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REVIEW

The adverse events of ibogaine in humans: an updated systematic review of the literature (2015–2020)

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Abstract

Context Ibogaine is the main alkaloid of the African shrub *Tabernanthe iboga*. It produces hallucinogenic and psychostimulant effects, but it is currently known for the anti-addictive properties. Despite the potential therapeutic effects, several cases of fatalities and serious adverse events related to ibogaine/noribogaine use can be found in the literature. Most studies consist in case reports or were conducted under non-controlled settings, so causation cannot be clearly established.

Objectives To update (2015–2020) the literature on the adverse events and fatalities associated with ibogaine/noribogaine administration.

Methods Systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results Eighteen studies were included in the final selection. Highly heterogeneous results were found in terms of kind of product used or the known dosages. The adverse events were classified in acute effects (< 24 h), mainly cardiac (the most common was QTc prolongation), gastrointestinal, neurological, and clinical alterations, and long-lasting effects (> 24 h), mainly persistent cardiac alterations, psychiatric, and neurological signs.

Conclusions There is a high need of phase I clinical trials that can describe the safety of different dosages of ibogaine with standardized products. Further research should perform clinical profiling of vulnerable populations, and design effective screening methods and clinical procedures.

Keywords Ibogaine · Noribogaine · Adverse events · Safety · Drug interactions

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Introduction

Ibogaine is the main alkaloid of the African shrub *Tabernanthe iboga*. Different indigenous cultures of West Central Africa have been using *T. iboga* for centuries for medicinal and religious purposes. Due to its hallucinogenic properties, it plays a central role in rites of passage of Bwiti and other traditions (Fernández 1982). In 1901, ibogaine was isolated from the root bark of *T. iboga*, and its pharmacodynamic properties were further explored during the first decade of the twentieth century. Instead of characterizing the effects of wide-dosing regimens, only low doses were tested. Since low doses of ibogaine seem to have psychostimulant effects, ibogaine was recommended as a treatment for asthenia. In fact, from 1939 until 1970, ibogaine was commercialized in France under the name of "Lambarène" as a neuromuscular stimulant Goutarel et al. 1993). Ibogaine is currently known for its anti-addictive effects, which were serendipitously discovered by H. Lotsoff, a heroin user, between 1962 and 1963 (Alper and Lotsof 2007; Alper 2001). Lotsoff and other heroin users tried ibogaine for its hallucinogenic effects but then discovered that many of them no longer experienced opioid withdrawal symptoms. Since then, many preclinical studies were conducted assessing the potential effects of ibogaine in animal models of substance use disorders (Belgers et al. 2016; Brown 2013).

Regarding the treatment of opioid dependence, it has been observed that the acute administration of ibogaine dose-dependently reduces the self-administration of morphine (Glick et al. 1994) and heroin (Dworkin et al. 1995) in rats. Additionally, in morphine-dependent rats, ibogaine doses ranging from 4 to 16 µm and administered intracerebroventricularly eliminate the withdrawal syndrome induced by naloxone or naltrexone (Dzoljic et al. 1988). Similar results were obtained in non-human primates administering 2–8 mg/kg of ibogaine through the subcutaneous route (Aceto et al. 1990). However, when the subcutaneous route was used in morphine-dependent rats to administer 5–40 mg/kg of ibogaine no reductions in withdrawal syndrome were observed, which suggests that ibogaine's pharmacokinetics is relevant for its anti-addictive effects (Sharpe and Jaffe 1990). The results in mice show differences regarding the dose and timing of ibogaine administration (before or after the induction of withdrawal syndrome using naloxone). Doses ranging from 40 to 80 mg/kg administered before naloxone reduce the withdrawal syndrome (Sharpe and Jaffe 1990; Popik et al. 1995), while a dose of 30 mg/kg administered after naloxone does not reduce the withdrawal syndrome (Popik et al. 1995; Frances et al. 1992). The evidence in humans is scarce and is mostly based on case series and observational studies. The available studies suggest that ibogaine has significant anti-addictive properties, however, most studies are open label and therefore causation cannot be established (dos Santos et al. 2016; Luz and Mash, 2021). In a randomized, double-blind, placebo-controlled, single-dose clinical trial (Glue et al. 2016), noribogaine (the main metabolite of ibogaine) was administered to 27 methadone-dependent patients, switched off to morphine before treatment. No reductions in the opioid withdrawal syndrome (OWS) were observed. Some authors pointed out that the noribogaine doses used were equivalent to those produced after the administration of a low dose of ibogaine (286 mg), and that more than a single dose would be required to eliminate the OWS (dos Santos et al. 2016; Luz and Mash, 2021). Importantly, serious adverse events, such as dose-dependent QTc prolongation, were reported in this trial. QTc prolongation can be induced by several drugs (including alcohol, opioids, antihistamine, or antipsychotic drugs), and it is associated with bradycardia and arrhythmia, which can be fatal. Indeed, one of the main preoccupations with ibogaine administration, especially in non-controlled clinical settings, is its possible cardiotoxic effects.

In this regard, two systematic reviews evaluated reports of fatalities or serious adverse events related to iboga/ibogaine use (Alper et al. 2012; Koenig and Hilber 2015), while a third review also analyzed the anti-addictive potential of ibogaine (dos Santos et al. 2016). Alper et al. (2012) collected the ibogaine-associated fatalities ($n = 19$) reported between 1990 and 2008, while Koenig and Hilber (Koenig and Hilber, 2015) collected the fatalities ($n = 3$) and serious adverse events ($n = 8$) associated with ibogaine reported between the years 2009–2014. All the cases came from case reports in which ibogaine were used in non-controlled settings, including private residences or private ibogaine clinics. Cases reported by Alper et al. (2012) consisted of 15 men and 4 women aged 24 to 54 years (mean 39.1 years). There were 8 men and 3 women aged 25 to 63 years (mean 38 years) in cases collected by Koenig and Hilber (2015). Most of the subjects of both reviews used ibogaine for detoxification purposes, mainly from opioid drugs, but also from cocaine and alcohol, among others. Notably, only 12 out of the 19 cases collected by Alper et al. (2012) described the exact dose of ibogaine taken, which ranged from 4.5 to 29 mg/kg (mean dose of 14.3 ± 6.1 mg/kg). This information was available for 9 out of 11 cases reported by Koenig and Hilber (2015), where doses ranged from 1.5 to 35 mg/kg. The authors of both reviews stated that the main metabolite of ibogaine (noribogaine) could be more directly involved in fatalities and adverse events, since ibogaine has a short half-life (4–7 h) and deaths occurred at ≥ 8 h (Alper et al. 2012) and 24–48 h post-ingestion (Koenig and Hilber 2015), respectively. Finally, both reviews coincide in having found

pre-existing medical conditions and the presence of one or more drugs of abuse that explained or contributed to most deaths. For instance, Alper et al. (2012) reported that 12 out of 19 cases had cardiovascular diseases, liver diseases, peptic ulcer disease, brain neoplasm, hypertension, and obesity, and the concomitant presence of benzodiazepines, cocaine, opioids, or ephedrine. Koenig and Hilber (2015) found that all the fatalities reported had hypokalemia, and 50% of them had hypomagnesemia. Thus, authors emphasized the need of carefully screening electrolyte levels before administering ibogaine, as well as performing proper drug screenings and even genotyping subjects for CYP2D6 activity, since poor metabolizers would be at a greater risk of cardiotoxic effects of ibogaine/noribogaine (Alper et al. 2012; Koenig and Hilber 2015).

Dos Santos et al. (2016) performed a systematic review of human studies assessing the anti-addictive potential of ibogaine. Most studies consisted in case series of individuals with opioid and stimulant use disorders seeking treatment, while there was one randomized, placebo-controlled clinical trial using noribogaine in methadone-dependent patients. According to authors, the results found in case series suggest that ibogaine significantly reduces OWS symptoms, since most subjects could remain drug-free for several days after treatment. Most of these case series did not differentiate between heroin/methadone users and given the absence of control groups and informal settings in which the treatments were performed, it is challenging to suggest causation. Importantly, most of these cases did not report significant adverse reactions. However, in most cases, there was no detailed information on how adverse events were measured (if they were measured at all). Thus, the absence of serious adverse events in these studies should be interpreted with caution. Regarding the clinical trial in which noribogaine was administered to methadone-dependent patients [15], non-significant effects on withdrawal syndrome were found. For this study, single doses of 60, 120, or 180 mg of noribogaine were used. Dos Santos et al. (2016) suggest that this absence of effects could be attributed to several factors. First, it should be noted the lack of knowledge regarding the equivalence between therapeutic doses of ibogaine and noribogaine. Additionally, since methadone has a long half-life, a single dose of noribogaine would be hardly able to interrupt the withdrawal syndrome. The subjects included in this clinical trial also showed dose-dependent QT prolongation, raising concerns regarding the safety profile of noribogaine. Dos Santos et al. (2016) concluded that the toxicity of both alkaloids (ibogaine and noribogaine) is an important limitation to their clinical use, and the absence of proper medical screening and monitoring procedures increases the possibility of hazardous situations.

Considering that the previous reviews were published including information until 2015/16, the aim of this manuscript was to perform an updated (2015–2020) systematic review of literature of the serious adverse events (SAEs) and fatalities associated with ibogaine administration. Moreover, special attention was given to those cases in which ibogaine was combined with other drugs, since in the previous reviews concomitant use of other drugs was associated with serious adverse reactions and/or fatalities.

Methods

Data for this systematic review were collected in accordance with the Systematic Reviews and Meta-Analyses guidelines (Moher et al. 2009).

Data acquisition

We attempted to identify all human studies available to review from July 2, 2015 to July 23, 2020 in which the adverse events of ibogaine or noribogaine were analyzed. We used this criterion because other systematic reviews have been recently published (dos Santos et al. 2016; Alper et al. 2012; Koenig and Hilber 2015).

Search strategy

Electronic searches were performed using PubMed, Scopus, Web of Science, Scielo, Google Scholar, and Core.ac.uk databases. The following keywords were used: ibogaine OR noribogaine AND humans OR addiction OR dependence. References were retrieved through searching electronic databases and manual searches through reference lists of identified literature. All the studies published from July 2, 2015 to July 23, 2020 were included without any language restriction.

Eligibility criteria

The following inclusion and exclusion criteria were established prior to the literature search.

Article type

All studies published in peer-reviewed journals involving the use of ibogaine in humans were included. These included case reports, clinical studies, observational studies, and letters. Preclinical studies (including in vitro and in vivo), reviews, abstracts, comments, and editorials were excluded.

Study design

The review included case reports, observational and clinical studies that reported ibogaine- or noribogaine-associated

adverse events, serious adverse events, fatalities, as well as potential drug-drug interactions with other drugs or prescribed medications.

Participants/sample

All subjects that used at least one dose of ibogaine or noribogaine were included.

Interventions

All designs evaluating the adverse events, serious adverse events, fatalities, and drug-drug interactions between ibogaine or noribogaine and other drugs or medications were included.

Outcomes

We included all reports that assessed adverse events systematically (with standardized scales and/or physical and biological measures) or non-systematically (any subjective or physical effect described by the authors as adverse or negative) and reports of intoxications and deaths.

Data extraction

Two independent reviewers screened all studies with discrepancies resolved by a third reviewer. From the articles included, we recorded the names of authors, year of publication, study location (city and country), study design (open label or controlled, observational, letters, and cases), characteristics of the context (hospital, clinic, private place, home) and participants (sample size, age, and gender), response criteria (adverse events), type of intervention (dose and other drugs), and type of outcome measure (adverse events, serious adverse events, and interactions with other drugs). Adverse events were further categorized as acute (< 24 h) or prolonged (> 24 h) effects.

NIH evaluation of selected studies

To grade and compare the studies found in our search in a standardized manner, we have utilized the NIH (National Heart, Lung and Blood Institute) checklists and guidelines for clinical trials as a template (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). We used three checklists: "Quality assessment of case series studies," "Quality assessment for observational cohort," and "Quality assessment of controlled interventions studies." All articles were analyzed to see whether they contained or not all the items presented in the checklist. Items from the checklist that were present within each article provided one positive point for the respective article. The final score was calculated by adding the positive points. In the case of "Quality assessment of case series studies," the total items to be added were 9 points; in the "Quality assessment for observational cohort" 14 points; and in the "Quality assessment of controlled interventions studies" 14 points. In cases of disagreement on subjective items, the reviewers discussed their reasons for giving positive, negative, or not applicable points, and if a consensus was not reached, a third author/reviewer was consulted. The overall grade of each article was calculated by dividing the positive points by the difference of the total number of points less the not applicable points. Grades go from 0 to 1 with 0 being the worst and 1 being the best.

Results

Selected studies

A flow diagram illustrating the different phases of the article selection for the systematic review is presented in Fig. 1.

The bibliographic search was performed in the PubMed, Scopus, Web of Science, Scielo, Google Scholar, and Core.ac.uk databases from July 2, 2015 to July 23, 2020, with 61 articles found in this first stage. After removing duplicates and reading the titles and abstracts of the articles found, 23 references were selected for full reading considering the inclusion and exclusion criteria. After full reading, five studies were excluded since they did not report adverse events. In summary, a total of 18 articles were included in the systematic review. Of the 18 selected articles, 15 were case reports or case series (Breuer et al. 2015; Marta et al. 2015; O'Connell et al. 2015; Cloutier-Gill et al. 2016; Hildyard et al. 2016; Meisner et al. 2016; Henstra et al. 2017; Wilkins et al. 2017; Knuijver et al. 2018; Mash et al. 2018; Steinberg and Deyell, 2018; Barsuglia et al. 2018; Grogan et al. 2019; Matamoros-Castillo et al. 2019; Wilson et al. 2021). There were also two randomized, double-blind clinical trials (Glue et al. 2016, 2015), and one observational study (Brown and Alper, 2018). Sample sizes were mostly small. In the case reports and cases series, except for one case series with 191 patients (Mash et al. 2018), most cases described a single subject. There were 22 patients in the clinical trials ($n = 21$ (Glue et al. 2015); $n = 27$ (Glue et al. 2016)) and 30 in the observational study (Brown and Alper 2018). The age range of the case reports ranged between 22 and 60 years. Regarding gender, in both clinical trials (Glue et al. 2015, 2016), in an open label case series (Mash et al. 2018), and in the observational study (Brown and Alper 2018), a higher number of males was found. The main reason for the use of ibogaine was the search for a treatment for opioid dependence, and in two cases a search for spiritual cleansing was reported (Breuer et al. 2015; Marta et al. 2015). In the case of the

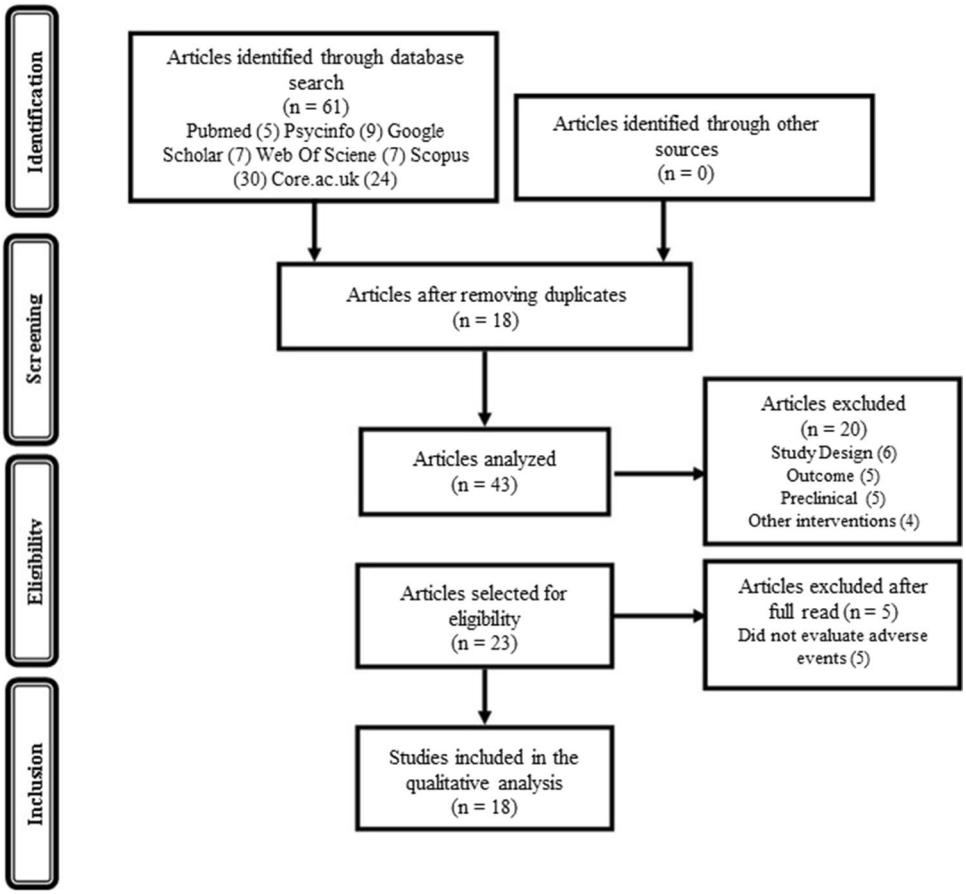

Fig. 1 Flowchart showing the different phases of the article selection for the systematic review

clinical trials, the first one was planned to assess pharmacokinetics and safety of ibogaine in healthy volunteers (Glue et al. 2015). The other clinical trial, carried out by the same group, aimed to evaluate the safety, tolerability, and pharmacokinetics of noribogaine in the treatment of methadone detoxification (Glue et al. 2016). In the observational study, the main objective was to evaluate the efficacy of ibogaine in the treatment of opioid dependence (Brown and Alper, 2018). Finally, in the open label case series, the authors sought to evaluate the safety and efficacy of ibogaine during abstinence due to the use of opioids (Mash et al. 2018).

The dose of ibogaine used in the case reports ranged from 725 mg of ibogaine (Wilson et al. 2021) to 38 g of dried *T. iboga* root bark (Breuer et al. 2015). The main route of administration was orally through capsules. It is important to highlight that in most cases there is a lack of detailed information about the ingested substance, such as appropriate analyses quantifying the alkaloid content. Additionally, the samples were acquired through unreliable sources, making it even more difficult to access reliable information. Regarding adverse events, the results obtained after analyzing the articles were divided between acute (< 24 h) and long-lasting effects (> 24 ho). Almost half of the citations (8 in 18) reported absence of effects after the first 24 h (Glue et al. 2016; O'Connell et al. 2015; Wilkins et al. 2017; Mash et al. 2018; Barsuglia et al. 2018; Wilson et al. 2021; Glue et al. 2015; Brown and Alper, 2018). In the case reports, most cases required hospital intervention, some of them being admitted to intensive care units (Breuer et al. 2015; Steinberg and Deyell 2018; Grogan et al. 2019). One case, despite the attempt of hospital intervention, died within the first 24 h (Meisner et al. 2016). Given the high heterogeneity of the studies with different designs, different dosages, and most of them with no description of quality analysis of the ibogaine, this review will contemplate only a qualitative analysis of the results. Findings are discussed in detail below and summarized in Supplementary material 1, 2 and 3.

Characteristics of the subjects

Among all the case reports ($n = 15$), there were only two subjects with no history of drug abuse/dependence or medical/psychiatric disorders (Breuer et al. 2015; Marta et al. 2015). The remaining subjects reported mainly drug abuse/dependence, consisting in opioids ($n = 163$), polysubstance use ($n = 5$), cocaine use disorder ($n = 89$), and alcohol use disorder ($n = 1$). In addition, five subjects had medical conditions such as hepatitis C virus (HCV), dyslipidemia, or

different types of pain. Regarding psychiatric diagnosis, these were reported by five subjects, mainly consisting in attention deficit disorder (ADHD), depression, or anxiety. Moreover, in the Mash et al. (2018) study ($n = 191$), a high number of patients with depression was observed (52.9% meeting clinical criteria for major depressive disorder or depression) and bipolar disorder. In one of the clinical trials, noribogaine was administered to patients under methadone treatment who were switched off to morphine before the trial (Glue et al. 2016). The observational study published by Brown and Alper (2018) consisted in subjects with a history of opioid dependence without any other medical condition.

Ibogaine/noribogaine information

Detailed information on ibogaine/noribogaine is shown for acute (< 24 h) and prolonged (> 24 h) adverse reactions in Supplementary material 1 and 2, respectively.

Only in five out of 15 case reports the presence of ibogaine could be determined (O'Connell et al. 2015; Henstra et al. 2017; Wilkins et al. 2017; Mash et al. 2018; Grogan et al. 2019), and in only one both the presence and the quantity of ibogaine were measured (O'Connell et al. 2015). Iboga root bark was supposedly used in three cases (Breuer et al. 2015; Grogan et al. 2019; Wilson et al. 2021), while the other ones supposedly used ibogaine HCl (O'Connell et al. 2015; Cloutier-Gill et al. 2016; Hildyard et al. 2016; Meisner et al. 2016; Henstra et al. 2017; Wilkins et al. 2017; Mash et al. 2018; Steinberg and Deyell, 2018; Barsuglia et al. 2018; Brown and Alper, 2018), or it was unknown (Marta et al. 2015; Matamoros-Castillo et al. 2019). The clinical trials used ibogaine HCl (Knuijver et al. 2018; Glue et al. 2015) or noribogaine HCl (Glue et al. 2016). Regarding toxicological analyses, the presence of ibogaine or noribogaine in hair samples was confirmed in one case (Breuer et al. 2015), in serum in another case (Henstra et al. 2017), and in both urine and serum in another case O'Connell et al. 2015). In the remaining cases where toxicological analyses were performed, the presence of ibogaine/noribogaine was not specifically measured.

Acute adverse events (< 24 h)

Detailed information on the acute adverse events of ibogaine/noribogaine is shown in Supplementary material 2. The most common acute adverse event described in the selected articles consisted of QTc prolongation (527 ms (O'Connell et al. 2015); 730 ms (Hildyard et al. 2016; Meisner et al. 2016); 647 ms (Henstra et al. 2017); 516 ms Knuijver et al. 2018); 714 ms (Steinberg and Deyell, 2018); 788 ms (Grogan et al. 2019); 512 ms (Wilson et al. 2021)). Other cardiac alterations were also reported, including tachycardia, hypotension, wide QRS complex (defined as a tachyarrhythmia with alternating morphologies of the QRS complex with irregular R-R intervals) (Jebberi et al. 2019), and Torsades de Pointes (Hildyard et al. 2016; Meisner et al. 2016; Henstra et al. 2017; Steinberg and Deyell, 2018; Grogan et al. 2019). Gastrointestinal symptoms, mainly nausea and vomit, were also observed in the case series (Breuer et al. 2015; O'Connell et al. 2015; Meisner et al. 2016; Wilkins et al. 2017; Mash et al. 2018; Steinberg and Deyell, 2018; Barsuglia et al. 2018). Clinical symptoms associated with alteration of consciousness, such as visions/hallucinations or space/time disorientation (Breuer et al. 2015; Knuijver et al. 2018; Grogan et al. 2019; Matamoros-Castillo et al. 2019), were also noted. Moreover, a high number of physical symptoms were reported, including ataxia, muscle tension, weakness, diaphoresis, akathisia, or tremors, among others (Breuer et al. 2015; O'Connell et al. 2015; Cloutier-Gill et al. 2016; Wilkins et al. 2017; Kuijver et al. 2018; Mash et al. 2018; Barsuglia et al. 2018). Finally, neurological alterations including seizures (Breuer et al. 2015; Hildyard et al. 2016; Grogan et al. 2019) dysmetria (O'Connell et al. 2015), anoxic brain injury (Meisner et al. 2016), and unconsciousness (Henstra et al. 2017) were also reported.

The first clinical study included in this review aimed to evaluate the pharmacokinetics of ibogaine and noribogaine in 21 healthy individuals divided into two groups previously treated with placebo or paroxetine (CYP2D6 inhibitor) (Glue et al. 2015). Both groups ingested 20 mg of ibogaine and demonstrated a rapid peak of noribogaine (4 h in the placebo group and 3 h in the paroxetine group), as well as similar profiles regarding the extent of exposure to noribogaine. However, the group pre-treated with paroxetine showed two times more exposure to ibogaine + noribogaine. This suggests that genetic variations of CYP2D6 could be clinically relevant in ibogaine treatments, and that drugs that inhibit this metabolic pathway could produce interactions with ibogaine/noribogaine (Glue et al. 2015). Subsequently, another clinical study (randomized, double-blind, placebo-controlled) carried out by the same group evaluated the safety, tolerability, and pharmacokinetics of noribogaine in 27 patients undergoing treatment to discontinue treatment of opioid substitution (OST) with methadone (Glue et al. 2016). Three different doses of noribogaine (60, 120, or 180 mg) or placebo were administered. Noribogaine produced only a non-significant effect in opioid withdrawal symptoms and showed a slow elimination time (24–30 h). In both clinical trials, ibogaine and noribogaine were well tolerated. No subjective effects were noted at the doses used. Only transitory changes in light perception, headache, and nausea were observed. No serious adverse events were reported (Glue et al. 2015, 2016).

Prolonged adverse events (> 24 h)

Detailed information on the prolonged adverse events of ibogaine/noribogaine is shown in Supplementary material 3. The most common prolonged adverse events described in the selected articles were mainly associated with psychiatric, neurological, and cardiac alterations. The mean number of days that patients remained hospitalized was 7.8 (range: 3–13 days). Among psychiatric alterations, insomnia (persisting 5–14 days), alterations in speech, delusions, aggressiveness, irritability, dissociation, and hallucinations were the most mentioned (Marta et al. 2015; Grogan et al. 2019; Matamoros-Castillo et al. 2019). Psychomotor slowness, bilateral ptosis, dysarthria, psychomotor agitation, and amnesia were reported as neurological signs (Breuer et al. 2015; Marta et al. 2015; Matamoros-Castillo et al. 2019). Lastly, among cardiac alterations, QTc prolongation remaining for 7 days was reported in some cases (Hildyard et al. 2016; Steinberg and Deyell 2018). With the controlled administration of noribogaine and ibogaine, prolonged adverse events were not observed (Glue et al. 2015, 2016). Alterations in the blood status were described in two studies and included increased C- reactive protein, white blood cell, and creatinine levels (first days) (Breuer et al. 2015), and hypokalemia and hypomagnesaemia the day after admission (Henstra et al. 2017).

Interventions used to manage adverse events

Three case reports informed about admissions in intensive care units (Breuer et al. 2015; Steinberg and Deyell 2018; Grogan et al. 2019). Regarding the administered medications, benzodiazepines and antipsychotics were the most used (Breuer et al. 2015; Marta et al. 2015; Wilkins et al. 2017; Matamoros-Castillo et al. 2019; Wilson et al. 2021). Anticonvulsants (Marta et al. 2015), atomoxetine (Marta et al. 2015), atropine (Hildyard et al. 2016), isoprotenerol (Hildyard et al. 2016; Henstra et al. 2017), and magnesium/sodium and saline (Hildyard et al. 2016; Henstra et al. 2017; Barsuglia et al. 2018; Grogan et al. 2019) were also reported. Cannabis oil was used in one case in a non-medical setting (Wilkins et al. 2017). The use of electrical cardioversion, a pacemaker, defibrillation, and intubation were necessary in five cases (Hildyard et al. 2016; Meisner et al. 2016; Henstra et al. 2017; Steinberg and Deyell 2018; Grogan et al. 2019). One fatality was reported after concomitant administration of naloxone, vasopressors, and morphine (Meisner et al. 2016). In the open label series cases, administration of intravenous fluids 1 h prior to ibogaine administration was employed to try preventing orthostatic hypotension and bradycardia, but this was not effective since these adverse events were observed anyway (Mash et al. 2018).

Potential drug-drug interactions

Marta et al. (2015) reported that one subject tested positive for benzodiazepines, another one for benzodiazepines, opioids, and methadone, and another one for cannabinoids. Meisner et al. (2016) found a positive result for opioids. Grogan et al. (2019) reported a positive test for opioids, cannabinoids, and cocaine. Remarkably, in five reports, these analyses were not performed (Cloutier-Gill et al. 2016; Hildyard et al. 2016; Wilkins et al. 2017; Wilson et al. 2021; Brown and Alper, 2018). Regarding medications used at hospital or medical settings, some of them might also have caused potentially dangerous interactions. This is the case of Meisner et al. (2016), where vasopressors and morphine were administered upon arrival at hospital, after the administration of naloxone (2 mg) in the field, which resulted in a fatality. However, it is important to observe the substances used after the dose of ibogaine used to handle with psychiatric symptoms (one of the most adverse events observed in the studies). It was reported the use of benzodiazepines (diazepam 2–10 mg) (Wilkins et al. 2017; Wilson et al. 2021), cannabis oil (Wilkins et al. 2017), and antipsychotics (quetiapine, risperidone, olanzapine, and others) (Marta et al. 2015; Matamoros-Castillo et al. 2019; Wilson et al. 2021), these medications seem to be well tolerated in the cases described, but it is important to highlight that there was a lack of information about this use, such as the dose and a follow-up treatment. The administration of intravenous fluids, magnesium sulfate, and anti-emetics was well tolerated (Henstra et al. 2017; Wilkins et al. 2017; Mash et al. 2018; Barsuglia et al. 2018; Grogan et al. 2019; Matamoros-Castillo et al. 2019).

Quality assessment

Our evaluation of the experiments assessed in the current review yielded an average of 80% in Quality assessment of case series studies, 78% in quality assessment of controlled interventions studies, and 64% in quality assessment for observational cohort completion. Therefore, we considered the evidence of most studies with moderate-to-high quality. However, it is important to consider the limitations present in cases, case series, and observational studies, such as the lack of control of external factors and the difficulty of translating the results to the general population. It is important to note that we were very strict in our considerations, and that the checklist was made to ensure that all information was given. Further studies should be aware of this checklist and try to fulfill its requirements as much as possible to ensure that all important information is present and to ease reproducibility. Detailed evaluation of the quality of the selected references is presented in Supplementary material 4.

Discussion

In this systematic review, we have collected the adverse events and fatalities associated with ibogaine and noribogaine reported in the last 5 years (2015–2020). Most of the included references were case reports. Two clinical trials (a phase I trial with ibogaine and a phase II trial with noribogaine) and one observational study were also included.

The case reports in the literature are the first source of evidence for new therapies and rare adverse effects, in addition to help in the formulation of new questions (Celeste 2008). This fits well with the purpose of the present review. However, as most studies are case reports, it is also important to consider the limitations of this study design. The main disadvantages involving this type of design are mainly related to the difficulty of drawing wide conclusions and translating the results to the general population, making it impossible to establish a cause relationship due to the small sample and the lack of a control group (Celeste, 2008). Since we are still lacking phase I clinical trials for the assessment of the safety of higher (> 20 mg) doses of ibogaine, the information provided in these cases is essential in the light of the emerging interest in this substance as a potential way to address the current opioid epidemic (Larsen 2019).

The clinical trials (Glue et al. 2015, 2016) were carried out in a hospital context, under the supervision of professionals, cardiac monitoring, and using low doses of pure ibogaine or noribogaine. Adverse events reported in these trials were mild/moderate (i.e., hallucinations/visual alterations, non-serious cardiovascular, motor, and gastrointestinal alterations). These same adverse events were reported in the case reports, but serious events were also observed (i.e., seizures, prolonged cardiovascular alterations). Case reports were described in non-controlled contexts and with a wide variation on ibogaine/noribogaine dose and purity. Thus, these cases are relevant in the context of the naturalist use of ibogaine and emphasize the importance of using these drugs in controlled contexts.

The doses of ibogaine differed widely between cases, and thus this becomes an important limitation to describe adverse events associated with certain doses. This is an issue previously mentioned in other reviews (dos Santos et al. 2016). In some cases, the root bark of *T. iboga* was used, so the content of ibogaine is not known. The lack of information regarding the safety of root bark or other iboga extracts as compared with pure ibogaine makes this practice especially risky. While there are plenty of examples in which the use of herbal extracts may reduce some of the adverse events found when using purified compounds (e.g., for the specific case of QTc prolongation, quinimax, a standardized mixture of cinchona alkaloids, produce less QTc prolongation than quinidine alone; (Sowunmi et al. 1990)), the presence of antagonistic or more toxic compounds in the herbal extract is also possible. A recently published article (Bouso et al. 2020) provides an illustrative example regarding the uncertainty when it comes to iboga/ibogaine use in uncontrolled settings. In this study, 16 products used by treatment providers were analyzed and highly heterogeneous results were found. In root bark materials, an ibogaine concentration ranging from 0.6 to 11.2% was found, in contrast to previous studies which claimed a concentration of approximately 7% (Mazoyer et al. 2013). In samples labeled as "total alkaloid," which supposedly consisted of *T. iboga* extracts, the concentration of ibogaine ranged from 8.2 to 32.9%. In one sample labeled as "purified total alkaloid," there was a concentration of ibogaine of 73.7%. Finally, in products labeled as ibogaine HCl, the ibogaine concentration ranged from 0 to 73.4%. The authors noted that one sample did not contain any ibogaine, and that other alkaloids and unknown substances were present in almost all samples (Bouso et al. 2020).

Apart from this high degree of uncertainty, the unknown dosages, and the high doses commonly used in non-medical settings (Brown and Alper, 2018; Alper et al. 2008; Luz and Mash, 2021), the presence of medical conditions and the concomitant use of other drugs should be mentioned among other risk factors that can contribute to adverse events. In the articles reviewed, only two subjects had no history of drug abuse/dependence or medical/psychiatric disorders (Breuer et al. 2015; Henstra et al. 2015). The relevance of previous health conditions, especially cardiac alterations, has been previously highlighted in two reviews (Alper et al. 2012; Koenig and Hilber, 2015). Alper et al. (2012) found that in 12 out of 19 deaths associated with ibogaine, previous cardiovascular, liver, and ulcerative alterations, among other diseases were reported. Koenig and Hilber (2015) reported that all fatalities were associated with hypokalemia, and 50% of them with hypomagnesemia. This information is crucial when evaluating the most susceptible people that can be at risk of suffering adverse events or even potential fatalities due to ibogaine or noribogaine. Therefore, performing adequate screenings is essential to enhance the safety of these compounds. Furthermore, even after an adequate screening, the risk of serious adverse events related with cardiotoxicity will remain, as observed in some case reports where subjects had no personal or familiar history of cardiac issues (Hildyard et al. 2016; Pleskovic et al. 2012; Vlaanderen et al. 2014). This risk can be attributed to both ibogaine and noribogaine potential of inhibiting hERG potassium channels and the subsequent prolongation of the cardiac action potential (Koenig and Hilber, 2015; Ruan et al. 2014; Alper et al. 2016). A recent study showed the IC50 values for hERG blockade for ibogaine were 4.09 ± 0.69 μM (manufactured

by semisynthesis via voacangine) and 3.53 ± 0.16 µM (by extraction from *T. iboga*), while for noribogaine it was 2.86 ± 0.68 µM (Alpern et al., 2016). This difference could be related to the observations of persistent QT prolongation and cardiac arrhythmia at delayed intervals of days following ibogaine ingestion, considering the extended half-life of noribogaine. Thus, continued cardiovascular monitoring is mandatory in people receiving ibogaine or noribogaine to ensure safety and reduce the occurrence of serious adverse events.

The reported adverse events were in line with the ones observed in previous reviews (Alper et al. 2012; Koenig and Hilber, 2015). They were mainly associated with gastrointestinal, motor, and cardiovascular alterations, but psychedelic-like effects such as hallucinations/visual alterations or disorientation were commonly reported. Moreover, some adverse events possibly associated with neurological alterations should be further investigated. Generalized seizures were reported in three cases (Breuer et al. 2015; Hildyard et al. 2016; Grogan et al. 2019), which could be associated with the agonistic effect of ibogaine at 5-HT_{2A} receptors, leading to increases in glutamatergic tone (dos Santos and Hallak, 2020). In this sense, it seems that the antagonistic effect of ibogaine on NDMA receptors was not effective in preventing seizures (Kapur 2018). Breuer et al. (2015) suggested that this phenomenon could be due to an enhanced disinhibition process by suppression of inhibitory interneurons. By this manner, high doses of ibogaine, like occurs with dizocilpine, could stimulate the release of glucocorticoids that eventually increase the susceptibility to seizures. Previous preclinical research has shown the degeneration of Purkinje cells in rats after the intraperitoneal administration of ibogaine at high doses (40–100 mg/kg) (Baumann et al. 2001; Glick et al. 1992). Helsley et al. (1997) did not find any neurotoxic effects after daily administration of low doses of ibogaine (10 mg/kg) over a 60-day period. Similarly, Mash et al. (2018) did not find evidence of neurotoxicity in monkeys after the administration of repeated doses of ibogaine, neither through the oral (5–25 mg/kg) nor the subcutaneous (100 mg/kg) route. Moreover, a neuropathological evaluation of a female volunteer who received four doses of ibogaine revealed no cerebellar damage (Mash et al. 2018). Remarkably, the fact that most hospitalizations and admissions to ICUs provided by case reports suggests that ibogaine-associated SAEs occur more frequently when it is used in unsupervised settings without proper medical control. Indeed, SAEs were observed when the drug was administered by unskilled people in unsafe settings. In the light of the adverse events observed in this review, further studies would be needed to confirm these findings.

The interaction between ibogaine and other medications or drugs is also worth mentioning, since an important percentage of the population that generally uses ibogaine are people with substance use disorders. Previous reports confirmed the presence of other drugs/medications in fatalities associated with ibogaine (Alper et al. 2012; Mazoyer et al. 2013). In the case of Mazoyer et al. (2013), the combination of ibogaine with methadone and diazepam was considered the most probable cause of death. The combination of benzodiazepines and ibogaine seems to be mostly safe as observed in other cases (Breuer et al. 2015; Wilkins et al. 2017; Wilson et al. 2021), but the concomitant use of diazepam and methadone has been associated with increased mortality due to a synergistically prolongation of repolarization (Ernst et al. 2002), as reported in an in vitro study (Kuryshev et al. 2010). Thus, ibogaine could indeed have contributed to the fatality.

Additionally, substrates or inhibitors of cytochrome P450 (CYP) liver isoforms, mainly CYP2D6, could hamper the effective O-demethylation of ibogaine, resulting in exposure to potentially toxic concentrations (Glue et al. 2016). Substrates of P-glycoprotein (P-gp) should also be avoided or used with caution when combined with ibogaine, since it has been reported that ibogaine inhibits P-gp (Tournier et al. 2010).

Both the complex pharmacokinetics and pharmacodynamics of ibogaine and noribogaine present a challenge to health professionals that may encounter intoxications related to these drugs at emergency departments. This can be clearly seen in the case reported by Meisner et al. (2016), where the patient received naloxone in the field and morphine and unspecified vasopressors at hospital. While naloxone could possibly be administered under the suspicion of an opioid overdose, the use of morphine and vasopressors would be associated with the intubation procedure but would not be indicated from a pharmacological point of view considering the above information.

Conclusion

Adverse events and fatalities associated with ibogaine/noribogaine are still a major concern that is challenging to address. The high degree of heterogeneity and uncertainty regarding alkaloid content, the lack of purity of the products used, and considering the limitations of the level of evidence produced by case studies results in a complex picture that prevents us from establishing associations (such as expected adverse events at certain doses). Considering that a growing number of people worldwide are using these drugs in search for a treatment for substance use disorders, phase I–II trials are urgent needed to assess their tolerance and safety, dose–effect relationships, and possible drug-drug interactions.

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Declarations

Conflict of interest The authors declare no competing interests.

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