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A systematic literature review of clinical trials and therapeutic applications of ibogaine

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ABSTRACT

Background: Iboga and its primary alkaloids, ibogaine and noribogaine, have been of interest to researchers and practitioners, mainly due to their putative efficacy in treating substance use disorders (SUDs). For many SUDs, still no effective pharmacotherapies exist. Distinct psychoactive and somatic effects of the iboga alkaloids set them apart from classic hallucinogens like LSD, mescaline, and psilocybin.
Aims: The study team performed this systematic review focusing on clinical data and therapeutic interventions involving ibogaine and noribogaine.
Methods: The team conducted a search for all publications up to December 7, 2020, using PubMed and Embase following PRISMA guidelines.
Results: In total, we identified 743 records. In this review, we consider 24 studies, which included 705 individuals receiving ibogaine or noribogaine. This review includes two randomized, double-blind, controlled clinical trials, one double-blind controlled clinical trial, 17 open-label studies or case series (including observational or retrospective studies), three case reports, and one retrospective survey. The published data suggest that ibogaine is an effective therapeutic intervention within the context of SUDs, reducing withdrawal symptoms and craving. Data also point toward a beneficial impact on depressive and trauma-related psychological symptoms. However, studies have reported severe medical complications and deaths, which seem to be associated with neuro- and cardiotoxic effects of ibogaine. Two of these fatalities were described in the 24 studies included in this review.
Conclusion: Treatment of SUDs and persisting comorbidities requires innovative treatment approaches. Rapid-onset therapies such as the application of ibogaine may offer novel treatment opportunities for specific individuals. Rigorous study designs within medical settings are necessary to warrant safe application, monitoring, and, possibly, medical intervention.

1. Introduction

Iboga and its main active alkaloids, ibogaine, and noribogaine, as well as structurally related alkaloids, have gained increasing scientific attention over the last decades, mainly due to their proposed "anti-addictive" properties. Although we do not yet fully understand their complete pharmacological mechanisms, available data suggest efficacy in the treatment of opioid use disorder (OUD), cocaine use disorder (CUD), and other substance use disorders (SUD). Previous research points out the necessity of conducting safe study designs and controlled clinical studies (dos Santos et al., 2016). Treatments with ibogaine are considered safe when properly medically supervised. However, several case reports have been published about fatalities or adverse events associated with the ingestion of iboga plant material or ibogaine. Global medical and legislative regulatory consensus is absent. Although classical hallucinogens have been studied and are currently under investigation for a wide array of psychiatric conditions, including SUDs (Bogenschutz & Johnson, 2016; Bogenschutz & Ross, 2018), controlled clinical trials with ibogaine are still scarce.

The main aim of this systematic review was to identify all human studies on the use of ibogaine or noribogaine with explorative or therapeutic intention that took place up to December 7, 2020, and assess effectiveness outcomes of included studies.

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1.1. Ibogaine

Ibogaine is an indole alkaloid found in the shrub *Tabernanthe iboga* (*T. iboga*), commonly known as iboga (Alper, 2001) and in the plant *Voacanga africana* (Kikura-Hanajiri et al., 2009). *Vatharanthus*, *Corynanthe*, and *Aspidosperome* genera also produce iboga alkaloids. Those plants belong to the family of the *Apocynaceae* (Kinghorn, 2017). These plants contain several alkaloids that are being researched or have yet to be identified. According to recent publications, about 100 natural or synthetic iboga indole alkaloids are defined based upon their typical ibogamine skeleton (Lavaud & Massiot, 2017). Researchers have investigated some of these compounds for different medical purposes and pharmacologic profiles (Cameron et al., 2020; da Silva Brum et al., 2016; Freissmuth et al., 2018; Gómez-Calderón et al., 2017; Ishikawa et al., 2008). From a psychiatric perspective, the use of *T. iboga* and its major alkaloid ibogaine seems compelling due to its putative anti-addictive properties (dos Santos et al., 2016; Winkelman, 2014). Researchers have explored other therapeutic indications, such as the treatment of psychological trauma and depressive symptoms, in recent years. In West Central Africa, "iboga" or "eboka" has traditionally been used by the indigenous *Bwiti* religion to conduct ceremonial rites. Eboka designates the root bark shavings of the Tabernanthe iboga plant, which is the major form used in rituals in Africa (Antonio et al., 2013; Fernandez & Fernandez, 2001). In the literature, the use of iboga plant material is referenced commonly by its ethnobotanical abbreviation *T. iboga*, whereas ibogaine refers to the indole alkaloid form (Alper, 2001). Initial studies looked at ibogaine's effects on the central nervous system and its cardiovascular actions. Ibogaine was marketed in France as Lambarene® and licensed as a "neurostimulant". France withdrew Lambarene® from the market in 1966 when the sale of ibogaine-containing products became illegal in that country (Glue, Winter, et al., 2015). The United States assigned ibogaine Schedule I classification, and the International Olympic Committee banned it as a potential doping drug (Mačiulaitis et al., 2008). Ibogaine is used in medical and nonmedical settings to treat addictive disorders, most commonly for opiate detoxification (Alper et al., 2008). In 2012, the U.S. National Institute on Drug Abuse (NIDA) supported the production of 18-methoxycoronaridine (18-MC) and pre-clinical studies investigating pharmacotherapeutic applications for SUDs. 18-MC is a synthetic iboga alkaloid (National Institutes of Health, 2012), which seems safer than ibogaine regarding cardiotoxicity (Corkery, 2018). Furthermore, research has found tabernanthalog, a recently engineered, non-hallucinogenic, non-toxic ibogaine analog, to produce antidepressant-like effects and reduce alcohol- and heroin-seeking in rodents (Cameron et al., 2020).

1.2. Theories about pharmacological mechanisms

Animal models in addiction research have shown that ibogaine, noribogaine,18-MC, and the novel analog tabernanthalog decreased self-administration or drug-seeking of various addictive substances (Cameron et al., 2020; Glick et al., 2000; Mačiulaitis et al., 2008; Pace et al., 2004; Rezvani et al., 2016). Multiple receptor systems are involved in this decrease, but we do not yet fully understand the exact mechanisms. Nevertheless, researchers have established some theories to explain the observed effects. Results from cell culture and animal models suggest that glia cell line-derived neurotrophic factor (GDNF) up-regulation contributes to reduced ethanol self-administration (Carnicella et al., 2010). *N*-methyl-D-aspartate (NMDA) receptor antagonism may also be involved in the effects of ibogaine (Baumann et al., 2001). Radioligand binding assay experiments suggest that ibogaine blocks nicotinic acetylcholine receptors (Arias et al., 2010). Research has proposed the blockage of nicotinic α3β4 receptors in the medial habenula as the potentially cause for the observed effects of reduced alcohol and nicotine intake after oral 18-MC ingestion (Glick et al., 2002). Other theories suggest modification of opiate receptor-mediated signaling as a possible mechanism. While serotonin (5-HT) receptor agonism and serotonin transporter (SERT) inhibition might be involved in hallucinogenic or putative antidepressant effects, its exact role remains unclear (Glick et al., 2001). Research has recently described the pharmacochaperone-activity of ibogaine and noribogaine on the SERT and the dopamine transporter (DAT) (Freissmuth et al., 2018). While ibogaine and noribogaine interact with several central nervous receptors, studies have reported the strongest affinities of ibogaine for the sigma2-receptor, the opioid receptors, SERT, and DAT (Preedy, 2016; Ray, 2010). However, Antonio et al. (2013) demonstrated that opioid agonism does not seem to account for the observed effects of the iboga alkaloids in opioid withdrawal. κ-opioid receptors (KOPR) may also play a specific role. Dynorphin and the KOPR system are essential in CUD (Bidlack, 2014). Research has proposed that pharmaceuticals displaying agonist and antagonist qualities upon KOPR can treat CUD (Maillet et al., 2015), and noribogaine seems to possess these qualities. High SERT affinity, especially documented for noribogaine, might explain sustained antidepressant effects. Considering affinity data (Ray, 2010), the specific multi-receptor targeting and the long action of ibogaine/noribogaine might be keys for disrupting neuronal circuits involved in SUDs. The involvement of multiple receptor systems and pharmacokinetic mechanisms might explain postulated effects upon substance craving (via DAT inhibition, NMDA antagonism), withdrawal symptoms (via opioid receptors), and post-withdrawal depression (via prolonged SERT inhibition). GDNF expression may play a role in neuroplasticity and hence foster behavioral change. Hallucinogenic properties (possibly via 5-HT_{2A} agonism, sigma receptor activity) might be necessary for insight and meaningful experiences. Pharmacochaperone activity might also be involved in long-term behavioral changes.

1.3. Pharmacokinetics and pharmacodynamics

The majority of ibogaine studies on humans have looked at the drug's effects on SUD symptoms. The administration route of ibogaine in these studies was oral (p.o.). Single ibogaine doses in earlier studies ranged from 500 to 800 mg (dos Santos et al., 2016). These doses yielded plasma concentrations C_{max} for ibogaine and noribogaine between 30 and 1250 ng/ml and 700–1200 ng/ml at T_{max} around 2 h and 5 h after ingestion, respectively (dos Santos et al., 2016; Glue, Lockhart, et al., 2015; Glue, Winter, et al., 2015). Blood concentrations of ibogaine and noribogaine show high interindividual variability. Poor metabolizers showed higher blood concentrations of ibogaine relative to noribogaine over time. Extensive metabolizers have shown an inverted blood concentration profile within measurement times, with relatively higher blood concentrations of noribogaine due to faster metabolization of ibogaine (Mačiulaitis et al., 2008). One research study has documented hepatic metabolism, primarily via CYP2D6, followed by CYP2C9 and CYP3A4 (Obach et al., 1998). Storage of ibogaine in adipose tissues suggests a protracted ibogaine/noribogaine release with time (Alper, 2001). Generally, ibogaine seems to be cleared quickly from the blood, while significant noribogaine concentrations could be measured 24 h after oral ingestion (Mačiulaitis et al., 2008). Lower doses of ibogaine showed no detectable plasma levels after 4 h post-ingestion. CYP2D6 inhibition significantly prolonged T_{max} and plasma availability (Glue, Winter, et al., 2015). The application of noribogaine 180 mg p.o. resulted in $t_{½}$ of 24–30 h (Glue et al., 2016).

1.4. Subjective effects

Research has divided the ibogaine experience into three phases (Alper, 2001). Phase I has been described as oneiric ("waking dream") state in which the individual experience visual and other sensory perception changes and panoramic recall of earlier life events (duration 4–8 h). After phase I, the experience changed to a subtler experience. Phase II has been described as evaluative, emotionally neutral, and reflective. Phase II lasts between 8 and 20 h. Phase III has been titled as a residual phase comprising heightened awareness, mild stimulation, and,

eventually, perturbed sleep patterns. Phase III can last up to 72 h after ingestion (Alper, 2001; Glick et al., 2001). Reports suggest that ibogaine can cause a more intense psychedelic experience than previous experiments with high doses of psilocybin. Participants have mentioned insights relating to the meaning of life, the evolution of the universe, life-after-death, and feeling relieved from guilt (Heink et al., 2017).

1.5. Safety and toxicity

The literature reports several fatalities and severe toxic adverse events in humans related to ibogaine treatments. Adverse symptoms range from nausea, tremors, ataxia, and psychiatric conditions (e.g., mania, psychosis) to severe clinical effects such as seizures, comas, pulmonary difficulties, and fatal outcomes (dos Santos et al., 2016; Litjens & Brunt, 2016; Schep et al., 2016). Cardiotoxicity and QT prolongation, which increases the risk for Torsade de Pointes, pose a significant problem. Ibogaine's modulatory action upon Human Related Ether-à-go-go Gene (hERG) channels seems to cause a reduction in electrical currents via potassium channels. This results in a delayed cardiac repolarization (Alper et al., 2016; Koenig et al., 2014; Koenig & Hilber, 2015). Eighteen of 33 previously analyzed fatality reports had preexisting medical conditions, such as coronary sclerosis or cardiac arrythmias. Twelve of 33 cases report concomitant drug or medication use, or the consumption of unknown origin and purity material (Corkery, 2018). Litjens and Brunt (2016) reviewed ibogaine's pharmacological profile and toxicity of ibogaine and its metabolites. Animal data showed neurodegenerative processes caused by ibogaine and to a lesser extent by noribogaine. Research has specially described excitotoxic effects on Purkinje cells in the cerebellum. Litjens & Brunt also present eight cases of cardiac abnormalities following the ingestion of ibogaine. An analysis of these cases revealed predominantly QTc-prolongation, ventricular tachycardia, and cardiac arrest as leading clinical manifestations. The study also discussed the importance of drug-drug interactions as a cause of adverse drug reactions. In conclusion of their review, the authors point to the risk of more ibogaine-related deaths and medical emergencies in the future, particularly in patients with cardiac comorbidities and concurrent medication (Litjens & Brunt, 2016). Structurally related congeners like 18-MC or tabernanthalog seem less cardiotoxic and non-hallucinogenic, but studies need to assess their clinical and therapeutic properties (Cameron et al., 2020; Corkery, 2018; Schep et al., 2016).

2. Methods

2.1. Data acquisition

The research team collected data for this systematic review according to the PRISMA guidelines for Systematic Reviews and Meta-Analyses.

2.2. Search strategy

For data acquisition, our group performed systematic electronic searches using PubMed and EMBASE. The team used the following keywords: “iboga” OR “ibogaine” OR “noribogaine” AND “withdrawal” OR “addiction” OR “dependence” OR “substance use disorder” OR “detoxification” OR “craving” OR “heroin” OR “opioid” OR “opiate” OR “cocaine” OR “alcohol” OR “cannabis” OR “tobacco” OR “nicotine” OR “therapy” OR “treatment” OR “therapy” OR “clinic”.

2.3. Eligibility criteria

Article type: The team included articles, case reports, and case-series in peer-reviewed journals. We also included book chapters, books, posters, abstracts, letters, and editorials if they were indexed in the databases mentioned above.

Study design: All kinds of study design.

Participants/sample: Human individuals.

Interventions: Administration of iboga, ibogaine, or noribogaine for investigative and therapeutic purposes.

Comparisons: Pre-post and placebo-controlled effects.

Outcomes: Substance use, SUD symptoms, depressive symptoms, and safety aspects.

2.4. Data extraction

Two independent reviewers (PK, KF) screened and assessed all electronically collected data. A third reviewer (KD) resolved discrepancies between rater PK and KF. From the articles included, our team recorded authors' names, publication date, setting (medical or nonmedical), study location (country), study type (case reports or case series, retrospective or observational studies, open-label clinical trials, placebo-controlled studies), number of participants receiving iboga/ibogaine/noribogaine, demographic data, study intention, substances used, dose, administration route, safety measures, serious adverse events, main results, and previous treatments.

3. Results

3.1. Selection of records

Following the PRISMA guidelines (Moher et al., 2009), we performed data acquisition and analysis for inclusion and exclusion of relevant literature (Fig. 1). Through the performance of database searches (PubMed, Embase), we identified 1038 records. In addition, we found four records via other sources (Research Gate). After the removal of duplicates, 743 records remained for screening. Through independent screening (PK, KF) of all records, the team excluded 710 papers (preclinical data, animal studies). Hence, we assessed for eligibility 33 full-text articles, and of those, we included nine. We excluded eight articles due to the absence of clinical data (Barber et al., 2020; Blessing et al., 2020; Schellekens et al., 2016) or redundant information (Alper et al., 2000; Calvey et al., 2020; Davis et al., 2018; Lotsof & Alexander, 2001; Mash, 2018). One record had not been published (Bastiaans, 2004). Finally, the team included 24 studies in this systematic review's qualitative synthesis, meeting pre-established eligibility criteria. We present the findings in Table 1 and Table 2. We split the dataset into two tables for better readability. The 24 selected studies included seven case reports (CR) or case series (CS), eight observational (OS) or retrospective studies (RS), six open-label clinical trials (OL, CT), and three double-blind, placebo-controlled clinical trials (DBPCT). All selected studies described the application of ibogaine or noribogaine. While most of the reviewed publications used ibogaine hydrochloride (HCl), some studies did not specify the exact chemical designation and we marked them accordingly in Table 2.

3.2. Case reports and case series

The first case series describing the administration of ibogaine for the treatment of OUD was published in 1994. Individuals ($n = 7$, from the UK, Switzerland, and the Netherlands) were treated for opioid withdrawal with a single oral dose of ibogaine (700–1800 mg) in a nonmedical setting in the Netherlands. The retrospective report states that all seven participants showed an immediate reduction of opioid withdrawal symptoms (OWS). Three of them remained abstinent for at least 14 weeks (Sheppard, 1994). A later medical report describes three cases of individuals with CUD and other SUDs who received domperidone 10 mg previous to ibogaine hydrochloride (HCl, 20–25 mg/kg). Electroencephalography did not show any abnormality during and after treatment. All neurological examinations after 24 h were normal. All three individuals had no subjective or objective withdrawal symptoms nor any kind of craving (Luciano, 1998). Another case series based on

Fig. 1. Flow diagram illustrating the different phases of the systematic review.

data from treatment records of 33 individuals with OUD who were treated in informal, nonmedical settings with ibogaine (9–29 mg/kg) between 1962 and 1993, was published in 1999. The mean duration of pre-treatment heroin use was 6.2 years, and more than three quarters used heroin predominantly intravenously. Immediate effects of ibogaine were absence or reduction of OWS, and 76% of the participants reported opioid abstinence for at least three days. A female participant died approximately 19 h after treatment. Forensic examination revealed no apparent conclusion, although concomitant (post-treatment) heroin use was probable. This fatality seemed to play a significant role in deciding not to conduct clinical trials following a NIDA review meeting in 1995 (Alper et al., 1999). More recently, Cloutier-Gill et al. (2016) described a remission of severe OUD with ibogaine in a 37-year-old female patient with a history of OUD for 19 years. Within a residential ibogaine program in Canada, she received a total of 32 mg/kg (2300 mg) of ibogaine HCl over four days. Additionally, she received hydromorphone 32 mg and 45 mg orally on the first and second day, respectively. After the ibogaine treatment, the patient maintained opioid abstinence for 18 months. She had previously undertaken various treatment modalities, including opioid-agonist-therapy (OAT) with methadone. Wilkins et al. (2017) published another case of a 47-year-old female patient treated for OUD by tapering her off methadone while increasing oral doses of ibogaine (max. 600 mg/d). The patient had been in OAT with methadone for 17 years before the ibogaine treatment. Post-ibogaine, she returned neither to OAT nor to the use of other illicit substances or benzodiazepines. Most recently, Wilson et al. (2020) published a case series of two individuals who underwent ibogaine treatment (up to 30.6 mg/kg) in a multiple-dosing regimen. Case 1 stayed abstinent from opioids for three years after a single treatment with ibogaine. Case 2 received repeated ibogaine therapies within four months and stopped all non-medical opioids after the first application. Another ibogaine administration followed to taper off the OAT medication. The patient maintained opioid abstinence for two years. Barsuglia et al. (2018) published a case report of a 31-year-old male military veteran with moderate alcohol use disorder (AUD) who was treated with ibogaine (17.9 mg/kg) on day 1, followed by inhaled, vaporized 5-MeO-DMT (5–7 mg) on day 3. The patient reported mood improvement, cessation of alcohol use, and reduced alcohol cravings for a month. Barsuglia et al. were the first to perform neuroimaging in a human receiving ibogaine. The SPECT imaging indicated pre- and post-treatment changes in several relevant brain regions associated with SUDs. Differences were most notable in the basal nuclei, the cerebellum, the temporal lobes, the occipital lobe, insular cortex, and anterior cingulate (Barsuglia et al., 2018).

3.3. Retrospective and observational studies

This review included 8 retrospective analyses or observational studies. These publications appeared between 2014 and 2020. Of these studies, we identified 6 with ibogaine as a treatment for OUD. One study ($n = 27$) reported that 78% of study participants sought the application of ibogaine for the treatment of problematic substance use. One study investigated the sequential application of ibogaine (on day 1) followed by vaporized 5-MeO-DMT (on day 3) as a psychedelic treatment for trauma-related psychological symptoms and cognitive impairment in U. S. veterans (Davis et al., 2020). Another study was a follow-up analysis of a previous study by Noller et al. (2018), which assessed the change of depressive symptoms and qualitative aspects of the "ibogaine experience" (Brown & Alper, 2018). Of the eight studies, five were data analyses conducted via retrospective surveys, and three were observational. Heink et al. (2017) collected data from individuals who received treatment within a medical context or other contexts (e.g., self-administration, informal therapeutic setting). The other studies collected data from participants treated in medical environments.

Table 1
Overview of safety measures, demographics, and previous treatments.

Study information	Safety measures and setting	N	Demographics	Ø prev. T_x
Case reports/ case series				
Sheppard, 1994	No description available, non-med. setting	7	Ø 29.29 yrs; 5 m, 2 f	Not stated
Luciano, 1998	Medical screening, EEG, neurological exam; in-patient	3	not stated	Not stated
Alper et al., 1999;	Med. screening, monitoring; non-med. setting	33	Ø 27.3 ± 4.7 yrs	Not stated
Cloutier-Gill et al., 2016	Med. screening, monitoring; in-patient	1	37 yrs; f	Several, incl. OAT
Wilkins et al., 2017	Med. screening, supervision; out-patient	1	47 yrs; f	OAT for 17 yrs
Barsuglia et al., 2018	Med. screening, monitoring; in-patient	1	31 yrs; m	ADHD- T_x
Wilson et al., 2020	Med. screening, monitoring; in-patient	2	Case 1: 35 yrs, m Case 2: 34 yrs, f	Case 1: none Case 2: div. OATs
Retrospective/ observational studies				
Schenberg et al., 2014	Med. screening, monitoring; in-patient	75	Ø 34.16 yrs; 67 m Ø 29.50 yrs; 8 f	92% had prior T_x
Davis et al., 2017	Med. screening, monitoring; in-patient	88	18–60 yrs	Several
Malcolm et al., 2018	Med. screening, monitoring; in-patient	40	Ø 31.28 yrs; 24 m, 16 f	75% ≥ 1 T_x
Davis et al., 2020	Med. screening, monitoring; in-patient	51	Ø 40.4 yrs; 50 m, 1 f, US-veterans	43% psychotherapy 41% medication
Brown and Alper, 2018	Med. screening, monitoring; in-patient	30	Ø 29.0 yrs; 25 m, 5 f	Ø 3.1 T_x
Noller et al., 2018	Med. screening, monitoring; in-patient	14	Ø 38.0 yrs; 7 m, 7 f;	Ø 4.7 T_x
Brown et al., 2019*	No description available; in-patient	0 *	Ø 38.0 yrs; 7 m, 7 f;	Ø 4.7 T_x
Heink et al., 2017	various settings: 33% med. supervision, 15% counselling, 52% "other"	27	Ø 35.11 yrs; 15 m, 12 f	Not stated
Open-label clinical trials				
Mash et al., 2000	Med. screening, monitoring; in-patient	27	Ø 37.5 yrs; 23 m, 4 f,	Not stated
Mash et al., 2001	Med. screening, monitoring; in-patient	32	Ø 33.6 yrs; 22 m,10 f	Not stated
Glue, Winter, et al., 2015	Med. screening, monitoring; in-patient	21	Ø 23.5 yrs, m, healthy	n.a.
Forsyth et al., 2016**	Med. screening, monitoring; in-patient	0**	Ø 23.5 yrs, m, healthy	n.a.
Geoffroy & Weis, 2017	Med. screening, monitoring; in-patient	9	Ø 31.2 yrs; 6 m, 3 f	OAT
Mash et al., 2018		191	OUD 35.8 ± 9.9 yrs	OUD Ø 5.5 T_x; CUD Ø 5.1 T_x
	Med. screening, monitoring; in-patient		CUD 36.1 ± 9.1 yrs	
Double-blind, placebo-controlled				
Prior & Prior, 2014	Med. screening, monitoring; in-patient	10	18–64 yrs; m	Not stated
Glue, Lockhart, et al., 2015	Med. screening, monitoring; in-patient	24	Ø 22.0 yrs; m	n.a.
Glue et al., 2016	Med. screening, monitoring; in-patient	18	Ø 41.2 yrs; 21 m, 6 f;	OAT

Ø = average, prev. = previous, T_x = treatment, med. = medical, yrs = years, m = male, f = female, OAT = Opioid Agonist Treatment, MMT = Methadone Maintenance Treatment, EEG = electroencephalography, OUD = Opioid Use Disorder, CUD = Cocaine Use Disorder, div. = diverse, n.a. = not applicable * = same population as in Noller 2017; ** = same population as in Glue, Winter, et al., 2015.

Bearing in mind the limitations of self-reports and retrospective analyses, most studies found reduced withdrawal symptoms and substance cravings. Schenberg et al. (2014) found that individuals with SUDs (n = 75, 72% classified as multiple substance users) showed a median of 5.5 months abstinence after a single dose administration and 8.4 months after multiple ibogaine sessions. Davis et al. (2020) found that 80% of their participants (n = 88) reported a reduction in OWS, 50% stated a decrease in craving for 7 days, and 25% a craving reduction for three months. Furthermore, the authors mentioned a ratio of responders vs. non-responders of 3:1. Symptoms of post-traumatic stress disorder (PTSD), depression, and anxiety in U.S. veterans (n = 51) were significantly reduced after ibogaine and 5-MeO-DMT administration. One of these eight studies reported a severe adverse event. Noller et al. (2018) reported the death of a 45-year-old woman, which occurred during ibogaine treatment in a medical setting. The case was sent to the Health & Disability Commissioner of New Zealand for clarification. The report stated that monitoring and protocols were not in line with medical standards (Health and Disability Commissioner, 2015).

3.4. Open-label clinical trials

We identified six open-label clinical trials. A phase I trial assessed the pharmacodynamics and -kinetics of a low dose of ibogaine (n = 21, ibogaine HCl 20 mg). The dose was well tolerated, with no safety concerns, and increased AUC and C_{max} with paroxetine pre-treatment. Due to CYP2D6 inhibition by paroxetine, the same hepatic pathway for ibogaine and noribogaine is likely (Glue, Winter, et al., 2015). Forsyth et al. (2016) evaluated the neurocognitive and psychological effects of ibogaine 20 mg in the same study population and found no significant impact (Forsyth et al., 2016). Another phase I trial assessed the safety of cumulative doses of noribogaine for five days in patients on OAT with methadone. They found a significant reduction in OWS and elevated mood, but only four of nine participants completed the study (Geoffroy & Weis, 2017).

The three other studies were all conducted and published by Mash et al. (2001, 2000, 2018). Single doses of ibogaine HCl were administered (max. 8–12 mg/kg p.o.) to treat OUD or CUD. In all studies, Mash and colleagues found a reduction in heroin or cocaine craving. One study measured depressive symptoms using the Beck Depression Inventory (BDI) and found substantial symptom reduction pre-treatment vs. discharge. Heroin craving, measured with the Heroin Craving Questionnaire subscale 29 (HCQN), was significantly reduced post-treatment and on discharge. Cocaine craving (Cocaine Craving

Table 2
Overview of intentions, substances and dosing, main findings, and adverse events.

Study information	N	Intention	Substance(s)	Dose	Main results	serious AE
Case reports/case series						
Sheppard, 1994; CR	7	T_x OUD	Ibogaine HCl	11.7–25 mg/kg, p.o.	Reduct. of WS for all; 3 subj. remained drug-free for >14 wk	None reported
Luciano, 1998; CS	3	T_x CUD/SUD	Ibogaine HCl domperidon	20–25 mg/kg, p.o. 10 mg, p.o.	No subj./obj. signs of WS or craving; neurological exams normal	None reported
Alper et al., 1999; CS	33	T_x OUD	Ibogaine***	19.3 ± 6.9 mg/kg, p.o.	Absence or reduct. of OWS; 76% abstinence for at least 3 days	1 fatality
Cloutier-Gill et al., 2016; CR	1	T_x OUD	Ibogaine HCl hydromorphone	To 32 mg/kg, p.o., multi-dose in 4 d; 30/45 mg (d1/d2), p.o.	Opioid abstinence for 18 mo	None reported
Wilkins et al., 2017; CS	1	T_x OUD, MMT-detox.	Ibogaine HCl methadone	Max. 600 mg/d, p.o. decreasing doses, p.o.	No relapse in 12 mo post-Tx; no OAT	None reported
Barsuglia et al., 2018; CR	1	T_x AUD; neuroimaging	Ibogaine HCl 5-MeO-DMT	17.9 mg/kg, p.o. (d1): ~ 6 mg, inh. (d3)	Improved mood; cessation of AU; reduct. craving for 1 mo	None reported
Wilson et al., 2020; CS	2	T_x OUD/SUD	Ibogaine HCl	To 30.6 mg/kg, p.o. multi-dose	>2 yrs total opioid abstinence	QTc 512 ms, 53 bpm –>ICU
Retrospective/ observational studies						
Schenberg et al., 2014; RA	75	T_x SUD	Ibogaine HCl domperidone	7.5–20 mg/kg p.o., multi-dose 20 mg	Median of abstinence 5.5 mo (1 T_x); and 8.4 mo (multiple T_x)	None reported
Davis et al., 2017; RA	88	T_x OUD	Ibogaine HCl	15 mg ± 5 mg/kg, p.o.	80% reduct. of WS; 50% reduct. of craving for 1 wk.; 25% reduct. of craving for 3 mo; 68 responders/20 non-responders	None reported
Malcolm et al., 2018; RA	40	T_x OUD	Ibogaine HCl	18–20 mg/kg p.o.	Sign. reduct. in COWS, SOWS, and BSCS	None reported
Davis et al., 2020; RA	51	T_x PTSD/depr./anx.	Ibogaine HCl 5-MeO-DMT	10 mg/kg, p.o. (d1) ~ 7.5 mg, inh. (d3)	Sign. reduct. of symptoms of PTSD, depr. and anx.	Not assessed
Brown et al., 2018; OS	30	T_x OUD	ibogaine HCl	1540 ± 920 mg, p.o.	SOWS decrease (post 76 h) in >50% of subjects; in 50% of subjects no OU for 1 mo; in 12 subjects reduct. of drug use 75%	none reported
Noller et al., 2018; OS	14	T_x OUD	Ibogaine HCl diazepam, zopiclone, odansetron	25–55 mg/kg p.o. (some received usual clinical doses, p.o.)	Sign. reduct. in SOWS; sign. Reduct. ASI-Lite Subscale "Drug" and BDI; 8 subj. Opioid-negative after 12 mo	1 fatality
Brown et al., 2019*; OS	0*	T_x OUD	Ibogaine HCl	31.4 ± 7.6 mg/kg, p.o.	Sign. reduct. BDI; ~ 75% report "transformational experience"	None reported
Heink et al., 2017; RA	27	92% psych. T_x, 78% T_x SUD	Ibogaine***	Not stated	96% reduct. of WS; 68% "dramatically" reduct. of WS; 41% report "important hallucinations"	Not assessed
Open-label clinical trials						
Mash et al., 2000; OL, CT	27	T_x OUD/CUD	Ibogaine HCl	To 800 mg, p.o.	Sign. reduct. in BDI, HCQN-29, CCQN-45; diminished craving 1 mo post-T_x	None reported
Mash et al., 2001; OL, CT	32	T_x OUD	Ibogaine HCl	800 mg, p.o.	Sign. reduct. in OOWS, HCQN-29, OP-SCL	None reported
Glue, Winter, et al., 2015; OL, CT	21	Pharm./safety assessment	Ibogaine*** 11 subj. pre-T_x paroxetine	20 mg, p.o. 10–20 mg/d, p.o.	Safe and well-tolerated; AUC and C*max* incr. with paroxetine pre-T_x due to CYP2D6 inhibition	None reported
Forsyth et al., 2016**; OL, CT	0**	Mood/psych. performance	Ibogaine***	20 mg, p.o.	No sign. effect on cognitive or psych. performance	None reported
Geoffroy & Weis, 2017; OL, CT	9	Safety assessment & T_x of OWS in OAT	Noribogaine	Cum. to 653 mg, p.o. multi-dose, in 5 d	Sign. reduct. OWS; elevated mood, yet only 4 completed study	None reported
Mash et al., 2018; OL, CT	191	T_x OUD/CUD	Ibogaine HCl	8–12 mg/kg, p.o.	Sign. Reduct. in HCQ, CCQ, BDI	None reported
Double-blind, placebo-controlled						
Prior & Prior, 2014; DBPCT	10	T_x CUD	Ibogaine HCl	1800 mg, p.o.	Sign. reduct. in MCCS; lower rates of cocaine-positive urine	None reported
Glue, Lockhart, et al., 2015; RDBPCT	24	Pharm./safety assessment	Noribogaine	to 60 mg, p.o.	Safe and well-tolerated; slow elimination	None reported, QTcF <500 ms
Glue et al., 2016; RDBPCT	18	Safety assessment & OWS in OAT	Noribogaine	to 180 mg, p.o.	Trend toward OWS reduct.; well-tolerated; QTc-increase in accordance with plasma levels	None reported

Ø = average, T_x = treatment, CR = case report, CS = case series, RA = retrospective analysis, OS = observational study, OL = open-label, CT = clinical trial, DBPCT = double-blind, placebo controlled clinical trial, RDBPCT = randomized, double-blind, placebo-controlled clinical trial, HCl = hydrochloride, OAT = Opioid Agonist Treatment, MMT = Methadone Maintenance Treatment, EEG = electroencephalography, OU/D = Opioid Use/Disorder, CUD = Cocaine Use Disorder, AU/D = Alcohol Use/Disorder, SUD = Substance Use Disorder, depr. = depressive disorder, anx. = anxiety disorder, p.o. = per os, HCl = hydrochloride, mo = month(s), wk. = week(s), sign. = significant, reduct. = reduction, C/O/S/OWS = clinical/objective/subjective/opioid withdrawal symptoms, WS = withdrawal symptoms, subj. = subjective,

obj. = objective, ICU = intensive care unit, incr. = increase, pharm. = pharmacological, AUC = area under the curve, Cmax = maximum concentration, psych. = psychological, CYP2D6 = Cytochrome P450 2D6, PTSD = post-traumatic-stress-disorder, sympt. = symptoms, QTc = corrected QT interval, QTcF = corrected QT interval by Fredericia formula, bpm = beats per minute, ASI-Lite = Addiction Severity Index Lite, BSCS = Brief-Substance-Craving-Scale, BDI = Beck Depression Inventory, HCQN = Heroin Craving Questionnaire, CCQN = Cocaine Craving Questionnaire, MCCS = Minnesota Cocaine Craving Scale, OP-SCL = Opiate Symptom Checklist * = same population as in Noller et al., 2018; ** = same population as in Glue, Winter, et al., 2015, *** = not specified if ibogaine HCl form or other ibogaine form was applied.

Questionnaire Subscale 45, CCQN) decreased significantly in three of five dimensions (Mash et al., 2000). Another study by Mash and colleagues compared pre- and post-treatment OWS of single doses of ibogaine in opioid-dependent individuals (n = 32). That study found significant reduction in both the objective opiate withdrawal scale and the self-report Opiate-Symptom Checklist (Mash et al., 2001). Another, larger (n = 191) open-label trial found similar significant reductions (at discharge and at follow-up one month later) in the respective HCQ and CCQ subscales, the Minnesota Cocaine Craving Scale (MCCS), the SCL-90-R Depression Subscale, the BDI, and the Profile Of Mood States (POMS) (Mash et al., 2018). All reviewed open-label clinical trials reported no serious adverse events.

3.5. Double-blind placebo-controlled clinical trials

This review included three double-blind placebo-controlled clinical trials (DBPCT). Two of them were randomized (RDBPCT) (Glue et al., 2016; Glue, Lockhart, et al., 2015). One trial assessed the pharmacological profile and the safety of noribogaine in ascending doses (3, 10, 30, and 60 mg; single doses, placebo-matched). No safety issues were reported. Pupillometry and a cold-pressor test did not detect opioid-agonist effects. The second RDBPCT evaluated the effects of ascending single-doses of noribogaine (60, 120, or 180 mg) in opioid-dependent patients. It found a dose-dependent QTc prolongation (0.17 ms/ng/mL). Opioid withdrawal ratings (Subjective, Objective, and Clinical Opioid Withdrawal Scales: SOWS, OOWS, COWS) showed a decreasing trend, which was not statistically significant. Patients had all been on OAT and were switched to oral morphine a week before noribogaine. They were permitted to continue their OAT after the trial. Another DBPCT was conducted in Brazil to examine the effect of ibogaine on cocaine craving and cocaine use in patients with CUD (n = 20). The verum group (n = 10), which received a single dose of 1800 mg ibogaine, showed a significant reduction in the MCCS after 72 h and 24 weeks post-dosing, while craving in the placebo group did not change. Urine samples of both groups indicated fewer relapses in the ibogaine group.

3.6. Intention for ibogaine treatment

Across the selected studies, the most common intention for study participation or treatment with ibogaine was for detoxification from opioids or assessment of changes in OWS. Among the 705 individuals described in the assessed studies, at least 379 (53.8%) participated in ibogaine treatments or studies due to OUD. We identified at least 164 individuals (23.3%) with CUD as the principle purpose for ibogaine treatment. As Mash et al. (2000) (n = 27 for CUD or OUD) and Heink et al. (2017) (n = 27, 78% for SUD) did not differentiate between the principal drugs of concern, we did not include them in this calculation. Roughly estimated, however, about 55% of all individuals included in this review underwent ibogaine treatment for OUD and 24% for CUD.

3.7. Adverse events and fatalities

In the 24 studies that we considered for this review, a total of two fatalities were reported (Alper et al., 1999; Noller et al., 2018), which we described in Sections 3.2, 3.3 and 4.2 of this article. Wilson et al. (2020) reported an individual with bradycardia and prolonged QT interval. The patient had to be transferred to an intensive care unit for stabilization but could be discharged in the course. All other included studies did not report severe adverse events. However, among the screened literature, we found several additional reports of ibogaine toxicity or fatalities, which did not meet eligibility criteria for this review and are discussed in Section 4.2.

4. Discussion

4.1. Potential benefits

This systematic review provides an updated overview of the available literature on the clinical findings and therapeutic application of iboga, ibogaine, and noribogaine. We have found that most of the reviewed studies assessed the effects of ibogaine for the treatment of SUDs. The last systematic review dates back to 2016 (dos Santos et al., 2016). Then, the authors identified 259 records through database searching and included eight studies in their review. Thus, in the past five years, the published records have almost tripled (743 records). Although most of the included studies lack rigorous clinical study designs (case reports, case series, retrospective surveys, observational studies), they suggest beneficial effects of ibogaine and noribogaine on OWS in patients who seek opioid abstinence. Furthermore, those studies that assessed substance craving via structured interviews or self-reports (HCQN, MCCN, CCQN, ASI-Lite) found an immediate and prolonged reduction in opioid or cocaine craving (Mash et al., 2000, 2001, 2018; Noller et al., 2018; Prior & Prior, 2014). Studies that examined depressive symptoms, with scales like BDI or POMS (Brown et al., 2019; Mash et al., 2000, 2001, 2018; Noller et al., 2018) and symptom severity of PTSD via PCL-5 (Davis et al., 2020), found significant symptom reduction for prolonged periods (weeks to months after discharge).

4.2. Safety concerns

An initial dose of 0.87 mg/kg bodyweight for humans is considered safe (Schep et al., 2016). Individuals in this review received between 0.28 mg/kg (Glue, Lockhart, et al., 2015) and up to 55 mg/kg of ibogaine (Noller et al., 2018). Severe adverse events and fatal outcomes associated with the ingestion of iboga/ibogaine have appeared in the literature (dos Santos et al., 2016; Schep et al., 2016; Alper et al., 2012; Corkery, 2018; Grogan et al., 2019; Steinberg & Deyell, 2018). Among the 24 studies included here, we identified two reported fatalities (Alper et al., 1999; Noller et al., 2018). The first case occurred 1990 (Alper et al., 1999) within an informal treatment setting and was associated with possible concomitant heroin use. More recently, another fatality took place in a medical environment (Noller et al., 2018). The New Zealand Health & Disability Commissioner report pointed out inadequate medical monitoring, unusually high doses, and vague instructions concerning the cessation of the patient's antidepressant medication venlafaxine (Health and Disability Commissioner, 2015). In addition to the two fatalities among the included literature, we identified another 56 deaths or emergencies associated with ibogaine use that did not meet inclusion criteria for this review. After cross-checking for duplicates in previously published systematic analyses of cases (Alper et al., 2012; Corkery, 2018; Koenig & Hilber, 2015; Litjens & Brunt, 2016) we found a total of 58 ibogaine-associated emergencies (n = 20) and deaths (n = 38). In 34.5% of these cases concomitant drug use was documented and in 70.7% ibogaine was administered with the intention of treating OUD. Most of the ibogaine-related adverse events were accompanied by cardiac arrhythmias as published previously (Alper et al., 2012; Corkery, 2018; Koenig & Hilber, 2015; Litjens & Brunt, 2016). However, in one

case a patient with schizophrenia experienced an exacerbation of psychotic symptoms (Houenou et al., 2011) and in two cases, individuals experienced symptoms of mania following ibogaine ingestion (Marta et al., 2015).

Research has made efforts to provide clinical recommendations for ibogaine treatments (Dickinson et al., 2016). Yet ibogaine-related health issues continue. As scheduling regimens for ibogaine vary between countries (Wikipedia, 2021), global consensus about the legal status and scientific investigation is missing.

In recent years, some studies evaluated the effects of microdosing of other hallucinogenic compounds like LSD, psilocybin, or ketamine (Higgins et al., 2021; Kuypers et al., 2019). The case report by Wilkins et al. (2017), which we included in this review, describes a successful treatment of OUD with repeated small doses of ibogaine. Another anecdotal article reported that three individuals with OUD benefited from repeated administration of small ibogaine doses (Kroupa & Wells, 2005). Microdosing of ibogaine could be a possible effective strategy to prevent toxicity and fatalities, while providing positive treatment effects. However, systematic approaches and rigorous studies of microdosing are lacking.

OAT, with methadone, buprenorphine, or other prescribed opioids such as morphine, is the first-line treatment for OUD, and substantially improves health issues related to illicit opioid use (Pearce et al., 2020). However, some individuals wish to stop OAT and attain opioid abstinence. Moreover, insufficient evidence still exists for routine pharmacological management of CUD or stimulant use disorders (Crits-Christoph et al., 2018; Lee et al., 2018; National Institute on Drug Abuse (NIDA), 2018). Although psychosocial treatments show efficacy in treating CUD and stimulant use disorders (Zastepa et al., 2020), the field needs effective pharmacotherapeutic interventions (Dürsteler et al., 2015).

4.3. Limitations and strengths

The heterogeneity among the studies, particularly with respect to their outcome measures, did not allow for statistical pooling. Thus, we had to discuss the results in a descriptive narrative format, which clearly limits the evidential value of this review. Nevertheless, we were able to show that the interest for ibogaine treatments is ongoing despite potentially lethal consequences. We provided an updated review of the existing literature on the therapeutic use of ibogaine in SUD across clinical contexts, and ibogaine's related risks and benefits.

4.4. Conclusion

The analyzed data suggest that rigorously designed studies could clarify the therapeutic benefits of ibogaine in human patients with SUDs. Future study designs with repeated lower doses of ibogaine could be a potential strategy to minimize the risk of adverse events. Studies should incorporate rapid intervention strategies and offer high-standard medical care. Increased public and medical awareness could potentially prevent unnecessary fatalities or other severe adverse events. Standardized information and medical guidelines may help to inform health practitioners, users, and treatment providers.

CRediT authorship contribution statement

Patrick Köck; conceptualization, data analysis, writing - original draft

Katharina Frölich; data analysis, tables

Marc Walter; proof-reading, substantial intellectual input

Undine Lang; supervision conceptual input

Kenneth M. Dürsteler; writing – review and editing

Declaration of competing interest

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References

Alper, K., Bai, R., Liu, N., Fowler, S. J., Huang, X.-P., Priori, S. G., & Ruan, Y. (2016). hERG blockade by iboga alkaloids. *Cardiovascular Toxicology, 16*(1), 14–22. https://doi.org/10.1007/s12012-015-9311-5

Alper, K. R. (2001). Ibogaine: a review. The alkaloids. *Chemistry and Biology, 56*, 1–38.

Alper, K. R., Lotsof, H. S., Frenken, G. M., Luciano, D. J., & Bastiaans, J. (1999). Treatment of acute opioid withdrawal with ibogaine. *The American Journal on Addictions, 8*(3), 234–242.

Alper, K. R., Lotsof, H. S., Frenken, G. M. N., Luciano, D. J., & Bastiaans, J. A. N. (2000). Ibogaine in acute opioid withdrawal. An open label case series. *Annals of the New York Academy of Sciences, 909*, 257–259. https://doi.org/10.1111/j.1749-6632.2000.tb06687.x

Alper, K. R., Lotsof, H. S., & Kaplan, C. D. (2008). The ibogaine medical subculture. *Journal of Ethnopharmacology, 115*(1), 9–24. https://doi.org/10.1016/j.jep.2007.08.034

Alper, K. R., Stajić, M., & Gill, J. R. (2012). Fatalities temporally associated with the ingestion of ibogaine. *Journal of Forensic Sciences, 57*(2), 398–412. https://doi.org/10.1111/j.1556-4029.2011.02008.x

Antonio, T., Childers, S. R., Rothman, R. B., Dersch, C. M., King, C., Kuehne, M., Bornmann, W. G., Eshleman, A. J., Janowsky, A., Simon, E. R., Reith, M. E. A., & Alper, K. (2013). Effect of iboga alkaloids on micro-opioid receptor-coupled G protein activation. *PloS One, 8*(10), Article e77262. https://doi.org/10.1371/journal.pone.0077262

Arias, H. R., Rosenberg, A., Targowska-Duda, K. M., Feuerbach, D., Yuan, X. J., Jozwiak, K., Moaddel, R., & Wainer, I. W. (2010). Interaction of ibogaine with human alpha3beta4-nicotinic acetylcholine receptors in different conformational states. *The International Journal of Biochemistry & Cell Biology, 42*(9), 1525–1535.

Barber, M., Gardner, J., Savic, M., & Carter, A. (2020). Ibogaine therapy for addiction: Consumer views from online fora. *International Journal of Drug Policy, 83*, Article 102857. https://doi.org/10.1016/j.drugpo.2020.102857

Barsuglia, J. P., Polanco, M., Palmer, R., Malcolm, B. J., Kelmendi, B., & Calvey, T. (2018). A case report SPECT study and theoretical rationale for the sequential administration of ibogaine and 5-MeO-DMT in the treatment of alcohol use disorder. In (1st ed.), *242. Progress in Brain Research*. Elsevier B.V.. https://doi.org/10.1016/bs.pbr.2018.08.002

Bastiaans, E. (2004). *Life after Ibogaine*. November, 27 http://www.ibogaine.org/ibogaine_udi_bastiaans.pdf.

Baumann, M. H., Pablo, J., Ali, S. F., Rothman, R. B., & Mash, D. C. (2001). Comparative neuropharmacology of ibogaine and its O-desmethyl metabolite, noribogaine. *The Alkaloids. Chemistry and Biology, 56*, 79–113.

Bidlack, J. M. (2014). Mixed Kappa/Mu partial opioid agonists as potential treatments for cocaine dependence. In *Advances in Pharmacology* ((1st ed., Vol. 69). Elsevier Inc.. https://doi.org/10.1016/B978-0-12-420118-7.00010-X

Blessing, E., Virani, S., & Rotrosen, J. (2020). Clinical trials for opioid use disorder. *Handbook of Experimental Pharmacology, 258*, 167–202. https://doi.org/10.1007/164_2019_304

Bogenschutz, M. P., & Johnson, M. W. (2016). Classic hallucinogens in the treatment of addictions. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 64*, 250–258. https://doi.org/10.1016/j.pnpbp.2015.03.002

Bogenschutz, M. P., & Ross, S. (2018). Therapeutic Applications of Classic Hallucinogens. In A. L. Halberstadt, F. X. Vollenweider, & D. E. Nichols (Eds.), *Behavioral neurobiology of psychedelic drugs* (pp. 361–391). Berlin Heidelberg: Springer. https://doi.org/10.1007/7854_2016_464.

Brown, T. K., & Alper, K. (2018). Treatment of opioid use disorder with ibogaine: Detoxification and drug use outcomes. *American Journal of Drug and Alcohol Abuse, 44*(1), 24–36. https://doi.org/10.1080/00952990.2017.1320802

Brown, T. K., Noller, G. E., & Denenberg, J. O. (2019). Ibogaine and subjective experience: Transformative states and psychopharmacotherapy in the treatment of opioid use disorder. *Journal of Psychoactive Drugs, 51*(2), 155–165. https://doi.org/10.1080/02791072.2019.1598603

Calvey, T., Woolf, J., Polanco, M., Malcolm, B., Kelmendi, B., Dickens, C., & Barsuglia, J. P. (2020). Combination psychedelic therapy to treat substance use disorders: Insights from human and rodent studies. *Journal of Anatomy, 236*(August), 1–364. https://doi.org/10.1111/joa.13163

Cameron, L. P., Tombari, R. J., Lu, J., Pell, A. J., Hurley, Z. Q., Ehinger, Y., Vargas, M. V., McCarroll, M. N., Taylor, J. C., Myers-Turnbull, D., Liu, T., Yaghoobi, B., Laskowski, L. J., Anderson, E. I., Zhang, G., Viswanathan, J., Brown, B. M., Tjia, M., Dunlap, L. E.Olson, D. E., … (2020). A non-hallucinogenic psychedelic analogue with therapeutic potential. *Nature, January*. https://doi.org/10.1038/s41586-020-3008-z

Carnicella, S., He, D. Y., Yowell, Q. V., Glick, S. D., & Ron, D. (2010). Noribogaine, but not 18-MC, exhibits similar actions as ibogaine on GDNF expression and ethanol self-administration. *Addiction Biology, 15*(4), 424–433. https://doi.org/10.1111/j.1369-1600.2010.00251.x

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

Corkery, J. M. (2018). Ibogaine as a treatment for substance misuse: Potential benefits and practical dangers. In *, 242. Progress in brain research* (pp. 217–257). Elsevier B.V. https://doi.org/10.1016/bs.pbr.2018.08.005.

Crits-Christoph, P., Wadden, S., Gaines, A., Rieger, A., Gallop, R., McKay, J. R., & Gibbons, M. B. C. (2018). Symptoms of anhedonia, not depression, predict the outcome of treatment of cocaine dependence. *Journal of Substance Abuse Treatment, 92*(February), 46–50. https://doi.org/10.1016/j.jsat.2018.06.010

da Silva Brum, E., da Rosa Moreira, L., da Silva, A. R. H., Boligon, A. A., Carvalho, F. B., Athayde, M. L., Brandao, R., & Oliveira, S. M. (2016). Tabernaemontana catharinensis ethyl acetate fraction presents antinociceptive activity without causing toxicological effects in mice. *Journal of Ethnopharmacology, 191*, 115–124. https://doi.org/10.1016/j.jep.2016.06.036

Davis, A. K., Averill, L. A., Sepeda, N. D., Barsuglia, J. P., & Amoroso, T. (2020). Psychedelic treatment for trauma-related psychological and cognitive impairment among US special operations forces veterans. *Chronic Stress, 4*. https://doi.org/10.1177/2470547020939564

Davis, A. K., Barsuglia, J. P., Windham-Herman, A.-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), 65–73. https://doi.org/10.1556/2054.01.2017.009

Davis, A. K., Renn, E., Windham-Herman, A. M., Polanco, M., & Barsuglia, J. P. (2018). A mixed-method analysis of persisting effects associated with positive outcomes following ibogaine detoxification. *Journal of Psychoactive Drugs, 50*(4), 287–297. https://doi.org/10.1080/02791072.2018.1487607

Dickinson, J., McAlpin, J., Wilkins, C., Fitzsimmons, C., Guion, P., Paterson, T., … MD Chaves, B. (2016). *Clinical guidelines for ibogaine-assisted detoxification.* http://www.ibogainealliance.org/guidelines/.

dos Santos, R. G., Bouso, J. C., & Hallak, J. E. C. (2016). The antiaddictive effects of ibogaine: A systematic literature review of human studies. *Journal of Psychedelic Studies, 1*(1), 20–28. https://doi.org/10.1556/2054.01.2016.001

Dürsteler, K. M., Berger, E.-M., Strasser, J., Caflisch, C., Mutschler, J., Herdener, M., & Vogel, M. (2015). Clinical potential of methylphenidate in the treatment of cocaine addiction: A review of the current evidence. *Substance Abuse and Rehabilitation, 6*, 61–74. https://doi.org/10.2147/SAR.S50807

Fernandez, J. W., & Fernandez, R. L. (2001). "Returning to the path": The use of iboga [ine] in an equatorial African ritual context and the binding of time, space, and social relationships. *The Alkaloids. Chemistry and Biology, 56*, 235–247.

Forsyth, B., Machado, L., Jowett, T., Jakobi, H., Garbe, K., Winter, H., & Glue, P. (2016). Effects of low dose ibogaine on subjective mood state and psychological performance. *Journal of Ethnopharmacology, 189*, 10–13. https://doi.org/10.1016/j.jep.2016.05.022

Freissmuth, M., Stockner, T., & Sucic, S. (2018). SLC6 transporter folding diseases and pharmacochaperoning. In *, 245. Handbook of Experimental Pharmacology* (pp. 249–270). https://doi.org/10.1007/164_2017_71

Geoffroy, P., & Weis, H. (2017). Safety, pharmacokinetic, and pharmacodynamic evaluation of a noribogaine multiple-dose regimen in opioid-dependent subjects. *The American Journal on Addictions, 26*(3), 232–293. https://doi.org/10.1111/ajad.12545

Glick, S. D., Maisonneuve, I. M., & Dickinson, H. A. (2000). 18-MC reduces methamphetamine and nicotine self-administration in rats. *Neuroreport, 11*(9), 2013–2015.

Glick, S. D., Maisonneuve, I. M., Kitchen, B. A., & Fleck, M. W. (2002). Antagonism of alpha 3 beta 4 nicotinic receptors as a strategy to reduce opioid and stimulant self-administration. *European Journal of Pharmacology, 438*(1–2), 99–105.

Glick, S. D., Maisonneuve, I. M., & Szumlinski, K. K. (2001). Mechanisms of action of ibogaine: Relevance to putative therapeutic effects and development of a safer iboga alkaloid congener. *The Alkaloids. Chemistry and Biology, 56*, 39–53.

Glue, P., Cape, G., Tunnicliff, D., Lockhart, M., Lam, F., Hung, N., Hung, C. T., Harland, S., Devane, J., Crockett, R. S., Howes, J., Darpo, B., Zhou, M., Weis, H., & Friedhoff, L. (2016). Ascending single-dose, double-blind, placebo-controlled safety study of noribogaine in opioid-dependent patients. *Clinical Pharmacology in Drug Development, 5*(6), 460–468. https://doi.org/10.1002/cpdd.254

Glue, P., Lockhart, M., Lam, F., Hung, N., Hung, C.-T. T., & Friedhoff, L. (2015b). Ascending-dose study of noribogaine in healthy volunteers: Pharmacokinetics, pharmacodynamics, safety, and tolerability. *Journal of Clinical Pharmacology, 55*(2), 189–194. https://doi.org/10.1002/jcph.404

Glue, P., Winter, H., Garbe, K., Jakobi, H., Lyudin, A., Lenagh-Glue, Z., & Hung, C. T. (2015a). Influence of CYP2D6 activity on the pharmacokinetics and pharmacodynamics of a single 20 mg dose of ibogaine in healthy volunteers. *Journal of Clinical Pharmacology, 55*(6), 680–687. https://doi.org/10.1002/jcph.471

Gómez-Calderón, C., Mesa-Castro, C., Robledo, S., Gómez, S., Bolivar-Avila, S., Diaz-Castillo, F., & Martínez-Gutierrez, M. (2017). Antiviral effect of compounds derived from the seeds of Mammea americana and Tabernaemontana cymosa on dengue and chikungunya virus infections. *BMC Complementary and Alternative Medicine, 17*(1), 57. https://doi.org/10.1186/s12906-017-1562-1

Grogan, J., Gerona, R., Snow, J. W., & Kao, L. (2019). Ibogaine consumption with seizure-like episodes, QTc-prolongation, and captured cardiac dysrhythmias. *Journal of Emergency Medicine, 57*(4), e99–e104. https://doi.org/10.1016/j.jemermed.2019.06.052

Health and Disability Commissioner. (2015). 13HDC00966 - monitoring of patient following administration of an unapproved, prescription-only medication. https://www.hdc.org.nz/decisions/search-decisions/2015/13hdc00966/.

Heink, A., Katsikas, S., & Lange-Altman, T. (2017). Examination of the phenomenology of the ibogaine treatment experience: Role of altered states of consciousness and psychedelic experiences. *Journal of Psychoactive Drugs, 1072*(March), 1–8. https://doi.org/10.1080/02791072.2017.1290855

Higgins, G. A., Carroll, N. K., Brown, M., MacMillan, C., Silenieks, L. B., Thevarkunnel, S., Izhakova, J., Magomedova, L., DeLannoy, I., & Sellers, E. M. (2021). Low doses of psilocybin and ketamine enhance motivation and attention in poor performing rats: Evidence for an antidepressant property. *Frontiers in Pharmacology, 12*, Article 640241. https://doi.org/10.3389/fphar.2021.640241

Houenou, J., Homri, W., Leboyer, M., & Drancourt, N. (2011). Ibogaine-associated psychosis in schizophrenia: a case report. *Journal of Clinical Psychopharmacology, 31*(5), 659. https://doi.org/10.1097/JCP.0b013e31822c6509

Ishikawa, H., Colby, D. A., & Boger, D. L. (2008). Direct coupling of catharanthine and vindoline to provide vinblastine: Total synthesis of (+)- and ent-(-)-vinblastine. *Journal of the American Chemical Society, 130*(2), 420–421. https://doi.org/10.1021/ja078192m

Kikura-Hanajiri, R., Maruyama, T., Miyashita, A., & Goda, Y. (2009). Chemical and DNA analyses for the products of a psychoactive plant, voacanga africana. *Yakugaku Zasshi, 129*(8), 975–982.

Kinghorn, A. D. (2017). Progress in the chemistry of organic natural products 105. In A. D. Kinghorn, H. Falk, S. Gibbons, & J. Kobayashi (Eds.), *105. Phytochemistry*. Springer International Publishing. https://doi.org/10.1007/978-3-319-49712-9. Issues 5–6.

Koenig, X., & Hilber, K. (2015). The anti-addiction drug ibogaine and the heart: A delicate relation. Issue 2. In *, 20. Molecules* (pp. 2208–2228). https://doi.org/10.3390/molecules20022208. MDPI AG.

Koenig, X., Kovar, M., Boehm, S., Sandtner, W., & Hilber, K. (2014). Anti-addiction drug ibogaine inhibits hERG channels: A cardiac arrhythmia risk. *Addiction Biology, 19*(2), 237–239. https://doi.org/10.1111/j.1369-1600.2012.00447.x

Kroupa, P., & Wells, H. (2005). Ibogaine in the 21st century: Boosters, tune-ups and maintenance. *Maps, 15*(1), 21–24.

Kuypers, K. P. C., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., Pani, L., Soula, A., & Nutt, D. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. *Journal of Psychopharmacology, 33*(9), 1039–1057. https://doi.org/10.1177/0269881119857204

Lavaud, C., & Massiot, G. (2017). The iboga alkaloids. *Progress in the Chemistry of Organic Natural Products, 105*, 89–136. https://doi.org/10.1007/978-3-319-49712-9_2

Lee, N. K., Jenner, L., Harney, A., & Cameron, J. (2018). Pharmacotherapy for amphetamine dependence: A systematic review. *Drug and Alcohol Dependence, 191*(December 2016), 309–337. https://doi.org/10.1016/j.drugalcdep.2018.06.038

Litjens, R. P. W., & Brunt, T. M. (2016). How toxic is ibogaine? *Clinical Toxicology (Philadelphia, Pa.), 54*(4), 297–302. https://doi.org/10.3109/15563650.2016.1138226

Lotsof, H. S., & Alexander, N. E. (2001). Case studies of ibogaine treatment: Implications for patient management strategies. *The Alkaloids. Chemistry and Biology, 56*, 293–313.

Luciano, D. (1998). Observations on treatment with ibogaine. *The American journal on addictions, 7*(1), 89–90.

Mačiulaitis, R., Kontrimavičiute, V., Bressolle, F. M. M., Briedis, V., Maciulaitis, R., Kontrimaviciute, V., Bressolle, F. M. M., Briedis, V., MačiIulaitis, R., Kontrimavičiute, V., Bressolle, F. M. M., Briedis, V., Maciulaitis, R., Kontrimaviciute, V., Bressolle, F. M. M., & Briedis, V. (2008). Ibogaine, an anti-addictive drug: Pharmacology and time to go further in development. A narrative review. *Human and Experimental Toxicology, 27*(3), 181–194. https://doi.org/10.1177/0960327107087802

Maillet, E. L., Milon, N., Heghinian, M. D., Fishback, J., Schurer, S. C., Garamszegi, N., & Mash, D. C. (2015). Noribogaine is a G-protein biased kappa-opioid receptor agonist. *Neuropharmacology, 99*, 675–688. https://doi.org/10.1016/j.neuropharm.2015.08.032

Malcolm, B. J., Polanco, M., & Barsuglia, J. P. (2018). Changes in withdrawal and craving scores in participants undergoing opioid detoxification utilizing ibogaine. *Journal of Psychoactive Drugs, 50*(3), 256–265. https://doi.org/10.1080/02791072.2018.1447175

Marta, C. J., Ryan, W. C., Kopelowicz, A., & Koek, R. J. (2015). Mania following use of ibogaine: A case series. *The American Journal on Addictions, 24*(3), 203–205. https://doi.org/10.1111/ajad.12209

Mash, D. C. (2018). Breaking the cycle of opioid use disorder with ibogaine. *American Journal of Drug and Alcohol Abuse, 44*(1), 1–3. https://doi.org/10.1080/00952990.2017.1357184

Mash, D. C., Duque, 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(JUN).. https://doi.org/10.3389/fphar.2018.00529

Mash, D. C., Kovera, C. A., Pablo, J., Tyndale, R., Ervin, F. R., Kamlet, J. D., & Hearn, W. L. (2001). Ibogaine in the treatment of heroin withdrawal. The alkaloids. In *, 56. Chemistry and Biology* (pp. 155–171).

Mash, D. C., Kovera, C. A., Pablo, J., Tyndale, R. F., Ervin, F. D., Williams, I. C., Singleton, E. G., & Mayor, M. (2000). Ibogaine: Complex pharmacokinetics, concerns for safety, and preliminary efficacy measures. *Annals of the New York Academy of Sciences, 914*, 394–401.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Altman, D., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J. A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J. J., Devereaux, P. J., Dickersin, K., Egger, M., Ernst, E., & Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-

analyses: The PRISMA statement. *PLoS Medicine, 6*(7). https://doi.org/10.1371/journal.pmed.1000097

National Institute on Drug Abuse (NIDA). (2018). *Cocaine*. https://www.drugabuse.gov/publications/drugfacts/cocaine.

National Institutes of Health. (2012). ND-enabling studies and GMP scale-up of 18-methoxycoronaridine hydrochloride (18 MC) project number: 1U01DA034986-01. https://projectreporter.nih.gov/project_info_history.cfm?aid=8448461&icde=16047111.

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

Obach, R. S., Pablo, J., & Mash, D. C. (1998). Cytochrome P4502D6 catalyzes the O-demethylation of the psychoactive alkaloid ibogaine to 12-hydroxyibogamine. *Drug Metabolism and Disposition: The Biological Fate of Chemicals, 26*(8), 764–768.

Pace, C. J., Glick, S. D., Maisonneuve, I. M., He, L.-W., Jokiel, P. A., Kuehne, M. E., & Fleck, M. W. (2004). Novel iboga alkaloid congeners block nicotinic receptors and reduce drug self-administration. *European Journal of Pharmacology, 492*(2–3), 159–167. https://doi.org/10.1016/j.ejphar.2004.03.062

Pearce, L. A., Min, J. E., Piske, M., Zhou, H., Homayra, F., Slaunwhite, A., Irvine, M., McGowan, G., & Nosyk, B. (2020). Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: Population based retrospective cohort study. *The BMJ, 368*(March), 1–13. https://doi.org/10.1136/bmj.m772

Preedy, V. R. (2016). Neuropathology of drug addictions and substance misuse. In *, 1. Foundations of understanding, tobacco, alcohol, cannabinoids and opioids*.

Prior, P. L., & Prior, S. L. (2014). Ibogaine effect on cocaine craving and use in dependent patients - A double-blind, placebo-controlled pilot study. *Journal of Addiction Therapy, 1*(1), 003.

Ray, T. S. (2010). Psychedelics and the Human Receptorome. *5*(2). https://doi.org/10.1371/journal.pone.0009019

Rezvani, A. H., Cauley, M. C., Slade, S., Wells, C., Glick, S., Rose, J. E., & Levin, E. D. (2016). Acute oral 18-methoxycoronaridine (18-MC) decreases both alcohol intake and IV nicotine self-administration in rats. *Pharmacology Biochemistry and Behavior, 150–151*, 153–157. https://doi.org/10.1016/j.pbb.2016.10.010

Schellekens, A., Oosteren, T., Knuijver, T., Verkes, R. J., & Belgers, M. (2016). Treatment of heroin dependence with ibogaine. *European Psychiatry, 33*(S1), S10–S11. https://doi.org/10.1016/j.eurpsy.2016.01.799

Schenberg, E. E., de Castro Comis, M. A., Chaves, B. R., & da Silveira, D. X. (2014). Treating drug dependence with the aid of ibogaine: A retrospective study. *Journal of Psychopharmacology (Oxford, England), 28*(11), 993–1000. https://doi.org/10.1177/0269881114552713

Schep, L. J., Slaughter, R. J., Galea, S., & Newcombe, D. (2016). Ibogaine for treating drug dependence. What is a safe dose? *Drug and Alcohol Dependence, 166*, 1–5. https://doi.org/10.1016/j.drugalcdep.2016.07.005

Sheppard, S. G. (1994). A preliminary investigation of ibogaine: Case reports and recommendations for further study. *Journal of Substance Abuse Treatment, 11*(4), 379–385.

Steinberg, C., & Deyell, M. W. (2018). Cardiac arrest after ibogaine intoxication. *Journal of Arrhythmia, 34*(4), 455–457. https://doi.org/10.1002/joa3.12061

Wikipedia. (2021). *Legal status of ibogaine by country*. https://en.wikipedia.org/wiki/Legal_status_of_ibogaine_by_country.

Wilkins, C., dos Santos, R. G., Solá, J., Aixalá, M., Cura, P., Moreno, E., Alcázar-Córcoles, M.Á., Hallak, J. E. C., & Bouso, J. C. (2017). Detoxification from methadone using low, repeated, and increasing doses of ibogaine: A case report. *Journal of Psychedelic Studies, 1*(1), 29–34. https://doi.org/10.1556/2054.01.2017.005

Wilson, C., Millar, T., & Matieschyn, Z. (2020). Novel treatment of opioid use disorder using ibogaine and iboga in two adults. *Journal of Psychedelic Studies, 1–7*. https://doi.org/10.1556/2054.2020.00133

Winkelman, M. (2014). Psychedelics as medicines for substance abuse rehabilitation: Evaluating treatments with LSD, peyote, ibogaine and ayahuasca. *Current Drug Abuse Reviews, 7*(2), 101–116. https://doi.org/10.2174/1874473708666150107120011

Zastepa, E., Sun, J. C., Clune, J., & Mathew, N. (2020). Adaptation of contingency management for stimulant use disorder during the COVID-19 pandemic. *Journal of Substance Abuse Treatment, 118*(July), Article 108102. https://doi.org/10.1016/j.jsat.2020.108102