

SECTION D: CLINICAL RATIONALE: 2

Brown, T.K., Apler, K. (2017). Treatment of opioid use disorder with Ibogaine: detoxification and drug use outcomes. *The American Journal of Drug and Alcohol Abuse*, 44(1), 24-36. <https://doi.org/10.1080/00952990.2017.1320802>

This study follows 30 participants after using ibogaine for opioid detoxification, with follow-ups occurring at 1, 3, 6, 9, and 12 months. Participants were heavy heroin and prescription analgesic opioid users, with 97% having previously received multiple treatment for substance use disorder, most commonly methadone or buprenorphine maintenance or residential treatment. Participants underwent a pre-treatment evaluation, which included a medical history, EKG, and electrolyte and liver function tests. Monitoring throughout the treatment included continuous pulse oximetry and three-lead EKG, and monitoring of blood pressure. Prior to the administration of ibogaine and subsequent to arrival at the clinic, subjects were stabilized on a short acting opioid, most often oxycodone, for two to three days. Subjects on long-acting opioids had been instructed to change over to short acting opioids for at least two weeks prior to their treatment. An average total dose of $1,540 \pm 920$ mg ibogaine HCl was administered to each subject. The treatment was initiated with a “test” dose of ibogaine of 3 mg/kg, which was given when subjects had begun to exhibit three or more initial signs of withdrawal, such as restlessness, sweating, yawning or watery eyes. In the experience of ibogaine treatment providers, the test dose typically has some effect of reducing withdrawal signs. A larger, “flood” ibogaine dose, typically four times the test dose is given approximately 2 to 12 hours after the test dose. The flood dose was sometimes followed by an additional “booster” dose of ibogaine of 3 to 5 mg/kg, at an interval following the flood dose commonly in the range of 1 to 16 hr. Providers administered booster dosages to alleviate residual or re-emergent withdrawal symptoms, or at the election of the patient to increase the intensity of the psychoactive experience.

Ibogaine appeared to have a substantive treatment effect in opioid detoxification, and group statistics and individual trajectories appear to indicate an effect of reducing drug use at 1 month, which was sustained up to 12 months in a subgroup of subjects. In this study 15 (50%) and 10 (33%) of subjects reported no opioid use during the previous 30 days at 1 and 3 months respectively. By comparison, a large recent study reported an 8.6% rate of treatment success, defined as self-report of ≤ 4 days of opioid use in the previous 30 days, at 8 weeks subsequent to tapering and discontinuing buprenorphine with no subsequent pharmacotherapy (68). The subset of 12 subjects with favourable outcomes averaged 2.0 ± 1.6 prior treatment episodes for OUD, indicating that ibogaine may have provided distinctive benefit for individuals with histories of previously unsuccessful treatment. Ibogaine therefore appears to have a clinical effect in some subjects with histories of failure of other treatments for OUD.

One theme among study participants was the attribution of insight and meaning to the content of the psychoactive state produced by ibogaine. One subject wrote, “*I saw my family from young to older and how everything has been and how I affected them.*” and, “*When I closed*

my eyes most of the time I had visions from my past... A profound sense of love for my family and their love for me and an intense, almost piercing agony as I was over-whelmed with the remorse and the waste and loss, feeling empathy with my family over all their hopes for me dashed by my relentless pursuit of drugs. . . I kept seeing clips – real memories, of high-school girlfriends and playing music with friends – but then also clips of the present day in an alternate reality where I hadn't squandered so much love or compassion that had been offered to me."

Another theme was the characterization of an interval of diminished post treatment drug craving as a window of opportunity for personal change, evident in comments such as, ". . .you could safely say that iboga will give an opiate addict several months to a half a year of freedom from cravings and an expanded awareness. This gives the user a period of time in which to get his/her life together and learn to face things straightforwardly, directly and honestly. Iboga will not do the work for you. However, it will help you do your own work."

No clinically significant cardiovascular or other medical events occurred in this study.

Cloutier-Gill, L., Wood, E., Millar, T, Ferris, C., & Socias, M.E. (2016). Remission severe opioid use disorder with ibogaine: a case report. *Journal of Psychoactive Drugs*, 48(3), 214-217. doi: 10.1080/02791072.2016.1180467

This study looks at a case of a 37 year old female with a 19-year history of severe opioid use disorder (OUD), who achieved an ongoing 18-month period of abstinence following a four day ibogaine treatment. The centre's protocol involved a series of ibogaine HCL test doses (up to 2.5 mg/kg) on the first day, followed by a series of larger doses (up to 20 mg/kg) on the second day, and booster doses on the last two days (5 mg/kg/ day). Over the course of the four-day admission, she received a total of 2300 mg (32 mg/kg) of ibogaine HCl. The clinic's protocol also allowed for the use of oral hydromorphone to manage acute withdrawal. The patient required 32 mg of hydromorphone on the first day and 45 mg on the second day to manage her withdrawal symptoms, which were already present on admission.

The participant attributed her sustained recovery to a spiritual awakening induced by the ibogaine. The patient described that the ibogaine experience allowed her to revisit various recent events of her life, including the loss of her partner to an opioid overdose, as well as other moments where the patient herself suffered nearly fatal overdoses. This new insight into her OUD became an eye-opening opportunity, giving her emotional strength to attempt and sustain abstinence.

No safety issues associated with ibogaine were observed. Various steps were taken to mitigate any adverse effects, which included a liver and cardiovascular screening prior to the initiation of the ibogaine treatment, and continuous nursing monitoring with hourly heart rate and blood pressure checks. The patient's baseline ECG was within normal parameters, including a normal QTC. The patient also maintained an overall stable blood pressure during the four-day treatment, but developed mild bradycardia (average measured heart rate on days

1, 2, 3, 4 was 67 beats per minute [bpm], 57 bpm, 51 bpm, and 57 bpm, respectively). In addition, she experienced mild and transitory side-effects such as weakness, dizziness, and diaphoresis. Minor concentration deficits were reported during the first few weeks following therapy, but the patient did not suffer from any other overt persistent side-effects.

Before undergoing her ibogaine treatment, the patient repeatedly tried and exhausted most available addiction treatment options, including 12-step programs, detoxification centres, support groups, sponsors, recovery houses, and MMT, all without sustained success. Her prior longest period of continuous abstinence was two months while on MMT. This is noteworthy in the setting of a 19-year history of severe OUD and multiple failed attempts at abstinence following various widely accepted treatment modalities.

Ibogaine shows potential as an alternative treatment for OUD, particularly among cases refractory to opioid antagonist therapy for a number of reasons. First, studies have suggested that ibogaine is effective in easing opioid withdrawal, as well as in reducing cravings (Brown 2013). Ibogaine and noribogaine (ibogaine's main metabolite) simultaneously act on a diversity of neurotransmitter transporters and receptors, providing a biological plausibility for its anti-addictive effects (Antonio et al. 2013; Koenig and Hilber 2015). Second, ibogaine is usually administered in a single session, not requiring ongoing administration (Brown 2013), which can be a substantial advantage for many individuals with OUD. Without the time and logistical constraints commonly associated with daily-witnessed ingestion of methadone, individuals could have an easier transition back to employment and other factors associated with recovery, which in turn could reduce direct and indirect societal costs. Third, it has been suggested that the mystical experiences associated with ibogaine and other traditional psychedelic drugs might result in the resetting of psychological processes or neuroadaptations underlying substance use disorders, which could contribute to long-term abstinence (Bogenschutz and Johnson 2016). Our patient herself volunteered that it was such transformative phenomenon that was the key to her success this time. Fourth, ibogaine has a low abuse potential, as indicated by animal models where ibogaine did not lead to either desire for the substance or aversion to it (Alper 2001; Brown 2013).

Twenty-two deaths temporally related to ibogaine use have been reported between 1991 and 2014, most associated with pre-existing medical comorbidities (particularly cardiovascular disease), concurrent use of other substances, and electrolyte imbalances (i.e., hypokalemia) (Alper, Stajic, and Gill 2012; Koenig and Hilber 2015). As such, ibogaine's safe administration would theoretically dictate, amongst other safety measures, the need for an electrolytes and ECG screening prior to treatment, abstinence from any other potentially QTC-prolonging substances, as well as exclusion of patients with cardiovascular disease (Alper 2001; Brown 2013). Although ibogaine is a promising compound, its use on individual patients must be based on a risk-benefit analysis (e.g., potential cardiotoxicity versus untreated substance use disorder), as well as on a careful selection of eligible candidates and ibogaine's administration in adequately safe settings (Koenig and Hilber 2015).

Davis, A. K., Barsuglia, J. P., Windham-Herman, M., Lynch, M., & Polanco, M. (2017). Subjective effectiveness of ibogaine treatment for problematic opioid consumption: Short- and long-term outcomes and current psychological functioning. *Journal of Psychedelic Studies*, 1(2), 1-9. doi: 10.1556/2054.01.2017.009

This study evaluates the short- and long-term effects of ibogaine treatment for 88 patients with problematic opioid consumption, with heroin and prescription opioids being the primary substance of choice. 72% of participants had been using their primary substance for 4 or more years, with 21% using for more than 10 years. Patients were treated with 15 mg/kg and ± 5 mg/kg of ibogaine, with dose depending on weight and polysubstance use severity.

To mitigate any adverse reactions, applicants underwent a physical examination prior to treatment, which included the patient history, 12-lead electrocardiogram, drug testing, a complete physical, and a complete blood count with differential and metabolic panel. Participants were excluded from treatment if they had prolonged QTc interval, history of heart disease, pulmonary embolism, deep vein thrombosis, severe respiratory conditions, obesity, gastrointestinal disorders, chronic infectious diseases, cerebellar dysfunction, delirium, organic brain disease or history of severe traumatic brain injury, epilepsy, current pregnancy, and abnormal electrolytes or impaired hepatic or renal function. Patients are also excluded from treatment if they have used alcohol, amphetamines, cocaine, or psychiatric medications in the prior week or have used long-acting opioids in the 4 weeks prior to treatment. For all patients who passed the screening and were treated with ibogaine, patients received live cardiac monitoring, intravenous saline and electrolytes, and medical monitoring throughout treatment, which was followed by a short residential stay including psychological support and aftercare planning.

The results showed that ibogaine eliminated or drastically reduced withdrawal symptoms in 80% of participants. Opioid cravings were also reduced in 50% of patients, with 25% reporting a reducing in craving lasting at least 3 months. Ibogaine was also effective in eliminating opioid use, as 30% of participants reported never using opioids again following treatment. Out of those who abstained, 54% had been abstinent for at least 1 year, and 31% had been abstinent for at least 2 years. Although 70% of the total sample relapsed following treatment, 48% reported decreased use from pretreatment levels and an additional 11% eventually achieved abstinence.

Another theme of ibogaine treatment is that it contributed to the participants gaining insight into the cause of their addiction, which was reported by 67% of participants. Outcomes appeared to be better for those who had spiritual experiences and gained insight into the cause of their addiction. An increase in mood and psychological well-being was also seen following treatment, with depression and anxiety rates decreasing.

Furthermore, out of 61% of participants, it was found that ibogaine was very effective, and 85% of the sample would have made the same decision to engage in they treatment. Compared to other opioid treatments, 71% stated that ibogaine was the better treatment.

Problems exist with conventional opioid maintenance therapies (OMT), however one way to address the problem is to provide access to a single-dose medication that could interrupt/reduce withdrawal and craving for opioids and provide important psychotherapeutic effects to the patient (e.g., insight, motivation to change), thus allowing the opioid user to address the environmental and behavioural problems associated with their consumption of opioids. An example of such a treatment is the use of ibogaine as an opioid detoxification treatment. Because one dose of ibogaine seems to work by minimizing opioid withdrawal and craving such that meaningful proportions are able to abstain from or reduce use, such a treatment might have far-reaching effects on individual opioid users and their families, and decrease the strain on communities and the healthcare/addiction treatment systems.

Malcolm, J. B., Polanco, M., & Barsuglia, J. P. (2018). Changes in Withdrawal and Craving Scores in Participants Undergoing Opioid Detoxification Utilizing Ibogaine. *Journal of Psychoactive Drugs*, 2018 Apr 02, 1-10. doi: 10.1080/02791072.2018.1447175

This study examines Ibogaine and its use to detoxify and reduce drug cravings of 50 participants with Opioid use disorder (OUD). The ibogaine treatment consists of oral administration of a total dose of 18–20 mg/kg of ibogaine hydrochloride. A test dose of 100 mg is administered initially, followed by the remainder of the calculated dose within two hours of the test dose. After 48 hours following ibogaine administration, withdrawal and craving scores were significantly lowered in comparison to baseline: 78% of patients did not exhibit objective clinical signs of opioid withdrawal, 79% reported minimal cravings for opioids, and 68% reported subjective withdrawal symptoms in the mild range. Ibogaine appears to be able to effectively detoxify participants from opioids while simultaneously reduce cravings.

The ability of ibogaine to address psychological aspects of OUD, such as drug craving, is a potentially important advantage compared to existing therapeutic approaches, since relapse after successful detoxification presents a high risk of overdose-related death due to participants overestimating their tolerance and using doses similar to what they were previously accustomed to. By addressing this aspect of OUD, ibogaine may help position participants for greater success in their path of recovery.

To mitigate any adverse reactions, patients undergo a physical examination, which includes the patient history, a complete physical, a 12-lead electrocardiogram, drug testing, and a complete blood count with differential and metabolic panel. Medical exclusions for treatment included prolonged QTc interval, history of heart disease, pulmonary embolism, deep vein thrombosis, severe respiratory conditions, chronic infectious diseases, cerebellar dysfunction, delirium, organic brain disease or history of severe traumatic brain injury, epilepsy, abnormal electrolytes, or impaired hepatic or renal function. Patients are also excluded from treatment if they have used alcohol, amphetamines, cocaine, or psychiatric medications in the week prior to treatment, or have used long-acting opioids such as buprenorphine or methadone in the four weeks prior to treatment.

While ibogaine carries risks that are potentially severe, such as fatalities that are suspected or confirmed with a cardiac etiology, there are more people dying in the US every day from opioid overdoses than have ever been reported in the literature to have occurred with ibogaine. In considering reports of adverse effects during ibogaine treatment, the populations presenting for ibogaine detoxification treatment often exhibit greater severity and chronicity of addiction, intravenous drug use, medical comorbidities and fragility after failing mainstream treatments, thus placing them at greater risk for medical complications during detoxification treatment. The epidemic degree of morbidity and mortality inflicted by licit and illicit opioid medications on US citizens may make it tempting to consider opioid detoxification with ibogaine if participants are refractory to first-line treatment options or are not interested in continued opioid dependence with buprenorphine or methadone.

Mash, D. C., Duqye, L., Page, B., Allen-Ferdinand, K. (2018). Ibogaine detoxification transitions opioid and cocaine abusers between dependence and abstinence: Clinical observations and treatment outcomes. *Frontiers in Pharmacology*, 9 (529). doi: 10.3389/fphar.2018.00529

This study reviews the clinical results from an open label case study of 191 participants who received a single dose ibogaine treatment to detoxify from opioids or cocaine. Participants were measured for withdrawal, cravings, health and mood, and depression, before and after treatment, at program discharge, and one-month after treatment. Clinical safety data and adverse events were also examined.

All individuals were subject to a physician's review of a history and physical examination, clinical laboratory results, and electrocardiograms. To diminish any negative side effects, participants who had a history of stroke, epilepsy, axis I psychotic disorders, cardiovascular and liver pathology, and HIV/AIDS were not treated. For those with opioid dependence, the average admission for treatment was 5.5 ± 7.2 , with a lifetime of use being 11.2 ± 8.6 years. Furthermore, 52.9% of those with opioid dependence had a depressive disorder. Opioid dependent patients were switched at program entry to morphine sulfate for opioid withdrawal control prior to ibogaine detoxification. For participants with cocaine dependence, there was an average of 5.1 ± 3.1 attempts for substance abuse treatment, with 40.4% having a depressive disorder. Participants were administered a range of 500-1000mg of ibogaine HCL.

After ibogaine treatment, it was found that there was a well tolerance amongst subjects, with nausea and ataxia of gait being the most common side effect. There were no changes noted on physical examination or safety laboratory tests across the dose range administered. There were no serious adverse events that occurred in this study. There were mild adverse events observed, which included rebound headaches in 7% of opiate abusers. Furthermore, orthostatic hypotension and bradycardia heart rate, which was caused by volume depletion, was observed in several cases of cocaine dependent subjects; an effective treatment of intravenous fluids was applied.

When looking at opiate dependant participants, it was found that opioid withdrawal symptoms after ibogaine treatment were lowered. Participants withdrawing from methadone,

after being switched to oral morphine, had the lowest rating of withdrawal symptoms. Participants were also rated on a craving questionnaire post-treatment and after one month, which was compared to baseline measures. The questionnaire measured negative mood state, desire or intent to use drug now, lack of confidence in ability to quit using drug, and expected positive benefits of drug use. It was found that there was a low rating in all craving categories in opiate dependent participants after treatment, which had a further lowered rating at a one month follow up. Depression scores were also lowered after ibogaine treatment and at the one month follow up. In regards to cocaine dependent participants, ibogaine significantly lowered drug cravings after administration, which was measured on craving intensity, frequency, and duration. These numbers were also lowered following the one month assessment. Depressive symptoms and mood scores were drastically improved after ibogaine treatment and at the one month follow up.

Subjects were also asked questions regarding their interpretation of the benefit of the ibogaine experience. A total of 92% of the subjects reported that they felt a benefit of the experience and that ibogaine was useful as a treatment for drug abuse. Subjects described that they had gained insight into the self-destructive behaviours and that they were mindful of the need to become sober/abstinent now. Some described that they saw images of their death and that they gained an impending awareness of their self-destruction if they failed to become abstinent. Many of the most intractable drug abusers reported that they felt “cleansed” or reborn and that they were given a second chance at life.

In conclusion, ibogaine and its active metabolite noribogaine offer an alternative approach to target the underlying neuroadaptations in the addiction circuits, and which contribute to an intractable cycle of relapse following abstinence. Ibogaine administration unlike a methadone or buprenorphine taper is a rapid detoxification method, shortening the time needed for withdrawal to 2–3 days. The after effects of ibogaine are likely mediated by noribogaine, which may explain the lasting improvement in mood and diminished drug cravings for opioids and cocaine reported by most subjects in this report. Opioid use disorder is a deadly disease that costs the healthcare system hundreds of billions of dollars each year. Controlled clinical trials of ibogaine for opioid detoxification are needed to demonstrate the benefits and risks in human drug review to advance this drug product to market. However, clinical trials take many years and countless millions of dollars to gain FDA approval. Given that traditional approaches to develop new treatments for opioid use disorder have not been advanced by the pharmaceutical industry, ibogaine may be non-addictive alternative that deserves fast-track review as a possible solution to the current opioid drug crisis in America.

Noller, G. E., Frampton, C. M., & Yazar-Klosinski, B. (2018). Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study. *The American Journal of Drug and Alcohol Abuse*, 44 (1), 37-46. doi: 10.1080/00952990.2017.1310218

This study follows 14 participants seeking ibogaine treatment for opioid dependence over 12 months. Methadone was the most prevalent dependent drug, followed by codeine and poppy seeds. Participants also had moderate comorbid depression symptoms, and had previously

received an average of 4.7 treatments for substance dependence. At the time of treatment, 71% of participants were receiving methadone maintenance treatment. Participants ingested their last dose of opioids between 12 and 33 hours before ibogaine treatment. Patients were initially given a test dose of 200mg when in withdrawal, followed by 400-600mg between 1 and 4 hours, and then 200mg at 20 minute intervals until the provider determined the appropriate level of dosing had been achieved. Participants received an average of 25-55mg/kg of ibogaine. The initial dosage was selected based on psychological and physical health, age, fitness, drug use of the patient and provider experience. Dosage was adjusted based on patient response and provider assessment through observation and questioning (SOWS scores, changes in proprioception, interoception, and mood).

The study concluded that a single ibogaine treatment significantly reduced opioid withdrawal, craving and depressed mood, and reduced or ceased opioid use over 12 months. By using the subjective opiate withdrawal scale (SOWS), it was seen that withdrawal symptoms were significantly reduced after 24 hours of ibogaine administration, and even more reduced after 42 hours. Using the Addiction severity index (ASI-Lite), a sustained reduction and/or cessation of opioid use was reported by 12 or 14 participants. More specifically, there was an 80% decrease in drug use, and a decrease in family/social status problems at 12 months. For those who provided samples testing positive for drugs, only a small percentage tested positive for opioids. There was also a 55% reported reduction in other drug use and 36% reduction in alcohol use. For those who did not cease opioid use entirely, their ibogaine experience was described in positive terms. A common theme found among participants was it provided insight into their situation. Lastly, using the Beck depression inventory 2 (BDI-II), a significant sustained reduction was seen in depression severity at 12 months, which is coupled with 2 of 3 participants ceasing their prescribe antidepressant medication post-treatment.

There are concerns however with ibogaine use, given the death of one subject during treatment. The coroner 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”. It is noteworthy however, that the Health and Disability Commissioner described the treatment provider as being in breach of their duty of care. Furthermore, after thoroughly reviewing all available autopsy, toxicological, and investigative reports of other ibogaine fatalities, it is suggested that advanced preexisting medical comorbidities, primarily cardiovascular, and/or the misuse of a range of substances, contributed or explained the fatalities. Seizures from alcohol and benzodiazepine withdrawal and the uninformed use of ethnopharmacological forms of ibogaine were considered other apparent risk factors.

Alper, K, R., Stajic, M., & Gill, J. (2012). Fatalities Temporally Associated with the Ingestion on Ibogaine. *Journal of Forensic Sciences*. 57(2), 398-412. doi: 10.1111/j.1556-4029.2011.02008.x

This study looks at 19 fatalities that occurred after ibogaine ingestion between 1990 and 2008, with an interval of 76 h or fewer between the most recent ingestion of ibogaine and death. The mean age of the individuals was 24 to 54 years. Fifteen individuals took ibogaine for opioid detoxification, four of who were also dependent on alcohol, three on cocaine, and one on methamphetamine. Two individuals used it for a spiritual/psychological purpose, and two took it for unknown reasons but had a history of substance abuse.

The study concluded that advanced preexisting medical comorbidities, which were mainly cardiovascular, and/or one or more commonly abused substances explained or contributed to the death in 12 of the 14 cases for which adequate postmortem data were available. Significant factors in this series appear to include preexisting medical, particularly cardiovascular disease, possible PE, drug use during treatment, seizures associated with withdrawal from alcohol and benzodiazepines, and the uninformed use of ethnopharmacological forms of ibogaine.

Twelve of the individuals had medical comorbidities including liver disease, peptic ulcer disease, brain neoplasm, hypertensive and atherosclerotic cardiovascular disease, and obesity. Among the three decedents in which no other drugs of abuse were detected in postmortem toxicology analysis, one had advanced heart disease and another had liver fibrosis. Full toxicology and autopsy results were not available in eight and five decedents, respectively.

Cardiac disease was a contributing condition or proximate cause in six deaths, suggesting cardiac mechanisms are an important mediator of fatal outcomes. QT prolongation is also regarded as a general correlate of cardiac instability that is associated with arrhythmias other than TdP (89,102,103), and with multiple risk factors relevant to the present study including bradycardia, coronary artery disease, dilated cardiomyopathy, recent myocardial infarction, ventricular hypertrophy, and liver disease (89,104). The frequently altered nutritional status of substance abusers puts them at risk of hypomagnesemia and hypokalemia (90), which are associated with QT prolongation, as are bulimia and anorexia (109). Methadone is associated with QT prolongation, particularly in the presence of other drugs (110). Alcohol or cocaine use is associated with prolongation of the QT interval both acutely (111,112) and during withdrawal (113–115). In patients with alcohol dependence, QT prolongation has been observed to persist for 7 days after the last intake of alcohol (116), and withdrawal seizures contribute further independent and additive risk (114). Epileptic seizures, even in the absence of substance use or withdrawal, are an independent risk factor for QT prolongation.

Pulmonary thromboembolism (PE) was the reported cause of death in three deaths. In all three of these cases, autopsy reports were inadequate as a basis for the determination of a proximate cause of death due the lack of evidence of systematic examination of the lungs and pulmonary vasculature. In the one individual that died under observation, the clinic diagnostic impression of PE on acute dyspnea, tachypnea, and desaturation indicated by pulse oximetry. The decedent had a family history of PE, and if he did indeed die from venous thrombotic disease, the family history suggests a possible etiological contribution because of genetic risk (126). Other possible risk factors for PE include travel to the

treatment location (127) and/or inactivity and immobility during the treatment (128). Intravenous drug use is a risk factor for deep venous thrombosis (129–131), and hence for PE, and appears to be associated with injection per se, independent of the use of opioids versus other substances (132).

In one fatality in this series, a GTCS occurred (case #10), which might have been due to alcohol or benzodiazepine withdrawal. In another death (case #14), a brain neoplasm might have explained the possibility of complex partial seizures mentioned in the autopsy report.

Postmortem toxicological analysis detected commonly abused drugs in eight of the 11 cases in which toxicological analysis was performed in this series. When considering a drug intoxication death because of multiple substances, it usually is not possible to differentiate the individual roles and complex interactions of these substances in causing the death. These deaths typically are certified as intoxications because of the combined effects of all substances detected. Therefore, it is not possible to determine whether the deaths in which drugs of abuse were detected were because of ibogaine alone, to one or more of the drugs of abuse, or a combination. There is also a general effect of the number of abused substances, with a larger number associated with a greater risk of death independent of the identity of specific substances involved (147). The unexplained variance of lethal outcome as a function of dose further adds to the difficulty of the determination of causality for ibogaine and drugs of abuse.

Systemic disease is a confounding factor that contributes to the mortality associated with substance use and further complicates the identification of the cause of death. The risk of death may represent a complex interaction involving a substance of abuse against a backdrop of systemic medical illness related to addiction. For example, the risk of death from opioid overdose is associated with cardiac hypertrophy and atherosclerotic disease (149), which were contributing conditions in this case series and which in turn are associated with a history of methamphetamine and cocaine use (150,151). The role of advanced preexisting medical comorbidities in this series of fatalities appears to be an instance of a more general association between systemic disease and risk of fatal overdose (149).

Another decedent (case #13) (70) may have ingested an amount of dried T. iboga root bark in excess of that which would typically be given in a full Bwiti initiation ceremony (5).

In this series, there appeared to be no clinical or postmortem evidence suggestive of a characteristic syndrome of neurotoxicity.

The lack of clinical and pharmaceutical controls in settings in which ibogaine has been given, and the limited data regarding toxic concentrations of ibogaine in humans make the determination of the causes of these deaths difficult. Nonetheless, advanced comorbidities and contributing conditions appear to include preexisting medical, particularly cardiovascular disease, and drug use around the time of treatment.

The incidence of fatalities may have decreased in the recent past. As indicated in Table 1, in 2008, there were no known fatalities, and in 2007, there were 2. In contrast, there were a total of nine fatalities that occurred in 2005 and 2006. Greater recognition of medical risk on the part of treatment providers may have been a factor in the apparent reduction in the incidence of fatalities. Pretreatment screening including basic blood chemistries and EKG, the exclusion of patients with significant medical, particularly cardiac illness, and the recognition of the need to stabilize physical dependence on alcohol and benzodiazepines prior to ibogaine treatment has gradually become more widely accepted norms in the settings of ibogaine use (161).

Paling, F, P., Andrews, L, M., Valk, G, D., & Blom, H, J. (2012). Life-threatening complications of ibogaine: three case reports. *The Netherlands Journal of Medicine*. 70(9), 422-424. <https://doi.org/10.3109/15563650.2016.1138226>

This study examines three case reports, where 3 people had ingested ibogaine to treat an alcohol or opioid dependence. Although there were no fatalities, the three case reports experienced life-threatening complications after ingesting ibogaine.

In case 1, a 49-year-old man with a history of heroin addiction presented to the emergency department with collapse. He had received his first anti-addictive dose of ibogaine one or two days earlier. The patient stated that he had no specific complications, besides hypothyroidism and asthmatic symptoms. Electrocardiography (ECG) of this patient showed intermittent ventricular tachyarrhythmias, with underlying sinus rhythm and a QT interval of >700 ms. Laboratory testing showed mild hypophosphataemia (0.76 mmol/l [reference 0.8-1.50]), and mild hypokalaemia (3.5 mmol/l [reference 3.5-5.0]) but no other deviations (calcium 2.23 mmol/l [reference 2.1-2.6]). A computed tomography (CT) scan of the brain showed no abnormalities. Urine screening showed traces of opioids. The patient was admitted to the intensive care unit (ICU), where he was defibrillated twice for tachyarrhythmias. Over the following days he recovered quickly; his QT interval, however, remained prolonged during the entire stay in our hospital. He was discharged after being free of ventricular tachyarrhythmias for ten days, with a QT interval of 475 ms.

In case 2, A 31-year-old woman, who had taken 3.5g of ibogaine for her treatment resistant alcohol dependence, presented to the emergency room with a seizure-like attack. She had not taken any other medication or drugs, and her family history was unremarkable. She only complained of nausea. ECG revealed a strikingly prolonged QT interval (corrected 616 ms) and torsade de pointes. Laboratory testing showed mild electrolyte deviations (magnesium 0.49 mmol/l [reference 0.65-1.05], potassium 3.2 mmol/l [reference 3.5-5.0]), which were rapidly corrected. The patient was admitted to the ICU, where after 42 hours of monitoring her QT interval normalized. No new seizures occurred and no further intervention was needed. She was discharged home in good condition.

In case 3, a 43-year-old woman, being treated with ibogaine for heroin and benzodiazepines addiction, was admitted to the emergency room in an unresponsive state, which had lasted

longer since she had been found earlier that morning. She had vomited and possibly had shown some contractions around her mouth. Physical examination showed a non-responsive, tachypnoeic and subfebrile woman, who moved her arms and legs symmetrically. Blood testing showed only leukocytosis (12.7 [reference 4.0-10.0]), slightly elevated erythrocyte sedimentation rate of 38 mm/h [reference 2-12] and mild hypokalaemia (3.1 mmol/l). A CT scan of the brain, chest X-ray and ECG (QTc around 480 ms) showed no abnormalities. Because urine screening tested positive for opioids, she was injected with flumazenil (Anexate) and naloxone upon which she developed mild withdrawal symptoms, but no improvement in consciousness. Electroencephalography showed encephalopathy of unknown origin, possibly related to earlier hypoxia. No epileptic activity was seen. She was admitted to the ICU, where she was intubated on day 2, due to respiratory insufficiency. She remained unstable for several days, but was extubated after 24 hours. No cardiac arrhythmias were observed, but she did develop urine retention and aspiration pneumonia during the ICU stay. Later, blood samples showed potentially lethal ibogaine levels (0.37 mg/ml).⁷ The patient was discharged home in good condition after seven days.

In cases 1 and 3 traces of opioids were found in serum and/or urine. The patient in case 1 claimed not to have used drugs recently before presentation, but in case 3 the patient was on a methadone regime. Thus, in case 3, a combination of ibogaine and opioid intoxication could be considered, especially in view of the dominant respiratory problems. In case 2 there appeared to be no other explanation for the symptoms. Electrolyte deviations in all three patients were too minimal to expect to produce the symptoms as presented here.