

Ibogaine as an Alternative and Efficacious Treatment for Heroin Addiction

Nicole K. Amadon, sixth year pharmacy student from North Canton, Ohio; Andrew M. Roecker, PharmD '00, RPh, BCPS, Professor of Pharmacy Practice

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-12-075-H01-P

Objectives

At the conclusion of this article, the participant should be able to:

1. Discuss current trends in heroin addiction and abuse
2. Explain the routes of administration and accepted dosage range of ibogaine
3. List the proposed mechanisms of action for ibogaine
4. Discuss serious adverse events associated with ibogaine use
5. Describe the differences between ibogaine and 18-methoxycoronaridine

Introduction to Heroin Abuse and Addiction

Addiction is a growing problem in society as more people experiment with illicit drugs and fall into drug addiction as a consequence. Addicts tend to exhibit symptoms of drug tolerance with continued abuse and may develop substance dependence. As one continues to use a drug to achieve a “rush” or a “high”, some must use increasing amounts of a given drug to achieve the same high that was experienced previously, depending on the substance used. Many addicts continue to increase doses until drug-induced overdose or death occurs. Addicts are also fueled by the desire to avoid withdrawal symptoms, which may range from nausea and resting tremors to anxiety and insomnia¹. If the search for drugs interferes with daily living, this is called substance dependence, as one plans time and resources around acquiring the next hit of drug.

Withdrawal symptoms can be viewed as negative reinforcement, since their presence pushes an addict to acquire more drugs. Addicts may report dysphoria, depression, or muscle cramps, and objective signs include midriasis, elevated pulse, and piloerection². These withdrawal symptoms are a

result in a decrease in dopamine and serotonin release in the nucleus accumbens, or the opposite event from when one ingests an illicit substance to achieve a high. The nucleus accumbens is called the reward center of the brain and addicts feel a mental and emotional reward for ingesting illicit drugs, particularly opioids. Heroin is a powerful and highly addictive opioid that exerts activity in the nucleus accumbens, but an herbal-derived drug called ibogaine may have a role in attenuating or ceasing the addictive and withdrawal effects of heroin.

Heroin (diacetylmorphine) is a drug derived from the opium poppy. Street names vary with region, but include black tar, China white, dust, caffeine “H”, and smack³. Heroin is an estimated two- to four-times more potent than morphine and it is converted to morphine, a μ opioid receptor agonist, by the liver if ingested orally. The most common route of administration by heroin abusers is by injection, after which the drug is hydrolyzed by serum cholinesterase to 6-monoacetylmorphine followed by morphine in the brain⁴. After hydrolysis, heroin conversion takes approximately 15 seconds and the amount of morphine released makes heroin three times more potent than taking morphine alone. This increased potency is responsible for the classification of heroin as a Schedule 1 controlled substance under the Controlled Substances Act of 1970⁵, which means the drug has no accepted medical use, a high potential for abuse, and lacks safety data. This classification does not stop some people from using heroin and it has become more dangerous in recent years as black market manufacturers increase the potency of their product, which has led to more deaths due to overdose. In a 2008 survey, it was estimated the average heroin sample sold on the street was 28% pure⁶, but this can vary greatly among suppliers.

In 2008, there were 213,000 current heroin users aged 12 and older⁷. Of these, 114,000 were first-time heroin users. An estimated 23% of heroin users become addicted to the drug, which lends itself to continued abuse of the drug. The majority of heroin users are aged 26 years or older and most

new users are male over the age of 18 years. In 2003, an estimated 314,000 Americans used heroin in the past year and 57.4% of these people were classified with substance dependence or abuse⁸. There were an estimated 281,000 treatments for heroin abuse in 2003⁹; this figure does not take into account the number of people who sought treatment, as some addicts may undergo multiple treatments. This number is higher than the estimated number of current users for a couple reasons: there is a degree of underreporting on the actual use of illicit substances, but also craving may persist for years after an addict has become clean and stopped using the drug. In 2008 the estimated retail price of 1 gram of heroin was \$29-39 in the United States, which is lower than the estimated prices of cocaine and methamphetamine because these drugs tend to be purer at purchase⁶.

According to a study by Monitoring the Future, around 0.7% of 8th, 10th, and 12th grade students used heroin in the past year¹⁰. The perceived risk of heroin among this population is around 60-70%, which seems low given the abuse potential for this drug, but disapproval of heroin use is 90%. This means a good target for prevention should be children in elementary school. Prevention should make children aware of the risks associated with the use of illicit drugs through programs such as D.A.R.E. (Drug Abuse Resistance Education). Since the disapproval rating is fairly high, another measure of prevention should target family and community associations. Children who are educated with their peers and elders are more likely to avoid use of heroin because of the strong sense of disapproval in the community.

Current pharmacotherapy for opioid addiction includes methadone, buprenorphine, and naltrexone. All medications are administered with a recommended psychosocial and medication adherence support with various dosage regimens for induction and maintenance therapy for opioid addiction. Patients with known or suspected opioid overdose are given intravenous naloxone in a clinical setting to prevent opioid-induced respiratory depression, followed by maintenance therapy for

addiction. Opioid management remains a problem as patients neglect to adhere to medication schedules and rehabilitation appointments. If a patient cannot escape the triggers and settings associated with past drug abuse, it is likely the patient will relapse.

Background Information on Ibogaine

Ibogaine is an indole alkylamine derived from the plant *Tabernanthe iboga*. This shrub is indigenous to the West African nation of Gabon and the surrounding area. The use of the plant in ritual sacraments is documented by observers of the Bwiti religion in Gabon. New members are instructed to eat the root bark of the plant at an initiation ceremony, during which the initiates will have a hallucinogenic experience. This “binding” ceremony is viewed as social cohesion among tribe members and ancestors, with whom many initiates may have contact during their hallucinogenic trip. Other sporadic reports suggest ibogaine has also been used as a traditional medicine for some somatic conditions, particularly for infertility and venereal disease¹¹.

Ibogaine is classified as a Schedule 1 drug in the United States. It is also illegal in Australia, Belgium, Denmark, France, Sweden, and Switzerland, but it is unscheduled in many other countries¹¹. This does not necessarily confer a legal status in other countries, but laws vary around the world. Reports indicate ibogaine is not often used as a recreational drug like other hallucinogens¹¹. The drug was the subject of research in the early 20th century, but most research remains classified or destroyed. It was marketed in France under the name Lambarène as an 8 mg tablet from 1939 to 1970 as a neuromuscular stimulant. However, further research from other countries revealed the abuse potential for the drug and it has been banned in France since 1970. The United States government conducted tests with ibogaine in secret during the 1960s under the name MK ULTRA¹¹, but after details of the project were made public and private researchers released more information on ibogaine, the National

Institute on Drug Abuse (NIDA) decided not to pursue the ibogaine project at a 1995 meeting¹². A representative at the meeting said the decision was made because ibogaine would likely be expensive, time-consuming and ultimately a failure, but it did not recommend against testing in humans. Most information on ibogaine is available online for either educational or promotional purposes.

Ibogaine Administration

Promotional websites direct customers to programs for opioid detoxification using ibogaine. These programs offer detoxification sessions in countries where ibogaine is a legal substance. There are four proposed models for ibogaine administration¹¹. The medical model is administered by a licensed physician in a country where ibogaine holds legal status, such as Mexico, Panama, or St. Kitts. This model emulates current conventional medical standards in addiction treatment and the main difference is using a drug that has little conclusive evidence for an addiction protocol. The cost for a stay at one of these facilities ranges from \$1,300 to \$1,900 if at a non-licensed facility, up to \$15,000 if at a facility licensed by the national government¹³. The lay provider model is similar to the medical model, but the provider does not hold any medical credentials. These providers are viewed as “guides” and use informal protocols that have been developed by various countries, such as the United States or the Netherlands¹⁴. These manuals are available for download online and include directions for dosage, monitoring, and how to address any adverse events that may occur while the patient is on the hallucinogenic trip. The third model is the activist or self-help model, in which the lay provider participates with an activist or evangelical, usually to gain acceptance of the use of ibogaine by a certain group. The final model is the religious or ceremonial model, which involves a lay provider at a Bwiti shrine or other ceremonial context.

According to one of the lay provider manuals, a single oral treatment of 6 to 19 mg/kg can effectively precipitate and maintain abstinence from drug abuse for approximately 6 months¹⁵. Ibogaine is currently available as root bark from the botanical shrub, an alkaloid extract containing 15% ibogaine, and purified ibogaine HCl (once marketed as Endabuse²) which is 99.4% pure. To increase efficacy, a series of four treatments is reported to maintain abstinence from opioids for up to three years. Early data suggest intermittent treatments over a period of at least two years are required to achieve long-term abstinence¹⁶. The greatest evidence from studies with similar treatment goals suggests using hypnodelic therapy¹⁷, which is a combination of hypnosis and psychotherapy. This uses a combination of therapies to target different approaches to altering behavior, which is sometimes seen in patients who wish to quit smoking. The dose of ibogaine is the same regardless of whether the patient is being for narcotic or stimulant abuse. The manual for ibogaine therapy¹⁸ is fairly complete considering it has not been approved by a credible medical association. The manual contains the procedure known as the Lotsof procedure¹⁶, which was developed by Howard Lotsof. The manual lists inclusion and exclusion criteria to ensure patient safety. Each patient must obtain an electrocardiogram prior to initiation of therapy and pulse and blood pressure should be recorded at regular intervals for a 24 hour period. Neurological and psychological assessments are also suggested and the manual includes scales for withdrawal symptoms.

Mechanisms of Action of Ibogaine

Ibogaine exhibits many proposed mechanisms of action that contribute to its psychological effects. It is primarily an agonist at the μ opioid receptor¹⁹, which accounts for its ability to reduce or eliminate opioid withdrawal symptoms. A study by Codd showed that ibogaine reduces naltrexone-induced withdrawal signs in morphine-dependent rats, reversing the antagonist effects of naltrexone. As mentioned previously, ibogaine works in the nucleus accumbens in the brain. Prior exposure to

morphine potentiates an ibogaine blockade of dopamine elevations in this region²⁰. In a study by French et al. intravenous administration of morphine increased the firing rate of dopaminergic neurons in the ventral tegmental area in a dose-dependent manner, but pre-treating the rats with ibogaine did not result in the expected neuronal excitation after morphine administration. Ibogaine does not prevent morphine from activating dopaminergic neurons, but it does attenuate the neuronal firing.

Other mechanisms of action have been suggested, although the evidence behind these is weaker than that supporting action at μ opioid receptors and the nucleus accumbens. A study by Leal et al. suggests ibogaine is a noncompetitive open channel N-methyl-D-aspartate (NMDA) receptor antagonist²¹. Withdrawal from morphine has been shown to cause glutamate release. In this study, ibogaine inhibited naloxone-induced jumping in morphine-dependent mice, suggesting activity at the NMDA receptor. Higher doses of ibogaine were tested to display signs of toxicity, including gait ataxia, myoclonus, depressed respiration and death in mice²². There is a dose-dependent relationship with lethality in mice and the LD₅₀ for this study was determined at 213 mg/kg, which is much higher than the dosage range suggested for opioid withdrawal in the lay provider's manual. This study also showed ibogaine is an effective anticonvulsant according to the maximal electroshock seizure test (MES) with an ED₅₀ of 31 mg/kg.

A final proposed mechanism of action involves serotonin receptors. Jupp et al. suggest ibogaine binds the cocaine receptor site of serotonin transporters²³. Studies show that opioid receptors are negatively coupled to adenylyl cyclase and Rabin et al. suggest ibogaine enhances inhibition of adenylyl cyclase activity when stimulated with morphine²⁴. The study suggests a functional antagonism since ibogaine is known to bind to the μ opioid receptor, but there is a lack of evidence supporting this theory and further research is required before making definitive conclusions.

In addition to direct mechanisms of action, ibogaine has an active metabolite. Ibogaine is metabolized by CYP2D6¹⁴ to noribogaine, which is the primary metabolite. A study by Glick et al. suggests noribogaine may be less potent than ibogaine because ibogaine is more lipid-soluble. Noribogaine displays similar effects to ibogaine, but it is not shown to induce tremors like ibogaine. Along those lines, ibogaine is sequestered in fat after administration, so a gradual release from fatty tissue and subsequent metabolism of the parent drug may account for the long half-life of noribogaine and the lasting effects patients may see after being treated for opioid addiction¹⁵. For this reason, the terminal half-life of noribogaine has not been established, but studies have shown a half-life of 5 to 8 hours for ibogaine²⁵. Elimination of the drug finally occurs via the kidney and the gastrointestinal tract¹⁴.

Clinical Effects of Ibogaine: The Three Phases

There are three phases associated with ibogaine therapy, which are described from case reports¹⁶ using the Lotsof procedure. One particularly useful case report is from a medical doctor who was dependent on meperidine after unsuccessful attempts to cease drug dependence. The first phase is a visualization phase which lasts approximately 4 to 8 hours after the administration of ibogaine. Patients in case reports describe this phase as a “waking dream” – a dream-like state in which the patient is awake and able to respond to questions from the provider. Electroencephalography has shown brain activity in this state to be analogous to the rapid eye movement stage of sleep. Most people prefer not to speak so they can focus on the images they see. The images present themselves in the form of a high-speed movie with each frame indicating a specific event in the viewer’s life. Subjects view and analyze the contents of this movie, so distracting the subject with questions can interrupt the process and providers should reserve patient stimulation for adverse situations.

After the waking dream, patients enter a phase of cognitive evaluation which lasts from 8 to 20 hours after ibogaine administration. This phase reflects on the situations seen in the waking dream and patients report understanding alternatives that were available in past decisions. This new knowledge allows patients to modify their current behavior involving illicit drug use and to overcome drug dependence. Some patients understand that they alone are responsible for their drug-seeking behavior and this realization empowers them to change their behavior. Finally, after cognitive evaluation, patients reach a phase of residual stimulation that may show effects for 24 to 72 hours after ibogaine administration. Patients often show behavioral immobility as they transition out of the acute effects of ibogaine and regain normal attention to the external environment. Behavioral immobility refers to a preference toward lack of movement, but patients are able to stand and move with difficulty if asked. At this point in treatment, the acute effects of the drug start to wear off, but the duration of long-term effects varies for each patient.

The acute effects are similar for patients using ibogaine therapy. Effects begin within an hour after the drug is administered and peak within 2 to 3 hours. The first symptom to appear in patient reports is a persistent oscillating sound. This disruption of balance in the ear is the likely cause of ataxia and nausea. Nausea is worse when a patient attempts movement, so protocols state that the patient should remain lying in bed with as little movement as possible. This position also helps patients to focus on the images in the waking dream. Providers will notice a 10 to 15% rise in blood pressure, which may be accompanied by a slowed pulse rate. Monitoring vital signs is important to maintain patient safety while they are under the influence of ibogaine.

As mentioned previously, patients are awake during the procedure even if they do not show signs of movement. This is because ibogaine temporarily reduces the need to sleep. The increased distribution of the drug in fat tissue and subsequent delayed metabolism account for long-term effects

of this drug. Insomnia can be troublesome for many patients since sleep is used as an escape mechanism when not abusing drugs. A support system of family and friends may be strong enough to help a recovering addict since this drug-induced insomnia is usually temporary and patients will still feel the effects of the drug for a few days after administration. If pharmacotherapy is desired, this insomnia is responsive to sleep medications². Ibogaine also altered the response for a non-drug reinforcer in trials with laboratory rats. The response for water was reduced in the first few hours after drug administration, which occurred along with a reduction in response for ibogaine itself²⁶. These findings suggest ibogaine affects the response for water, making a rat less likely to acknowledge thirst, which may negatively impact the effect ibogaine has on heroin addiction because the rats show delay when enforcing non-drug behavior.

Adverse Effects of Ibogaine

Ibogaine use is associated with a few serious adverse drug events. The most pronounced of these are cardiac rhythm abnormalities¹¹. One case report submitted to the New England Journal of Medicine²⁷ describes a prolonged QT interval of 548 msec and ventricular tachyarrhythmias in a 31-year-old American woman. She had no significant past medical history and was admitted to the emergency department after taking a single dose of 3.5 grams of ibogaine 15% alkaloid extract (the case report mentions a usual dose between 2 and 6 grams). Laboratory testing showed mild hypomagnesemia (0.49 mmol/L, range 0.7 to 1) and hypokalemia (3.2 mmol/L, range 3.8 to 5). The QT interval remained prolonged despite corrections for the electrolyte imbalances and finally normalized at 42 hours after presentation.

Risk factors including prior myocardial infarction, pulmonary embolism or mixed drug overdoses may predispose a patient to cardiac abnormalities with ibogaine administration. These

cardiac events are also noted more frequently with the alkaloid extract and dried root bark as opposed to the powder that is used to make tablets and capsules. The severity of cardiac adverse events necessitates the use of an EKG throughout a patient's treatment with ibogaine, as specified in protocols. Many of the exclusion criteria for treatment focus on cardiac diseases the patient may have¹⁶.

In vitro, ibogaine has been shown to cause degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis of rats¹⁷. High dose ibogaine of 100 mg/kg induced strong, high-frequency tremors in rats¹¹. One study suggested that ibogaine causes sustained excitation of glutamatergic neurons and the excess release of glutamate caused excitotoxic injury to Purkinje cells in rats²⁸. Evidence for this event is believed to be linked to ibogaine's affinity for σ_2 receptors. Although laboratory rats displayed neurotoxicity after ibogaine administration, evidence of neurotoxicity is absent in reports of laboratory mice, primates, and a postmortem woman¹¹. This indicates ibogaine may have different neurological effects in rats and other animals and a dose of 100 mg/kg is much greater than the recommended range for addiction treatment.

Reports of Death Associated with Ibogaine

Although treatment with ibogaine is underreported, there are a few reported cases where treatment adversely resulted in the death of the patient. A 40-year-old female treated in France in 1989¹⁸ was given a dose of 8 mg/kg and died four hours after the dose was administered; the autopsy revealed blockage in the main arteries leading to the heart. Another female treated in 1994¹⁴, whose age and treatment location were not reported, received four separate ibogaine treatments over a period of 15 months preceding her death. Her autopsy revealed mesenteric arterial thrombosis related to chronic cellulitis. Both of these cases emphasize taking a patient's full medical history and following

recommended exclusion criteria when using ibogaine. A third female, aged 24 years, was treated in the Netherlands in 1993². The patient reported muscle aches and nausea at 17 hours post-administration and subsequently went into respiratory arrest and died. No definitive conclusion was offered about the cause of death, but the provider did note the presence of heroin paraphernalia among her belongings at the treatment facility. This case report suggests the possibility that concomitant heroin use during or preceding treatment with ibogaine may increase the toxicity of the drug. For this reason, protocols suggest the provider should monitor the patient for 24 hours before initiating treatment to ensure there is a drug-free window. Finally, a 38-year-old male was treated in the United Kingdom in 2000¹⁸. He died suddenly at 38 hours post-administration of the *Tabernanthe iboga* plant extract while in apparent recovery. His death suggests there is no greater toxicity with plant extract versus purified powder, but the concentration of either preparation may vary depending on supplier.

Ibogaine and the Treatment of Addiction

In patients who used ibogaine to pharmacologically abstain from a primary drug of dependence, 36% self-reported an abstinence period of at least six months after treatment¹¹. Patients saw a decrease in physical withdrawal signs from morphine, heroin, cocaine, and amphetamines¹⁷, which are the primary drugs for which treatment with ibogaine is sought. Heroin users reported drug-free intervals ranging from weeks to months. There are no randomized controlled clinical trials of ibogaine, but information is available from patient case reports.

One case compilation from Alper et al.² assessed 33 opioid-dependent individuals treated with ibogaine that were presented as cases at the Ibogaine Review Meeting in 1995. After treatment, 27 patients reported resolution of withdrawal signs and did not immediately seek drugs. Five patients sought drugs within the 72 hour post-treatment interval; two of these patients had full resolution of

withdrawal symptoms. One fatality at 19 hours post-administration was reported in this compilation. This patient was mentioned previously in the discussion of patient deaths: heroin paraphernalia, including tin foil, was found in her belongings and it was believed she was “chasing the dragon” after ibogaine administration. Chasing the dragon entails heating heroin on a piece of tin foil and inhaling the smoke produced, which usually looks like a dragon to the user.

Case reports listed online in the Ibogaine Dossier²⁹ offer a more detailed evaluation of the efficacy of ibogaine. Out of seven cases reported, three were drug-free at 18 weeks post-administration; this number increased to four cases at one year post-treatment. One case reported heroin use three times in the first two weeks post treatment but was drug-free after this point, while another case reported intermittent heroin use during several months post-treatment before reporting a drug-free state. Two additional cases reported total relapse to heroin use (at eight months and 12 months post-treatment) and the seventh case relapsed to daily heroin use by 10 weeks and reported methadone use after 17 weeks. Some of the cases reported addiction to one opioid, primarily heroin, while a few reported multiple drug addictions. Based on the information available from these cases, there are no correlations between efficacy and the number of drugs abused. However, there may be a correlation with gender. All three cases that relapsed to regular heroin use were males. Weights were reported but not heights, so we cannot make conclusions about ibogaine distribution in fat tissue without an indication of body mass index or body build. The doses for each patient were reported and there was no correlation between a high or low dose and efficacy. The authors did not report rationale for choosing high or low doses for the cases.

A longitudinal study was conducted by Bastiaans³⁰ in 2004 as online questionnaires adapted from the Europe-Addiction Severity Index. This study assessed the long-term effects of ibogaine therapy at one year post-treatment. 67% of the patients reported heroin as the primary drug of abuse,

with an additional 10% of patients reporting another opiate as primary. Out of 21 participants, five reported no substance abuse with an average drug free period of 41 months. Of the remaining 16 participants, 56% stopped using their primary drug of abuse but continued to use other drugs, primarily alcohol and cannabis. The average drug free period in this group was almost 21 months, which is significantly lower than the average if a patient stopped using drugs altogether. Among the patients that continued to use their primary drug of abuse, the average drug free interval was one week. The form of ibogaine used to treat patients was assessed and researchers found that the average drug free interval with the HCl powder was almost 27 months, compared to 2 months with the plant extract. The study also reported longer drug free intervals with more ibogaine treatments and fewer drugs abused. The author addressed limitations of the study, which can be inferred by the type of study performed, but the data support trends among other case reports of ibogaine therapy.

For patients who abuse heroin, acute withdrawal syndrome begins approximately eight hours after the last hit of drug¹⁴. The associated symptoms peak around 24 to 48 hours and subside after 7 to 10 days. Ibogaine has shown resolution of acute withdrawal symptoms during the first week after treatment, but the patient may not see a reduction in craving and depression until one month later. The residual craving is one reason why patients may use heroin during the post-treatment interval, but they eventually maintain a drug free interval. However, if an individual is not mentally prepared to give up addiction before treatment with ibogaine, it is likely that drug abuse will resume²⁹. Two case reports listed in the Ibogaine Dossier reported a return to heroin abuse after taking a hit of their abused drug after treatment with ibogaine to see what the effect would be like. Other case reports mention similar events. A hypothesis for the anti-addiction effects of ibogaine may involve potentiating of a patient's feelings toward addiction cessation by bringing back memories during the visualization phase, which may help them overcome drug dependence²⁵.

Evidence of a Synthetic Ibogaine Congener

Some of the concerns over the toxicities associated with ibogaine have led to the development of a synthetic congener. 18-Methoxycoronaridine (18-MC) decreased morphine and cocaine self-administration in 80% of laboratory rats²⁶. The doses of 18-MC used were comparable to experimental doses of ibogaine. 18-MC did not affect the response for water, but it significantly reduced food intake, an indication that this drug may have a different effect on nondrug reinforcers. It showed dose-dependent reduction of five out of seven acute withdrawal syndrome signs in rats (teeth chattering, wet-dog shake, burying, diarrhea, and weight loss, but not grooming or flinching), which is similar to the results seen with ibogaine. Tremors were not reported even at high doses (100 mg/kg intraperitoneal administration) with 18-MC and pathological examination of the rats did not show degeneration of Purkinje cells. Cardiovascular effects were evaluated at 200 mg/kg of 18-MC and did not show an effect on blood pressure or heart rate. Thus, 18-MC does not show the serious toxicities that are associated with ibogaine.

18-MC shows similar pharmacokinetic parameters and mechanisms of action compared to ibogaine²⁶. 18-MC has a terminal half life of 100 minutes and is sequestered in fat. However, the drug level in fat is less than 10% of the administration dose, which suggests that 18-MC is rapidly metabolized. 18-MC has low affinity for all opioid receptors and the 5-HT₃ receptor, but unlike ibogaine, it has no significant affinity for the NMDA receptor or the serotonin transporter. An equivalent dose of 18-MC did not increase serotonin levels in the nucleus accumbens, so this drug may not be hallucinogenic.

The Role of the Pharmacist

The role of the pharmacist concerning ibogaine is small. Ibogaine is either administered at an approved clinic overseas or illegally by a lay provider. Therefore, it is important for the pharmacist to counsel any struggling drug addicts on the importance of becoming clean, especially if the addict is a patient of the pharmacy. In the retail setting, a pharmacist can recommend supportive measures and educate the patient about potential interactions with any chronic medications, especially since heroin is metabolized by extensive first-pass effects by the liver. In a hospital setting, a pharmacist can explain the serious adverse events of a drug overdose and recommend rehabilitation before discharge. The development of 18-MC seems to be a safer alternative to ibogaine, but there remains no approved treatment for heroin addiction other than the opioid antagonists. Education remains the pharmacist's most powerful skill when interacting with patients who are dependent on a drug of abuse.

References

1. American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC: American Psychiatric Association.
2. Alper KR, Lotsof HS, Frenken GMN, Luciano DJ, Bastiaans J. Treatment of acute opioid withdrawal with ibogaine. *Am J Addiction*. 1999; 8:234-242.
3. Slang/street names for heroin, cocaine, and other narcotics. [Updated 2011 May; cited 2012 Apr 22]. Available from: <http://web4health.info/en/answers/bio-drug-slang.htm>
4. Lockridge O, Mottershaw-Jackson N, Eckerson HW, La Du BN. Hydrolysis of diacetylmorphine (heroin) by human serum cholinesterase. *J Pharmacol Exp Ther*. 1980; 215(1):1-8.
5. U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control. (1970). Title 21 United States Code Controlled Substances Act. Washington, DC: Government Printing Office.
6. Opiate: retail and wholesale prices and purity levels. United Nations Office on Drugs and Crime [updated 2010 Jul 30; cited 2012 Feb 18]. Available from: <http://www.unodc.org/documents/data-and-analysis/WDR2010/AllPrices.pdf>
7. InfoFacts: Heroin. National Institute on Drug Abuse. Bethesda (MD): National Institutes of Health [revised 2010 Mar; cited 2012 Feb 18]. Available from: <http://www.drugabuse.gov/publications/infofacts/heroin>
8. Heroin: abuse and addiction. Cleveland Clinic. Accessed 22 Apr 2012. Available from: http://my.clevelandclinic.org/disorders/heroin_addiction/hic_heroin_abuse_and_addiction.aspx
9. Heroin: abuse and addiction. National Institute on Drug Abuse Research and Report Series. Bethesda (MD): National Institutes of Health [revised 2005 May; cited 2012 Feb 18]. Available from: <http://www.drugabuse.gov/sites/default/files/rrheroin.pdf>
10. Johnston LD, O'Malley PM, Bachman JG, & Schulenberg JE (2012). Monitoring the future: national results on adolescent drug use: overview of key findings, 2011. Ann Arbor: Institute for Social Research, the University of Michigan.
11. Alper KR, Lotsof HS, Kaplan CD; The ibogaine medical subculture. *J Ethnopharmacol*. 2008; 115:9-24.
12. Ritter M. (1999). Anti-addiction drug in limbo: illegal in U.S., ibogaine advocates say it blocks withdrawal symptoms. The Associated Press. Available from: <http://ibogaine.mindvox.com/Media/AssociatedPress02.html>.
13. Ibogaine supply and treatment options. [Updated 2011 Nov; cited 2012 Feb 18]. Available from: <http://www.ibogaine.co.uk/options.htm>
14. Maciulaitis R, Kontrimaviciute V, Bressolle FMM, Briedis V. Ibogaine, an anti-addictive drug : pharmacology and time to go further in development. A narrative review. *Hum Exp Toxicol*. 2008; 27:181-194.
15. Glick SD, Pearl SM, Cai, J, Maisonneuve IM. Ibogaine-like effects of noribogaine in rats. *Brain Res*. 1996; 713: 294-297.
16. Lotsof HS. Ibogaine in the treatment of chemical dependence disorders: clinical perspectives. The Ibogaine Dossier. 1994 [cited 2012 Feb 16]. Available from: <http://www.ibogaine.desk.nl/clin-perspectives.html>
17. Halpern, JH. The Use of hallucinogens in the treatment of addiction. *Addict Res*. 1996; 4(2):177-189.
18. Lotsof HS, Wachtel B. Manual for ibogaine therapy. [Cited 2012 Feb 16]. Available from: <http://www.ibeginagain.org/manual.shtml>
19. Codd EE. High affinity ibogaine binding to a mu opioid agonist site. *Life Sci*. 1995; 57: 315-320.
20. French ED, Dillon K, Ali SF. Effects of ibogaine, and cocaine and morphine after ibogaine, on ventral tegmental dopamine neurons. *Life Sci*. 1996; 59:199-205.
21. Leal MB, Michelin K, Souza DO, Elisabetsky E. Ibogaine attenuation of morphine withdrawal in mice: role of glutamate N-methyl-D-aspartate receptors. *Prog Neuro-Psychoph*. 2003; 27: 781-785.
22. Chen K, Kokate TG, Donevan SD, Carroll FI, Rogawsky MA. Ibogaine block of the NMDA receptor: *in vitro* and *in vivo* studies. *Neuropharmacology*. 1996; 35:423-431.

23. Jupp B, Lawrence AJ. New horizons for therapeutics in drug and alcohol abuse. *Pharmacol Therapeut.* 2010; 125:138-168.
24. Rabin RA, Winter JC. Ibogaine and noribogaine potentiate the inhibition of adenylyl cyclase activity by opioid and 5-HT receptors. *Eur J Pharmacol.* 1996; 316:343-348.
25. Freedlander J. Ibogaine: a novel anti-addictive compound: a comprehensive literature review. Erowid. Originally published in *J Drug Educ* 2003; 1:79-98. Available from: http://www.erowid.org/chemicals/ibogaine/ibogaine_article3.shtml
26. Bandarage UK, Kuehne ME, Glick SD. Chemical synthesis and biological evaluation of 18-methoxycoronaridine (18-MC) as a potential anti-addictive agent. *Curr Med Chem.* 2001; 1:113-123.
27. Hoelen DW, Spiering W, Valk GD. Long-QT syndrome induced by the anti-addiction drug ibogaine. *N Engl J Med.* 2009; 360(3):308-309.
28. O'Hearn E, Molliver ME. The olivocerebellar projection mediates ibogaine-induced degeneration of Purkinje cells: a model of indirect, trans-synaptic excitotoxicity. *J Neurosci.* 1997; 17(22):8828-8841.
29. Sheppard SG. A Preliminary investigation of ibogaine: case reports and recommendations for further study. *J Subst Abuse Treat.* 1994; 11:379-385.
30. Bastiaans E. Life after ibogaine: an exploratory study of the long-term effects of ibogaine treatment on addicts. Doctorandus thesis. Vrije Universiteit Amsterdam, Faculty of Medicine. Available from: http://www.ibogaine.org/ibogaine_udi_bastiaans.pdf.