Addiction Pharmacology and Ibogaine

Psychedelic Pharmacology
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Spirit Pharmacist LLC

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About Your Instructor
- BS Pharmacology 2008 – UC Santa Barbara
- Doctor of Pharmacy 2014 – Touro University California
- Master of Public Health 2014 – Touro University California
- Post Graduate Year 1 – Acute Care – Scripps Mercy Hospital
- Post Graduate Year 2 – Psychiatry – UC San Diego Health
- Assistant Professor – Western U College of Pharmacy
- Board Certified Psychiatric Pharmacist & Psychopharmacology Consultant

Learning Objectives
- Review the history of iboga, ibogaine, and available forms
- Describe pharmacological properties of ibogaine
- List contraindicated drugs and conditions with ibogaine
- Discuss pharmacologic mechanisms and candidates for ibogaine use

Introduction

History of Ibogaine
- Iboga discovered by West in 1864, ibogaine first isolated in 1901
- Ibogaine marketed under name Lambarene in France during 1930s
- First observed to have ability to detoxify opioids by Howard Lotsof in 1962, when he managed to stop heroin ‘cold turkey’ after using ibogaine
- Patented as 'interrupter of narcotic addiction' for several substances beginning in 1985 by Lotsof
- Despite apparently ‘miraculous’ nature of addiction interruption, there has yet to be a formal clinical trial conducted for use of ibogaine in addiction
What is Ibogaine?

- Psychedelic alkaloid found in *Tabernanthe iboga* and *Voacanga Africana*
- Notorious for anti-addictive properties as well as cardiotoxicity
- Provides long (18-30 hour) psychedelic experience
- Unique ability to detoxify persons physically dependent on opioids
- Currently a schedule I substance in the United States

![Molecular structure of ibogaine](https://www.ibogainealliance.org/iboga/)

What is Iboga?

- Traditional sacrament of West Africa
- Refers to root bark of *Tabernanthe iboga* or *Tabernanthe* spp.
- Grows in Congo basin & West African rainforests
- Used for millennia by pygmies, Bantu and more recently Bwiti peoples of Gabon → Bwiti temples spreading to nearby countries
- Known to contain psychedelic alkaloid ibogaine
- Traditional uses:
  - Low doses to combat fatigue or as an aphrodisiac
  - Higher doses for ceremonial rites of passage

![Forms of Ibogaine](https://www.ibogainealliance.org/iboga/)

### Forms of Ibogaine

<table>
<thead>
<tr>
<th>Form Type</th>
<th>Preparation/Extraction</th>
<th>Ibogaine HCl Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root Bark Total Alkaloid</td>
<td>Dried and ground up root bark, large quantities of floral plant material needed for full experience; contains all alkaloids in &quot;iboga&quot;</td>
<td>Yes</td>
</tr>
<tr>
<td>Extracted Psychoactive</td>
<td>Extraction of psychedelic alkaloid content of iboga, lower quantities needed for full experience; contains all alkaloids in &quot;iboga&quot;</td>
<td>Yes</td>
</tr>
<tr>
<td>Semi-Synthetically Produced</td>
<td>Extracted and purified or semi-synthetically produced; smaller quantity needed for full experience; isolates the alkaloid ibogaine</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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**Psychedelics Compared**

<table>
<thead>
<tr>
<th>Psychedelics</th>
<th>Tryptamines</th>
<th>Ayahuasca</th>
<th>Ibogaine</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenethylamines</td>
<td>Tryptamines</td>
<td>Ayahuasca</td>
<td>Ibogaine</td>
<td>Ketamine</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Release of 5HT&gt;&gt; NE &amp; DA, 5HT2A binding</td>
<td>Binds to 5HT2A receptors</td>
<td>Blocks MAO and binds 5HT2A receptors</td>
<td>Blocks NMDA receptors</td>
</tr>
<tr>
<td>Prototypes</td>
<td>Most data for PTSD Depression, life-threatening illness, alcohol use disorder</td>
<td>Depression, addiction, PTSD</td>
<td>Depression, addiction, PTSD</td>
<td>Depression, narcolepsy</td>
</tr>
<tr>
<td>Uses</td>
<td>Most data for PTSD Depression, life-threatening illness, alcohol use disorder</td>
<td>Depression, addiction, PTSD</td>
<td>Depression, addiction, PTSD</td>
<td>Depression, narcolepsy</td>
</tr>
<tr>
<td>Safety</td>
<td>Overall good, some risks associated with amphetamines</td>
<td>Good physical safety profile, alone or in combination with other substances</td>
<td>Good physical safety profile as monotherapy, dangerous with other 5HT based drugs</td>
<td>Good physical safety profile as monotherapy, dangerous with other 5HT based drugs</td>
</tr>
</tbody>
</table>

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**Pharmacodynamics**

"Ibogaine’s biological mechanisms of action are completely opaque, pushing the limits of what traditional neuropharmacology is capable of explaining."
Rewarding and Reinforcing Effects of Drugs

- Addictive drugs increase dopamine via a variety of mechanisms, leading to reinforcement
- Ibogaine appears to be able to target several anti-addictive ‘targets’
- Ibogaine has anti-addictive effects in rodent models of SUDs for nicotine, alcohol, cocaine, and opioids

GDNF Release Linked to Anti-Addictive Effects

- Ibogaine increases expression of neurotrophic factors such as GDNF and BDNF in the midbrain (VTA) as well as mesocorticolumbic and nigrostriatal dopamine pathways

Reverse Tolerance and Opioid Receptors

- Despite binding opioid receptors, ibogaine lacks classic μ-opioid responses
- Ibogaine use re-sensitizes users to opioids & possibly other addictive drugs
- Drug users may die by mixing opioids, cocaine, or other drugs with ibogaine

Ibogaine, Detoxification, & Dependence

- Ibogaine observed to address BOTH psychological (craving) and physical dependence in Opioid Use Disorders (OUD)
- Ibogaine observed to address psychological dependence (craving) of other drugs that cause SUDs, but DOES NOT address physical dependence
- It may be possible to both detoxify and address psychological dependence in OUD, although persons with other SUDs may need detoxification prior to use of ibogaine
- E.g., Acute alcohol or benzodiazepine withdrawal can increase risks of seizures with ibogaine

Anti-Addictive Pharmacology Cont.

- Nicotinic - α3β4
  - Ibogaine and 18-MC block α3β4 receptors
  - Implicated in indirect anti-addictive effects by dampening dopamine responses to addictive drugs

- Sigma 1 and 2 – σ1 and σ2
  - σ receptors are intracellular, mitochondrial membrane chaperone proteins or signal transduction amplifiers
  - σ2 properties unique to ibogaine

Glutamate, NMDA, and Neuroplasticity

- Ibogaine blocks NMDA receptors, which may play a role in synaptic plasticity or psychedelic effects
  - Can result in ‘rewiring’
  - Neurons that fire together wire together...
  - Use it or lose it...
Ibogaine and Monoamine Transporters

- Ibogaine inhibits dopamine and serotonin reuptake pumps (DAT and SERT) non-competitively
- Ibogaine stabilizes a unique ‘inward-facing’ conformation of the reuptake pump, which is unique relative to SSRIs or cocaine
- Ibogaine can upregulate and 'correct' deficiently folded reuptake pumps


Pharmacokinetics

Metabolism of Ibogaine

- Dependent on liver function
- CYP2D6 is most implicated liver enzyme
- Active metabolite noribogaine may be critical in mechanisms of detoxification or to therapeutic effects
- Lipophilic drug, sequesters in body tissues, complex pharmacokinetics
  - Impairments in metabolism of ibogaine may significantly increase risks of toxicity

Ibogaine & Noribogaine

- Noribogaine is a long-acting and active metabolite, which could explain self-tapering detoxification effect
- Paroxetine, a CYP2D6 inhibitor, increases ibogaine/noribogaine exposure by 2X

Ibogaine Noribogaine
~7.5 hours ~28-49 hours

Ibogaine and CYP2D6

Toxicology of Ibogaine
Ibogaine in OUD: A Risky Proposition?

- Ibogaine has serious cardiac risk due to potential for arrhythmias
  - Over 20 cases of death reported in medical literature 1990-2021
  - Increased utilization may increase numbers of persons helped and/or harmed
- How to make inherently risky things safer?
  - Research, utilization under medical supervision, thorough screening, lab work, cardiac monitoring, and access to emergency medical care
- How to make inherently risky things less safe?
  - Avoid research, regulation, education, or support for participants
  - Criminalize use and keep drugs available only in black markets or clandestine clinics

Fatalities and Ibogaine Dosing

- General lack of clarity between ‘safe’ and ‘unsafe’ doses
- Estimation of ‘safe’ dose = 0.87mg/kg → Likely too low to be of therapeutic value
- Observational studies used doses ranging from 8-31mg/kg for detoxification
- Cases of death in ‘clinical’ settings with doses of 20-31mg/kg
- Forensic case series reported dose range (4.5-29mg/kg) in fatal cases
- Polydrug ingestions and concurrent cardiac disease common findings
- Relatively low doses capable of significant EKG changes

Cardiotoxicity

- Ibogaine affects potassium channels in cardiac tissue leading to prolonged ‘QTc interval’ and potentially fatal ventricular arrhythmias such as Torsades de Pointes
- Many drugs prolong QTc intervals and combining them increases risk of arrhythmias
- Website for checking if medications can prolong the QTc interval:
  - https://www.crediblemeds.org/
  - Case reports of ventricular arrhythmias with ibogaine use even without concurrent medication or risk factors. Significant QTc prolongation (>500msec; >60msec increase from baseline) has occurred with relatively low doses

Serial EKG dose-ranging studies of noribogaine

<table>
<thead>
<tr>
<th>Opioid Use Disorder</th>
<th>Healthy Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>One participant had a QTc interval &gt;480 msec once (180mg)</td>
<td>One participant (10mg group) with a QTc interval increase &gt;60msec 24 hours post ingestion</td>
</tr>
<tr>
<td>One had QTc &gt;500msec x4 (180mg)</td>
<td></td>
</tr>
<tr>
<td>Two had QTc interval increases &gt;60msec (120, 180mg)</td>
<td></td>
</tr>
</tbody>
</table>

Cardiac Monitoring with Ibogaine Use

- Prior to use → cardiac workup with EKG recommended
  - Prolonged baseline QTc interval contraindication to ibogaine use
  - Electrolytes balanced and within normal limits
  - Screening for other risk factors
- During use → continuous cardiac monitoring (telemetry) recommended
  - Personnel with advanced cardiac life support (ACLS) training
  - Medications to treat cardiac arrhythmias and/or access to nearby ER

Neurologic Toxicity

- Nystagmus, tremors, and ataxia common in first few hours after use with one time emesis in response to motion
- Case reports of muscle spasms, seizures, decorticate posturing and coma reported
Contraindications to Ibogaine

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia or bipolar disorder</td>
<td>Medications known to prolong QTc interval</td>
</tr>
<tr>
<td>Pre-existing cardiac illness</td>
<td>Medications that slow heart rate</td>
</tr>
<tr>
<td>Prolonged baseline QTc interval</td>
<td>Medications that inhibit CYP2D6</td>
</tr>
<tr>
<td>Liver damage and/or cirrhosis</td>
<td>Psychotropic medications</td>
</tr>
<tr>
<td>Cerebellar dysfunction</td>
<td>Long-acting opioids</td>
</tr>
<tr>
<td>Epilepsy or seizure disorders</td>
<td></td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Dementia &amp; organic brain disease</td>
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<tr>
<td>Advanced respiratory conditions</td>
<td></td>
</tr>
<tr>
<td>Electrolyte abnormalities (Mg, K)</td>
<td></td>
</tr>
<tr>
<td>Unrecovered thyroid disorders</td>
<td></td>
</tr>
</tbody>
</table>

Summary & Conclusions

- Ibogaine modulates many neurotransmitter systems to affect mood and substance use, including a unique ability to block opioid withdrawal symptoms
- Ibogaine is limited by cardiotoxicity, lack of rigorous clinical research, and legal status
- Further research into the therapeutic potential of ibogaine (including metabolites and analogues) along with removal of legal barriers to study is emergently needed in the context of epidemic OUD

Question 1

Which of the following is true of ibogaine?

A) It was invented by researchers in France during the early 1900s
B) It is a naturally occurring alkaloid derived from Tabernanthe iboga
C) It is always consumed in the form of an alkaloid extract
D) Iboga root is native to South America

Question 2

Which of the following is true regarding the pharmacology of ibogaine?

A) It has a long-acting metabolite called noribogaine
B) It relies on CYP2D6 for metabolism
C) It binds opioid and NMDA receptors amongst other receptor targets
D) All of the above

Question 3

Choose the condition that is contraindicated with ibogaine:

A) Heroin use disorder
B) Major depression
C) Congenital QTc prolongation
D) Cocaine use disorder
E) Allergic rhinitis

Question 4

Which of the following is a pharmacologic effect of ibogaine supported by observational research?

A) Detoxification of heroin use disorder
B) Detoxification of alcohol use disorder
C) Detoxification of benzodiazepine use disorder
D) Detoxification of Selective Serotonin Reuptake Inhibitors (SSRIs)
Question 5

Which adverse effect has been reported with ibogaine use?

A) Serotonin Toxicity
B) Neuroleptic Malignant Syndrome
C) Ventricular arrhythmias
D) Laryngospasm
E) Respiratory depression