kg inhibited convulsions induced by NMDA at 24 and 72 hours after administration (Leal et al., 2000). A 2022 preclinical observation of paroxysmal EEG activity at 30 mg/kg i.p. ibogaine in mice, accompanied by relative delta-band increase and alpha-band decrease characteristic of CNS depression, and not blocked by the 5-HT1A antagonist WAY100635, suggests that ibogaine may carry a distinct seizure-related liability that warrants attention in the human safety database (González-Trujano et al., 2022). Additionally, the 2025 UK NPIS case series documented convulsions and stupor among the most frequently reported neurological features in seven ibogaine poisoning cases (Edwards et al., 2025), reinforcing the need for seizure precautions in the clinical setting and exclusion of patients with significant epilepsy history.

Pregnancy and Breastfeeding

There have not been any studies on reproductive toxicity or studies of ibogaine's effects on pregnant or lactating females. Because we do not know if ibogaine and noribogaine might have adverse effects on fetuses, pregnancy should be a contraindication, except perhaps in cases where a patient's substance use disorder is so severe that the likelihood of harm from continued use of the addictive drug is considerably greater than the likelihood of harm from ibogaine. In such cases, written informed consent should document that patient and physician have discussed this risk-benefit assessment.

Special Warnings and Special Precautions for Use

When administering ibogaine to drug-dependent subjects, it must be clearly explained that the drug can reduce tolerance to addictive drugs. If, after ibogaine administration, subjects decide to use an addictive drug or any medication that might produce an adverse interaction, the dose used the last time should be considerably diminished in order to avoid potential overdoses. This phenomenon has contributed to multiple post-treatment fatalities documented in a number of reviews, and the compilation of 33 ibogaine-related fatalities between 1990 and 2020 (K. R. Alper et al., 2012; Corkery, 2018; Luz & Mash, 2021).

Low Level Risks

The fairly common minor side-effects (such as tremors, ataxia, nausea, headaches, and non-euphoric changes in light perception) are low-level risks because they are not serious and provide only transient annoyance or discomfort. A 2024 PK/PD analysis documented that ataxia (SARA scale) correlated significantly with ibogaine plasma concentration ($r = 0.668$, $p < 0.01$) but not with metabolite concentration (Knuijver et al., 2024), indicating that cerebellar ataxia reflects acute ibogaine action and resolves as ibogaine is eliminated.

Minimal Risks

Research suggests that prolonged adverse psychological reaction to the psychedelic effects of ibogaine are rare. But as recounted elsewhere in this Investigator's Brochure, the medical literature does document that ibogaine was associated with three cases of mania (Marta et al., 2015), one case of psychosis in a man who took ibogaine on a daily basis (Houenou et al., 2011), and one case of hallucinogen persisting perceptual disorder (Knuijver et al., 2018) that may have been a misdiagnosed case of unresolved traumatic psychological material that emerged during the ibogaine session. Although the risk of ibogaine-induced adverse psychiatric events is low, it is possible that psychiatric illness might be unmasked when people become abstinent from drugs that were previously suppressing their condition. Thus, it is possible that some latent mental illness might come to the fore in a minority of patients who seek recovery from dependence on addictive drugs.

Reference Safety Information for Regulatory Reporting

The Reference Safety Information (RSI) below outlines expected Serious Adverse Reactions (SARs) for regulatory reporting purposes in the European Economic Area (EEA) region, but the information within the RSI does not present a comprehensive overview of the safety profile of the Investigational Medicinal Product (IMP).

Table 19 shows serious adverse reactions for the IMP considered expected for safety-reporting purposes in the EEA region.

Table 19: Serious Adverse Reactions Observed for the IMP in Clinical Trials

System, Organ, Class	SAR (Serious Adverse Reaction)	As of December 1, 2019: Number of subjects exposed within the development program: (N)=0. Number exposed outside the development program: (N)=0		
		All SARs	Fatal SARs	Life-threatening SARs
		N=(%)	N=(%)	N=(%)
None	None	0 (0.0)	0 (0.0)	0 (0.0)

Conclusions

Ibogaine is a dissociative psychedelic with oneiric properties that exerts multiple antiaddictive mechanisms targeting key stages of the substance use disorder cycle, including the withdrawal/negative affect phase and the preoccupation/anticipation of the rewarding effects of abused substances. The protracted negative affective state that persists following drug detoxification drives an intractable cycle of compulsive drug use and relapse (Evans & Cahill, 2016).

The proposed therapeutic benefits of ibogaine as a "psychoplastogen" that addresses the underlying neurobiological substrate of substance use disorder, rather than merely targeting symptomatic manifestations to prevent relapse (Olson, 2018), provide a rational basis for clinical development of ibogaine as an inpatient pharmacotherapy (Luz & Mash, 2021). The role of noribogaine as an active metabolite of ibogaine is supported by experimental evidence from in vitro binding assays and animal pharmacology studies. These investigations have identified biological activities of noribogaine that warrant consideration in evaluating both the overall therapeutic profile and the potential off-target adverse effects associated with oral ibogaine administration. An ibogaine analogue is currently being advanced toward clinical development with the goal of achieving efficacy comparable to ibogaine while offering an improved cardiac safety profile (Cameron et al., 2021; Olson, 2018; Peters & Olson, 2021).

While randomized clinical trials remain the gold standard for establishing causality in drug development, the weight of real-world evidence continues to grow as patients seek substance use disorder treatment

with ibogaine outside the United States. It is imperative that researchers and drug developers gain an awareness and understanding of traditional uses and contemporary clinical practices, and expand both the scale and pace of clinical investigation to rigorously determine whether the therapeutic benefits of ibogaine outweigh its associated risks.

The current state of scientific knowledge supports the continued investigation of ibogaine as a candidate therapeutic agent across multiple clinical indications. For participants meeting appropriate eligibility criteria—including comprehensive cardiac, hepatic, and psychiatric screening—the risk profile associated with clinical investigation of ibogaine within controlled research settings appears acceptable in the context of the unmet clinical need addressed by ongoing study programs. Clinical investigations of ibogaine should be designed with attention to the established cardiac liabilities of the compound, the substantial interindividual variability in metabolism attributable to CYP2D6 polymorphism, and the prolonged systemic persistence of the active metabolite noribogaine.

The available preclinical and observational evidence indicates that ibogaine attenuates withdrawal symptomatology and reduces drug craving across multiple substance use disorders, with parallel signals of efficacy emerging in trauma-related conditions and other neuropsychiatric indications. The compound additionally produces a distinctive subjective experience that has been proposed to support psychotherapeutic processing and the development of patient insight into maladaptive behavioral patterns. The multitarget pharmacological profile of ibogaine and its active metabolite, encompassing modulation of dopaminergic, serotonergic, opioid, glutamatergic, and nicotinic systems alongside induction of neurotrophic factor expression and reported plasticity-promoting effects, distinguishes ibogaine from existing pharmacotherapies and provides a mechanistic rationale for continued clinical investigation.

Rigorously designed clinical trials remain essential to establish the efficacy, safety, and optimal administration parameters of ibogaine across candidate indications. The combination of preliminary therapeutic signals, distinctive pharmacological properties, and substantial unmet clinical need across substance use disorders, trauma-related conditions, and additional neuropsychiatric indications supports the study of long-standing traditional uses and contemporary clinical practices, and the continued development of ibogaine within appropriately controlled clinical research programs.

Appendix

Noribogaine and 18-Methoxycoronaridine: Compound Information

Regulatory identifiers, nomenclature, and physicochemical properties for the principal ibogaine metabolite noribogaine and the second-generation ibogaine analogue 18-methoxycoronaridine (USAN: zolunicant). All data verified against FDA Global Substance Registration System (GSRS), PubChem (NIH), CAS Common Chemistry, DrugBank, and primary literature.

1. Noribogaine

Principal pharmacologically active metabolite of ibogaine. Noribogaine is formed via CYP2D6-mediated O-demethylation of ibogaine and is hypothesized to mediate a substantial portion of the sustained antiaddictive effects and prolonged cardiac electrophysiological liability observed following oral ibogaine administration.

Parameter	Value
REGULATORY IDENTIFIERS	
UNII (FDA, noribogaine free base)	87T5QTN9SK
UNII (FDA, noribogaine hydrochloride)	9DZ432F7DT
CAS Registry Number (free base)	481-88-9
CAS Registry Number (hydrochloride)	110514-35-7
PubChem CID (noribogaine)	12313547
PubChem CID, alternate listing [(−)-Noribogaine]	3083548
PubChem CID (noribogaine HCl)	321672
ChEBI ID	146264
EPA CompTox DTXSID	DTXSID90963998
EVMPD (EMA)	SUB79173
STN (SciFinder) / Nikkaji Code	J666.099A
NOMENCLATURE	
Approved Name	Noribogaine
Chemical Name	12-Hydroxyibogamine
IUPAC Name	(1R,15R,17S,18S)-17-ethyl-3,13-diazapentacyclo[13.3.1.$0^{2,10}$.$0^{4,9}$.$0^{13,18}$]nonadeca-2(10),4(9),5,7-tetraen-7-ol
Other Names / Synonyms	(−)-Noribogaine; 12-Hydroxyibogamine; O-Demethylibogaine; O-Noribogaine; Ibogaine, O-demethyl-; Ibogamin-12-ol
Relationship to Ibogaine	Principal O-demethylated metabolite of ibogaine, formed primarily via CYP2D6-mediated biotransformation
MOLECULAR PROPERTIES	
Molecular Formula (free base)	$C_{19}H_{24}N_2O$
Molecular Formula (hydrochloride)	$C_{19}H_{25}ClN_2O$
Molecular Weight (free base)	296.41 g/mol
Molecular Weight (hydrochloride)	332.87 g/mol

Exact Mass (hydrochloride)	332.1655
Stereochemistry	Absolute; 4 defined stereocenters (1R, 15R, 17S, 18S configuration)
Charge	0 (neutral base)
InChIKey (hydrochloride)	BFLJLOKFWZLUTR-IMLBMZRZSA-N
PHYSICOCHEMICAL PROPERTIES	
Physical Form	Solid
Structural Difference from Ibogaine	Replacement of the C-12 methoxy ($–OCH_3$) substituent with a hydroxyl (–OH) group
Lipophilicity	Lower than ibogaine due to the free phenolic hydroxyl group, but retains CNS penetrance
Elemental Analysis (HCl)	C, 68.56%; H, 7.57%; Cl, 10.65%; N, 8.42%; O, 4.81%
SOLUBILITY	
Noribogaine hydrochloride	Sparingly soluble in DMSO (1–10 mg/mL); soluble in water and alcohols
PHARMACOLOGICAL NOTES	
Primary Pharmacological Activity	Serotonin reuptake inhibitor; G-protein-biased κ-opioid receptor agonist; weak μ-opioid receptor agonist
Metabolic Origin	Formed from ibogaine via CYP2D6-mediated O-demethylation
Clinical Relevance	Long terminal half-life (28–49 h) relative to ibogaine (~7.5 h); implicated in the sustained antiaddictive and cardiotoxic effects of ibogaine treatment

18-Methoxycoronaridine (Zolunicant, 18-MC)

Synthetic iboga alkaloid congener developed as a second-generation analogue of ibogaine. 18-Methoxycoronaridine (assigned the USAN name zolunicant in 2021) exhibits selective non-competitive antagonism at α3β4 nicotinic acetylcholine receptors and was rationally designed to preserve antiaddictive efficacy while attenuating the hallucinogenic, cerebellar neurotoxic, and cardiac liabilities associated with the parent alkaloid.

Parameter	**Value**
REGULATORY IDENTIFIERS	
UNII (FDA, (−)-zolunicant / (−)-18-MC)	KX8NQX91Z8
UNII (FDA, zolunicant racemate)	VG463BM9RL
UNII (FDA, (−)-zolunicant hydrochloride)	85Z0P8329N
CAS Registry Number	308123-60-6
PubChem CID	15479177
DrugBank ID	DB15096
EPA CompTox DTXSID	DTXSID40437331
USAN Designation	Zolunicant (USAN Council, 2021)
NOMENCLATURE	
Approved Name (USAN)	Zolunicant
Common Name	18-Methoxycoronaridine (18-MC)
Chemical Name	Ibogamine-18-carboxylic acid, 21-methoxy-, methyl ester
IUPAC Name	methyl (1*S*,15*R*,17*R*,18*S*)-17-(2-methoxyethyl)-3,13-diazapentacyclo[13.3.1.$0^{2,10}$.$0^{4,9}$.$0^{13,18}$]nonadeca-2(10),4,6,8-tetraene-1-carboxylate
Other Names / Synonyms	(−)-18-Methoxycoronaridine; (−)-Zolunicant; 18-MC

Chemical Class	Synthetic iboga alkaloid congener; second-generation ibogaine analogue
MOLECULAR PROPERTIES	
Molecular Formula	$C_{22}H_{28}N_2O_3$
Molecular Weight	368.47 g/mol
Stereochemistry	Absolute; 5 defined stereocenters
Optical Activity	Levorotatory [(−)-enantiomer]
Charge	0 (neutral base)
METABOLISM	
Primary Metabolite	18-Hydroxycoronaridine (UNII: WD3MZG9WTB)
Responsible Enzyme	Cytochrome P450 2C19 (CYP2C19; UNII: 081I12ZA58)
Reference	Zhang W. et al. (2002) Metabolism of 18-methoxycoronaridine, an ibogaine analog, to 18-hydroxycoronaridine by genetically variable CYP2C19. *Drug Metab. Dispos.* 30(6): 663–669
PHARMACOLOGICAL NOTES	
Primary Pharmacological Activity	Selective non-competitive antagonist at α3β4 nicotinic acetylcholine receptors
Rationale for Development	Designed as a second-generation iboga alkaloid congener to preserve antiaddictive efficacy while attenuating the hallucinogenic, tremorigenic, cerebellar neurotoxic, and cardiac (hERG) liabilities intrinsic to the parent alkaloid ibogaine
Therapeutic Indication (Investigational)	Substance use disorders, including opioid, stimulant, nicotine, and alcohol dependence
Comparative Profile vs. Ibogaine	Reduced hERG affinity; reduced serotonergic activation; lower hallucinogenic burden; retained α3β4 nAChR antagonism; reduced engagement of GDNF-related neurotrophic pathways

Noribogaine and 18-Methoxycoronaridine: Literature Summaries

Noribogaine Summary

Noribogaine (12-hydroxyibogamine) is ibogaine's primary active metabolite, formed via CYP2D6-mediated O-demethylation. It has a substantially longer half-life than ibogaine and is increasingly recognized as a major contributor to ibogaine's therapeutic effects.

Pharmacology & Mechanism

Noribogaine acts at multiple receptor targets. It is a mixed agonist/antagonist at opioid receptors — a mu-opioid antagonist (G-protein IC50 ~20μM) and a kappa partial agonist (~75% efficacy, 9μM) with profound functional selectivity, poorly recruiting beta-arrestin while blocking dynorphin-A beta-arrestin signaling (Maillet et al., 2015). It inhibits alpha3beta4, alpha7, and habenula-type nicotinic acetylcholine receptors, reducing nicotine self-administration by up to 64%, comparable to varenicline (Maillet et al., 2015). It has ~10x higher serotonin transporter (SERT) affinity than ibogaine and blocks T-type calcium channels in thalamocortical neurons in a sex- and 5-HT2A receptor-dependent manner (Villalba et al., 2025). Unlike 18-MC, noribogaine upregulates GDNF expression in the VTA, a key anti-addictive mechanism shared with ibogaine (Carnicella et al., 2010). The polypharmacology paradigm, simultaneous modulation of opioid, nicotinic, serotonergic, and glutamatergic systems, is considered central to its anti-addictive profile (Ona et al., 2023).

Behavioral Effects

Noribogaine promotes wakefulness, reduces slow-wave sleep, and completely suppresses REM sleep in rats, mirroring ibogaine's effects (Castro-Nin et al., 2023). In 5-HT2A knockout mice, noribogaine produces sex-dependent differences in locomotion, immediate early gene expression (Npas4, Egr1, cFos), and NMDA-mediated current density in mPFC pyramidal neurons — effects that are more pronounced in males (Villalba et al., 2024).

Safety & Toxicology

The oral LD50 of noribogaine in mice is 630 mg/kg, ~2.4x less toxic than ibogaine (263 mg/kg) (Kubiliene et al., 2008). A GLP-quality video-EEG study in cynomolgus monkeys found no seizure activity at doses up to 320 mg/kg orally, with clinical signs (decreased activity, emesis, poor coordination) that were dose-related and self-resolving (Authier et al., 2016).

Analytical Methods

Validated LC-ESI-MS methods exist for ibogaine and noribogaine quantitation in human plasma and whole blood, with stability documented up to 1 year in frozen plasma (Kontrimaviciute et al., 2006, 2006). Light degradation pathways have been characterized.

Structural Analogs

Oxa-noribogaine (a benzofuran analog from the Sames lab) reduces alcohol self-administration in rats through aversion learning, with KOR EC50=43nM and NMDAR IC50=24μM, and no detectable motor impairment or cardiac liabilities (Meinhardt et al., 2026).

18-Methoxycoronaridine (18-MC) Summary

18-MC is a synthetic iboga alkaloid congener designed by Glick and Kuehne to retain ibogaine's anti-addictive properties while eliminating its neurotoxicity and cardiovascular risks.

Design Rationale & Safety Advantages

Unlike ibogaine, 18-MC produces no tremorigenic activity at 40 mg/kg, no cerebellar Purkinje cell degeneration even at multiple 100 mg/kg doses, and no cardiovascular effects at 200 mg/kg orally (Glick et al., 1998). It has markedly lower sigma-2 receptor affinity (~30x less than ibogaine) and no NMDA receptor binding at concentrations up to 100μM. Acute LD50 in mice is ~100 mg/kg (males) and ~200 mg/kg (females), with a repeated-dose NOAEL of 50 mg/kg/day in both mice and nonhuman primates (Delorenzi et al., 2026).

Mechanism — The Habenulo-Interpeduncular Pathway

18-MC's primary mechanism of action involves antagonism of alpha3beta4 nicotinic receptors concentrated in the medial habenula (MHb) and interpeduncular nucleus (IPN). Intracerebral microinjection studies established that 18-MC in the MHb and/or IPN decreases morphine self-administration without affecting sucrose intake, blocks sensitized (but not acute) dopamine responses to morphine in the nucleus accumbens, and attenuates various morphine withdrawal signs (Glick et al., 2006; Panchal et al., 2005; Taraschenko et al., 2007). For methamphetamine, 18-MC acts through MHb, IPN, and basolateral amygdala, while natural reward (sucrose) circuits involve different regions (dorsolateral tegmentum, BLA), demonstrating dissociable drug vs. natural reward pathways (Glick et al., 2008).

Broad-Spectrum Anti-Addictive Efficacy

18-MC reduces self-administration of morphine, cocaine, nicotine, and alcohol in rats at 20–40 mg/kg. Oral dosing is effective — 40 mg/kg oral significantly reduces nicotine self-administration and dose-dependently reduces alcohol intake in alcohol-preferring rats (A. Rezvani, 1997; A. H. Rezvani et al., 2016). Effects are protracted (2+ days) and repeated oral dosing shows increasing efficacy by days 4–5. Both (+) and (−) enantiomers are active (King et al., 2000).

Key Distinction from Ibogaine/Noribogaine

18-MC does NOT upregulate GDNF expression in the VTA and does NOT increase nucleus accumbens serotonin — mechanisms central to ibogaine and noribogaine's anti-addictive effects (Carnicella et al., 2010). This confirms fundamentally different mechanisms: ibogaine/noribogaine act through GDNF/VTA/serotonergic pathways, while 18-MC acts through alpha3beta4/habenulo-interpeduncular pathways.

SAR & Chemistry

Fifteen 18-MC congeners have been synthesized, with alpha3beta4 nAChR potency correlating with in vivo anti-addictive activity and opioid receptor activities being generally low (Kuehne et al., 2003). PK shows rapid initial half-life (~5–10 min) with a prolonged terminal phase (>100 min) and high fat sequestration.

Novel Application

18-MC also shows antileishmanial activity, achieving 99.7–99.9% parasite reduction in mice and dose-dependent lesion reduction in nonhuman primates, with an estimated therapeutic index of ~5.4 (Delorenzi et al., 2026).

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