Addiction Pharmacology and Ibogaine

Psychedelic Pharmacology
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- Dr. Malcolm has no relationship with an ineligible company
- This activity may contain discussion of unlabeled/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of (insert organization) or University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings

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About Your Instructor

BS Pharmacology 2008 – UC Santa Barbara

Doctorate 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

Spiritpharmacist.com

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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

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Introduction

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History of Ibogaine

Lambarene

- 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

Popik P, Layer RT, Skolnick P. Pharmacological reviews 1995;47:235-53.

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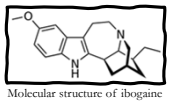
What is Ibogaine?

- 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/

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What is Iboga?

Tabernanthe 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

https://www.ibogainealliance.org/iboga/

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Forms of Ibogaine

'Iboga' Root Bark	Total Alkaloid (TA) Extract	Ibogaine hcl
Dried and ground up root bark; large quantities of fibrous plant material needed for full experience; contains all alkaloids in 'iboga'	Extraction of psychoactive alkaloid content of iboga; lesser quantities needed for full experience; contains all alkaloids in 'iboga'	Extracted and purified or semi-synthetically produced; smallest quantity needed for full experience; isolates the alkaloid ibogaine

Table 1 Approximate yields of iboga alkaloids isolated from the whole root bark of various sources. Percentages indicate the weight of the alkaloid free base relative to the weight of the plant source. TR = trace (<0.01%). NR = not reported

Plant species	Ibogaine	Ibogamine	Voacangine	Coronaridine	Catharanthine
T. iboga[9–12]	0.27–0.32	0.097–0.40	0.043–0.28	NR	NR
V. africana[13]	0.25	TR	1.67	TR	NR
T. arborea[12,13]	0.27	0.036	0.96	0.073	NR
C. roseus[14]	NR	NR	NR	NR	0.003–0.099
T. alba[12]	0.046–0.22	0.042–0.30	0.033–0.96	0.075–0.52	NR
T. donnell-smithii[12]	0.069–0.74	0.028–0.032	0.21–0.44	0.046–0.23	NR
T. amygdalifolia[12]	0.047	0.76–0.96	0.19–0.22	1.092–1.38	NR

Table 1 from Iyer, R. N., et al. (2021). Nat Prod Rep 38(2): 307-329.

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Psychedelics Compared

	Phenethylamines	Tryptamines	Ayahuasca	Ibogaine	Ketamine
Mechanism	Release of 5HT>> NE & DA, $5HT_{2A}$ binding	Binds to $5HT_{2A}$ receptors	Blocks MAO and binds $5HT_{2A}$ receptors	Modulators of opioid, glutamate and other systems	Blocks NDMA receptors
Prototypes	Mescaline, MDMA	LSD, Psilocybin, DMT	Harmalas from ayahuasca vine + DMT	Ibogaine	Ketamine
Others	MDA, 2Cx, NBOMe, & DOx compounds	5-MeO-DMT, 5-MeO-DiPT	Harmalas from Syrian Rue + DMT or psilocybin	Noribogaine	Methoxetamine
Uses	Most data for PTSD	Depression, life-threatening illness, alcohol use disorder	Depression, addiction, PTSD	Opioid and cocaine use disorders	Depression, suicidality
Safety	Overall good, some risks associated with amphetamines	Good physical safety profile, alone or in combination with other substances	Good physical safety profile as monotherapy, dangerous with other 5HT based drugs	Requires medical workup, notorious for cardiotoxicity	Good physical safety profile as monotherapy

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Pharmacodynamics

"Ibogaine's biological mechanism of action is completely opaque, pushing the limits of what traditional neuropharmacology is capable of explaining"

Iyer, R. N., et al. (2021). Nat Prod Rep 38(2): 307-329.

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Receptor Binding of Ibogaine & Noribogaine

- Long-acting active metabolite noribogaine likely play significant clinical role
- Both have complex pharmacology with binding to several receptor types
  - Opioid
  - Glutamate
  - Sigma
  - Serotonin transporter
  - Dopamine transporter
  - Nicotinic receptor

Receptor	Ibogaine	Noribogaine
k opioid	2-4	0.6-1
μ opioid	10-100	3
Δ opioid	>100	25
NMDA	1-3	6
σ-1	9	15
σ-2	0.09-0.2	5
DAT	2	2
SERT	0.5	0.04
α3β4	0.02	1.5

Affinity for receptor sites (K_i in *μM*)

Litjens RP, Brunt TM. Clinical toxicology (Philadelphia, Pa) 2016;54:297-302.
Mash DC, et al. Annals of the New York Academy of Sciences 1998;844:274-92.
Glick, S. D. and I. S. Maisonneuve (1998). Ann N Y Acad Sci **844**: 214-226.

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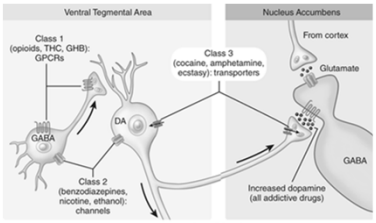
Rewarding and Reinforcing Effects of Drugs

- 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



Belgers M, et al. Translational psychiatry 2016;6:e826.

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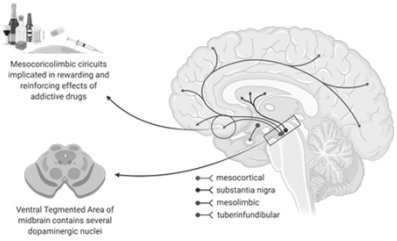
GDNF Release Linked to Anti-Addictive Effects

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



Marton, S., et al. (2019). Front Pharmacol 10: 193.
Carnicella, S., et al. (2008.) Proc Natl Acad Sci U S A 105(23): 8114-8119.

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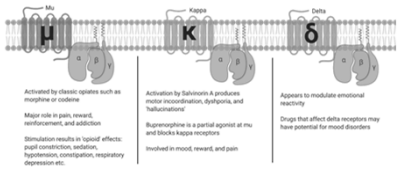
Reverse Tolerance and Opioid Receptors

- 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

Receptor	Ibogaine	Noribogaine
μ opioid	10-100	3
k opioid	2-4	0.6-1
Δ opioid	>100	25



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Mash DC, et al. Annals of the New York Academy of Sciences 1998;844:274-92.
Glick, S. D. and I. S. Maisonneuve (1998). Ann N Y Acad Sci **844**: 214-226.

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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

Clinical Guidelines for Ibogaine-Assisted Detoxification. Global Ibogaine Therapy Alliance, 2015. https://www.ibogainealliance.org/guidelines/
Alper KR, Stajic M, Gill JR. Journal of forensic sciences 2012;57:398-412.

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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

Rousseaux, C. G. and S. F. Greene (2016). Journal of receptor and signal transduction research 36(4): 327-388.
Floresta, G., et al. (2019). Int J Mol Sci 20(3): 488.
Wilhyard, C. (2015). Nature 522(7557):353-55.

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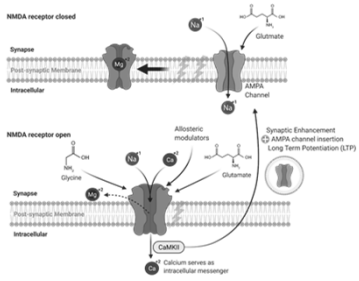
Glutamate, NMDA, and Neuroplasticity



- Ibogaine blocks NDMA 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..

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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

Bulling, S., et al. (2012). J Biol Chem 287(22): 18524-18534.
Coleman, J. A., et al. (2019). Nature **569**(7754): 141-145.
Möller, I. R., et al. (2019). Nat Commun **10**(1): 1687.
Sucic, S., et al. (2016). J Neurol Neuromedicine **1**(9): 34-40.

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Pharmacokinetics

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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

Glue P, Winter H, Garbe K, et al. Journal of clinical pharmacology 2015;55:680-7.
Glue P, et al. Journal of clinical pharmacology 2015;55:189-94.
Litjens RP, Brunt TM. Clinical toxicology (Philadelphia, Pa) 2016;54:297-302.
Mash DC, Kovera CA, Buck BE, et al. Annals of the New York Academy of Sciences 1998;844:274-92.

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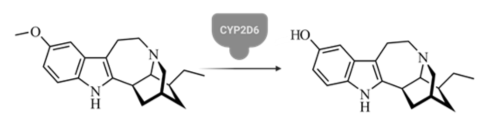
Ibogaine & Noribogaine

- 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

Half-life or ibogaine & noribogaine in CYP2D6 extensive metabolizers

Glue P, Winter H, Garbe K, et al. Journal of clinical pharmacology 2015;55:680-7.
Glue P, et al. Journal of clinical pharmacology 2015;55:189-94.
Litjens RP, Brunt TM. Clinical toxicology (Philadelphia, Pa) 2016;54:297-302.
Mash DC, Kovera CA, Buck BE, et al. Annals of the New York Academy of Sciences 1998;844:274-92.

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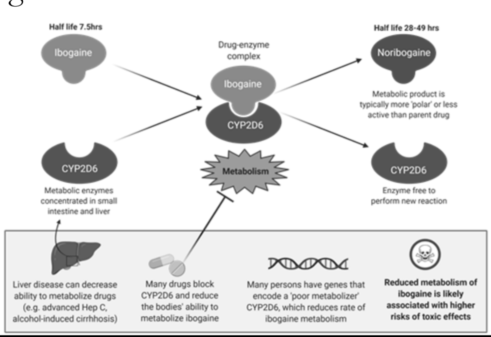
Ibogaine and CYP2D6



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Toxicology of Ibogaine

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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

Alper KR, Stajic M, Gill JR. Journal of forensic sciences 2012;57:398-412.

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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 29-31mg/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

Alper KR, Lotsof HS, Frenken GM, Luciano DJ, Bastiaans J. The American journal on addictions 1999;8:234-42.
Alper KR, Lotsof HS, Frenken GM, Luciano DJ, Bastiaans J. Annals of the New York Academy of Sciences 2000;909:257-9.
Maleeko BJ, Polanco M, Barsuglia JP. Journal of psychoactive drugs 2018:1-10.
Mash DC, Kovera CA, Pablo J, et al. Alkaloids Chemistry and biology 2001;56:155-71.
Noller GE, Frampton CM, Yazar-Klosinski B. The American journal of drug and alcohol abuse 2017:1-10.
Sehgal LJ, Slaughter RJ, Galea S, Newcombe D. Drug and alcohol dependence 2016;166:1-5.

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Cardiotoxicity

- Ibogaine affects potassium channels in cardiac tissue leading to prolonged 'QTc interval' and potentially fatal ventricular arrythmias 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

Hilchard C, Macklin P, Prendergast B, Barber Y. The Journal of emergency medicine 2016;50:e83-7.
Hoslan DW, Sperring W, Valk GD. The New England journal of medicine 2009;360:308-9.
Glue P, Cape G, Tunnicliff D, et al. Clinical pharmacology in drug development 2016;5:460-8.
Glue P, Lockhart M, Lam F, Hung N, Hung CT, Friedhoff L. Journal of clinical pharmacology 2015;55:189-94.

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Serial EKG dose-ranging studies of noribogaine

Opioid Use Disorder

- One participant had a QTc interval >480 msec once (180mg)
- One had QTc >500msec x4 (180mg)
- Two had QTc interval increases >60 msec (120, 180mg)

Healthy Persons

- One participant (10mg group) with a QTc interval increase >60msec 24 hours post ingestion

Dose-dependent effects of noribogaine on QTc intervals

Dose of Noribogaine	Mean Increase in QTc (msec)
60	16
120	28
180	42

Glue P, Cape G, Tunnicliff D, et al. Clinical pharmacology in drug development 2016;5:460-8.
Glue P, Lockhart M, Lam F, Hung N, Hung CT, Friedhoff L. Journal of clinical pharmacology 2015;55:189-94.

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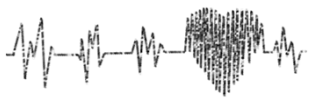
Cardiac Monitoring with Ibogaine Use

- 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



Clinical Guidelines for Ibogaine-Assisted Detoxification. Global Ibogaine Therapy Alliance, 2015. https://www.ibogainealliance.org/guidelines/

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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

Mash DC, Kovera CA, Pablo J, et al. The Alkaloids Chemistry and biology 2001;56:155-71.
Alper KR, Stajic M, Gill JR. Journal of forensic sciences 2012;57:398-412.
Litjens RP, Brunt TM. Clinical toxicology (Philadelphia, Pa) 2016;54:297-302.
Luciano D. The American journal on addictions 1998;7:89-90.

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Contraindications to Ibogaine

Conditions	Medications
• Schizophrenia or bipolar disorder • Pre-existing cardiac illness • Prolonged baseline QTc interval • Liver damage and/or cirrhosis • Cerebellar dysfunction • Epilepsy or seizure disorders • Pregnancy • Dementia & organic brain disease • Advanced respiratory conditions • Electrolyte abnormalities (Mg, K) • Untreated thyroid disorders	• Medications known to prolong QTc interval • Medications that slow heart rates • Medications that inhibit CYP2D6 • Psychotropic medications • Long-acting opioids

*For greater detail see: https://www.ibogainealliance.org/guidelines/patient-criteria-considerations/
Clinical Guidelines for Ibogaine-Assisted Detoxification. Global Ibogaine Therapy Alliance, 2015. https://www.ibogainealliance.org/guidelines/
Mantu CJ, Ryan WC, Kopelowicz A, Kosk RJ. American journal on addictions 2015;24:203-5.

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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

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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

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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

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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

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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)

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Question 5

• Which adverse effect has been reported with ibogaine use?

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

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