

LONG COVID & PCVS | THERAPEUTICS

Ibogaine Side Effects: Comprehensive Clinical Safety Profile

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Mobeen Syed, MD; Mehmood, MD; Madhava, MD; Joel Wallksog, MD; Danice Hertz, MD; Jeffrey M Jones, MD; Suzanne K. Gazda, MD, Douglas H. Jones, MD, FAAAAI; Phillip A. Triantos, MD; Jan Maisel, MD; Molly Rutherford, MD; Diane Counce, MD; Elise Mecham, MD.

INTRODUCTION

This document provides a comprehensive **pharmacovigilance and clinical safety synthesis of ibogaine** integrating controlled human trials, systematic reviews, mechanistic studies, case reports, forensic analyses, and pharmacogenetic data.

It demonstrates that while low-dose, medically supervised ibogaine protocols have been used with relative safety in selected populations, there exists a narrow and unpredictable therapeutic window driven by: This document is divided into following sections:

- Dose-dependent cardiotoxicity (QTc prolongation and malignant arrhythmias)
- Long-lived active metabolites with delayed toxicity
- High interindividual variability in metabolism
- Substantial product purity and dosing uncertainty
- Compounding risks from electrolyte abnormalities, comorbidities, and polypharmacy

1. CARDIOVASCULAR TOXICITY

Study 1

Randomized Controlled Trial - Clinical Pharmacology in Drug Development

N=27 opioid-dependent patients receiving noribogaine in placebo-controlled dose-escalation study.

Demonstrated dose-dependent QTc prolongation: **16ms at 60mg, escalating to 42ms at 180mg doses.**

Established concentration-response relationship of 0.17 ms per ng/mL plasma concentration. No serious cardiac events occurred with controlled dosing and continuous monitoring protocols [1].

Supporting Clinical Context

Normal QTc Values:

- Males: <450 milliseconds
- Females: <470 milliseconds [17]

Clinical QTc Prolongation Thresholds (from clinical studies):

- <5ms increase: Not associated with increased torsades de pointes risk [19]
- 5-10ms increase: Potential increased risk - some drugs withdrawn for this level [19]
- 20ms increase: Significant increased risk of torsades de pointes [19]
- For every 10ms increase: ~5-7% increase in arrhythmic event risk [20]

ICH E14 Discontinuation Criteria: QTc >500ms or >60ms increase from baseline are commonly used thresholds for potential discontinuation [20].

Clinical Arrhythmia Risk: QTc >500 milliseconds indicates significantly increased torsades de pointes risk requiring immediate intervention [20].

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Noribogaine Clinical Significance: The observed 16ms and 42ms drug-induced QTc prolongations exceed the ICH E14 regulatory threshold of around 5ms [18].

- **Long-lasting effects (> 24 hours):** Persistent cardiac alterations, psychiatric, and neurological signs. [3].

Study 2

Systematic Review - Journal of Substance Abuse Treatment

Systematic literature review by Köck et al. analyzing clinical trials and therapeutic applications of ibogaine for substance use disorders (SUDs). The review analyzed 24 studies encompassing 705 individuals receiving ibogaine or noribogaine for **treatment of opioid use disorder (OUD), cocaine use disorder (CUD), and other substance use disorders** through December 2020.

Dosing ranges documented across studies:

- **Ibogaine:** 11.7-55 mg/kg (oral)
- **Noribogaine:** 3-180 mg total dose (oral)

Safety findings: Two fatalities reported within the reviewed studies. The authors noted severe medical complications and deaths associated with neuro- and cardiotoxic effects. [2].

Study 3

Systematic Review - Psychopharmacology

Systematic review by Ona et al. following PRISMA guidelines, analyzing adverse events and fatalities associated with ibogaine/noribogaine administration from 2015-2020 literature. The review included 18 studies examining adverse events in humans receiving ibogaine or noribogaine for anti-addictive therapeutic applications.

Adverse event classification:

- **Acute effects (< 24 hours):** Cardiac complications (**QTc prolongation identified as most common**), gastrointestinal, neurological, and clinical alterations.

Study 4

Clinical Safety Study - Addiction

Open-label observational study by Knuijver et al. evaluating cardiac, cerebellar and psychomimetic safety of ibogaine in opioid use disorder treatment. N=14 opioid-dependent patients on opioid substitution treatment receiving **single-dose ibogaine HCl 10 mg/kg orally** under controlled medical supervision.

Critical safety findings:

- **QTc prolongation:** Maximum prolongation averaged 95ms (range 29-146ms). 50% of subjects reached QTc >500ms during observation period
- **Persistent effects:** 6 of 14 subjects had QTc prolongation >450ms lasting beyond 24 hours post-administration
- **Additional effects:** Ataxia(occurred in **all patients**), bradycardia and decreased blood pressure documented

Clinical significance: Despite relatively low dosing and controlled medical environment, clinically significant QTc prolongation occurred, emphasizing need for specialized cardiac monitoring [4].

Study 5

Clinical Case Report - Clinical Toxicology

Case report by Henstra et al. documenting prolonged cardiac arrhythmias following internet-purchased ibogaine ingestion for heroin addiction treatment. A 46-year-old female ingested a total **1400 mg ibogaine** over 12 hours (approximately **20 mg/kg based on average female weight**).

Critical safety findings:

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- **Severe QTc prolongation:** Maximum QTc 647ms with multiple cardiac arrhythmias including atrial tachycardia, ventricular tachycardia, and **Torsades de Pointes**
- **Medical interventions:** Temporary pacemaker insertion required, isoproterenol infusion, pacemaker rate set at 130/min initially.
- **Prolonged effects:** QTc prolongation persisted for **12 days** due to long-acting metabolite noribogaine
- **Toxicokinetics:** Peak ibogaine concentration **1.45 mg/L**, peak noribogaine **0.569 mg/L**

Clinical significance: Demonstrates **prolonged cardiac toxicity** lasting nearly two weeks, primarily attributed to the long elimination half-life of the active metabolite noribogaine rather than parent ibogaine [5]

Study 6

Case Report with Literature Review - Therapeutic Advances in Psychopharmacology

Case report by Meisner et al. documenting ibogaine-induced cardiac arrest and death in a 40-year-old male using ibogaine for heroin withdrawal symptoms.

Key findings:

- **Fatal outcome:** Patient suffered acute cardiac arrest leading to cerebral edema and brain death
- **Cause:** Presentation consistent with ibogaine-induced cardiotoxicity [6]

Study 7

Clinical Case Report - Journal of Arrhythmia

A 61 year old male developed man experienced massive QT prolongation and ventricular flutter at a rate of 270 beats per minute requiring defibrillation after ingestion of a large dose of Ibogaine.

Key Findings:

- The ingested dose of **65-70 mg/kg** represents the highest survived ibogaine dose reported to date.
- As a result of the long plasma half-life of ibogaine, it took 7 days for the patient's QT interval to normalize.[12].

Study 8

Forensic Case Series - Journal of Forensic Sciences

Analysis of 19 fatalities temporally associated with ibogaine ingestion. Deaths occurred within 8-76 hours of administration. Identified dose-dependent mortality risk and highlighted the critical role of product quality control in safety outcomes [7].

Study 9

Cardiovascular Safety Analysis - Cardiovascular Toxicology

Human induced pluripotent stem cell-derived cardiomyocyte study demonstrating ibogaine prolongation of action potential duration. Confirms hERG potassium channel blockade as mechanism underlying QT prolongation and arrhythmia risk [8].

2. NEUROLOGICAL COMPLICATIONS

Study 1

Animal Toxicology Study - Toxicological Sciences

This study examined the dose-dependent neurotoxic effects of ibogaine on rat cerebellum, testing doses of 25, 50, 75, and 100 mg/kg and evaluating damage using multiple histochemical markers including silver staining, calbindin immunohistochemistry, and GFAP staining. The researchers found a clear dose-response relationship, with cerebellar Purkinje cell degeneration occurring at doses **as low as 50 mg/kg, while 25 mg/kg was identified as the no-observable-adverse-effect level (NOAEL)**. The study used female Sprague-Dawley

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rats and examined tissue 7 days post-treatment to assess neurodegeneration patterns.[\[9\]](#).

Key findings:

- **Dose-dependent cerebellar toxicity:** All rats receiving 75-100 mg/kg showed characteristic bands of degenerating Purkinje neurons, while 2 of 6 rats at 50 mg/kg showed neurodegeneration, establishing 25 mg/kg as the NOAEL.
- **Axonal damage precedes cell body death:** At the 50 mg/kg dose, degenerating Purkinje cell axons were detectable in deep cerebellar nuclei even when few neuronal cell bodies showed damage, suggesting axonal degeneration may be an early indicator of ibogaïne toxicity.

Study 2

Clinical Observational Study - Frontiers in Pharmacology

This clinical study examined ibogaïne treatment in 191 opioid and cocaine-dependent individuals using oral doses of **8-12 mg/kg**, monitoring for adverse events and treatment outcomes over a 12-day inpatient program. The most common neurological side effects were mild ataxia (difficulty walking), nausea and vomiting, and perceptual changes including dream-like visualizations lasting 4-8 hours, with headaches reported in 7% of subjects. The study found no serious adverse events or deaths at these therapeutic doses, though some cocaine-dependent subjects experienced orthostatic hypotension and bradycardia that resolved with IV fluid administration.

Key Findings:

- Oral ibogaïne at **8-12 mg/kg (typically 500-1000 mg total dose)** was well-tolerated with no serious adverse events, deaths, or significant cardiovascular complications when proper medical monitoring and patient screening were implemented. [\[10\]](#).

Study 3

Clinical Case Report - Journal of Medical Case Reports

This case report describes a 22-year-old man who experienced severe neurological complications after consuming **38g of dried ibogaïne root bark (equivalent to approximately 2,260 mg or 35 mg/kg of ibogaïne)**, which is far above typical therapeutic doses. He developed generalized tonic-clonic seizures beginning 10 hours post-ingestion, followed by multiple grand mal seizures requiring treatment with midazolam and levetiracetam over several days. Additional neurological symptoms included mild dysarthria, bilateral ptosis, psychomotor slowness, and diffuse encephalopathic changes on EEG, with complete recovery occurring within 5 days.[\[11\]](#).

Study 4

Clinical Case Report - The Journal of Emergency Medicine

This case report describes a 34-year-old woman who ingested **2g of ibogaïne** powder purchased online for opioid self-detoxification and subsequently experienced severe cardiac and neurological adverse events.

Key findings:

- **Severe cardiac toxicity with life-threatening arrhythmias:** The 2g dose of ibogaïne caused extreme QTc prolongation (788 ms on presentation) and multiple episodes of torsades de pointes, a potentially fatal ventricular arrhythmia, which responded to intravenous magnesium sulfate (2g) (QTc prolongation 615 ms after magnesium treatment) but required intensive cardiac monitoring and management.
- **Neurological complications including seizures and prolonged confusion:** The patient experienced 4-5 seizure-like episodes with altered mental status, teeth clenching, and arm extension, followed by persistent confusion that required psychiatric unit monitoring for 5 days, demonstrating ibogaïne's significant neurotoxic potential at higher doses.[\[14\]](#).

3. PSYCHIATRIC ADVERSE EVENTS

Study 1

Prospective Study- Nature Medicine

This clinical study examined the MISTIC protocol (Magnesium-Ibogaine therapy) in 30 male Special Operations Veterans with traumatic brain injury, using oral ibogaine doses of 12.1 ± 1.2 mg/kg (with magnesium supplementation) administered.

Key Findings:

- No serious psychiatric adverse events occurred, with the most common side effects being mild and transient neurological symptoms including ataxia and intention tremor that resolved within 24 hours, plus manageable symptoms like headache (40%), nausea (23%), and anxiety (10%) during the acute treatment phase.
- The study found no instances of psychotic symptoms, severe mood disturbances, or long-term psychiatric complications at these therapeutic doses. [13].

Study 2

Systematic Review - Psychopharmacology

This systematic review (2015-2020) analyzed 18 studies documenting adverse events from ibogaine/noribogaine use, with dosages ranging from 725 mg to 38g of dried root bark, finding highly heterogeneous psychiatric complications.

Key findings:

- The most common prolonged psychiatric adverse events (>24h) included insomnia persisting 5-14 days, delusions, aggressiveness, irritability, dissociation, and hallucinations.
- **High variability in psychiatric adverse events with dose-dependent severity:** Psychiatric complications ranged from mild hallucinations/visual alterations in controlled

clinical trials using low doses (20mg ibogaine, 60-180mg noribogaine) to severe prolonged psychiatric symptoms including persistent insomnia (5-14 days), delusions, aggressiveness, and dissociation in case reports using higher, uncontrolled doses (725mg to 38g of root bark).

- **Critical safety concerns with uncontrolled use:** Most serious psychiatric adverse events occurred in non-medical settings with unverified ibogaine products, where purity ranged from 0% to 73.4% in products labeled as "ibogaine HCl," and root bark concentrations varied dramatically from 0.6% to 11.2% ibogaine content, making dose estimation nearly impossible. [3].

4. PHARMACOGENETICS AND GENETIC RISK FACTORS

Study 1

Clinical Toxicology Review - Molecules

This comprehensive review examined ibogaine's cardiac safety profile and identified critical pharmacogenetic and individual risk factors that predispose patients to life-threatening cardiac complications.

Key findings:

- The study found that ibogaine is metabolized primarily by CYP2D6 enzymes (with minor contributions from CYP2C9 and CYP3A4), creating significant inter-individual variability in drug metabolism due to genetic polymorphisms affecting approximately 5-10% of Caucasians who are poor metabolizers.
- Key individual risk factors consistently associated with fatal outcomes included hypokalemia (present in 100% of tested cases, often as low as 2mM vs. normal 3.5-5mM), hypomagnesemia (present in 50% of cases), pre-existing cardiovascular disease, and

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concomitant drug use (particularly methadone, cocaine, alcohol, and benzodiazepines).

- The study revealed that ibogaine and its long-lived metabolite noribogaine (half-life 28-49 hours vs. ibogaine's 4-7 hours) both inhibit cardiac hERG potassium channels, causing QT prolongation that can persist for days to weeks, with poor metabolizers at particularly high risk for prolonged cardiotoxic effects.[\[16\]](#).

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