The antiaddictive effects of ibogaine: A systematic literature review of human studies

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Background and aims: Ibogaine is a naturally occurring hallucinogenic alkaloid with a therapeutic potential for reducing drug craving and withdrawal. To the best of our knowledge, no systematic review was previously performed assessing these effects. Thus, we conducted a systematic literature review of human studies assessing the antiaddictive effects of ibogaine. *Methods:* Papers published up to July 2, 2016 were included from PubMed, LILACS, and SciELO databases following a comprehensive search strategy and a pre-determined set of criteria for article selection. *Results:* Two hundred and fifty-nine studies were identified, of which eight met the established criteria. Seven studies were open-label case series with ibogaine and one study was a randomized, placebo-controlled clinical trial with noribogaine. Case series suggest that a single dose or a few treatments with ibogaine may significantly reduce drug withdrawal, craving, and self-administration in dependent individuals lasting from 24 h to weeks or months. No significant effects of noribogaine on opiate/opioid withdrawal were observed in the clinical trial. *Conclusions:* Considering the necessity of new drugs that may produce fast-acting and sustained effects in opiate/opioid and cocaine dependence, the potential beneficial effects of ibogaine/noribogaine should be further investigated in controlled trials.

Keywords: ibogaine, noribogaine, substance use disorders, dependence, withdrawal

INTRODUCTION

Ibogaine is a naturally occurring indole alkaloid derived from the root barks of *Tabernanthe iboga*, a plant native to western Central African countries such as Gabon and Cameroon, where it has been used traditionally by the Pygmies and other African ethnic groups for several centuries, and more recently, as a sacrament in initiatory rites and for social cohesion in the Bwiti religion (Alper, 2001; Alper, Lotsof, & Kaplan, 2008; Brown, 2013; Mash et al., 1998). Although *T. iboga* contains several other alkaloids, ibogaine is considered to be the main psychoactive substance present in this plant. The mechanism of action of ibogaine – and its *O*-demethylated active metabolite noribogaine – is poorly understood and considered to involve antagonism of the *N*-methyl-D-aspartate (NMDA) glutamate receptor and α3β4 nicotinic acetylcholine receptor, inhibition of the serotonin (5-HT) reuptake transporter and dopamine release, agonism of the σ2 receptor, κ- and μ-opioid receptors, M1/2 muscarinic receptor, and 5-HT2A receptors [similar to classic hallucinogens such as lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT)], and enhancement of glial cell line-derived neurotrophic factor (GDNF) (Alper, 2001; Alper et al., 2008; Brown, 2013; Donnelly, 2011; Lotsof & Alexander, 2001; Mash et al., 1998).

In the 1960s, Lotsof et al. showed that ibogaine could reduce heroin withdrawal (Alper, 2001; Alper et al., 2008; Brown, 2013; Donnelly, 2011; Lotsof & Alexander, 2001; Mash et al., 1998). On the basis of the initial observations

and several treatments provided in non-medical contexts, Lotsof et al. proposed ibogaine as a new method to treat dependence to opiates/opioids (morphine, heroin, and methadone), stimulants (nicotine, cocaine, amphetamine, and methamphetamine), and ethanol and acquired several patents for such uses (United States patents: US 4499096 1985, 4587243 1986, 4857523 1989, 5026697 1991, and 5152995 1992). It has been estimated that more than 3,400 people have been treated with ibogaine for drug dependence in clinics around the world, mainly in countries such as The Netherlands, the United States, Mexico, and Brazil (Alper, 2001; Alper et al., 2008; Brown, 2013; Donnelly, 2011).

In the context of drug dependence treatment, ibogaine is usually ingested orally in the form of extracts/hydrochloride (HCl) in doses ranging from 4 to 25 mg/kg (Alper, 2001; Alper et al., 2008; Brown, 2013; Donnelly, 2011; Forsyth et al., 2016; Glue, Lockhart, et al., 2015; Glue, Winter, et al., 2015; Lotsof & Alexander, 2001; Mash et al., 1998). About 1 hr after oral administration, subjects experience decreased muscular coordination, increased sensitivity to light and sound, nausea and vomiting if they move, and visual effects that the ibogaine supporters refer to them as "oneirogenics"

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(similar to dreams). These visual effects are sustained for around 4–8 hr and are followed by a contemplative state of 12–24 hr in which lucid dreaming may occur accompanied by the emergence of autobiographical memories. Insomnia and increased energy may be present for 72 hr following ibogaine intake (Alper, 2001; Alper et al., 2008; Brown, 2013; Donnelly, 2011; Forsyth et al., 2016; Glue, Lockhart, et al., 2015; Glue, Winter, et al., 2015; Lotsof & Alexander, 2001; Mash et al., 1998). Lower oral doses of ibogaine (20 mg) and noribogaine (3–60 mg) were administered to healthy male volunteers in recent open-label (ibogaine) and double-blind, placebo-controlled (noribogaine) studies, and both drugs were found to be safe and well tolerated (Forsyth et al., 2016; Glue, Lockhart, et al., 2015; Glue, Winter, et al., 2015). At this dose levels, subjects did not experience the above-mentioned psychoactive effects, reporting basically transient nausea, gastrointestinal symptoms, and dizziness.

Ibogaine administration has been associated with several fatalities (>25 cases), which appear to involve increases in cardiac arrhythmias, previous cardiovascular diseases, and use of opiates/opioids or other drugs during the acute effects of ibogaine (Alper, 2001; Alper, Stajić, & Gill, 2012; Brown, 2013; Koenig & Hilber, 2015; Litjens & Brunt, 2016; Meisner, Wilcox, & Richards, 2016). Ibogaine intake has also been associated with psychosis (Houenou, Homri, Leboyer, & Drancourt, 2011), mania (Marta, Ryan, Kopelowicz, & Koek, 2015), and seizures (Breuer et al., 2015). However, most of these cases happened in uncontrolled/non-medical settings, using unknown doses of ibogaine of variable purity. When administered in more controlled/supervised contexts, to individuals without previous cardiovascular diseases or under the acute effects of drugs, ibogaine appears to be relatively safe (Alper, 2001; Alper et al., 2008, 2012; Brown, 2013; Donnelly, 2011; Forsyth et al., 2016; Glue, Lockhart, et al., 2015; Glue, Winter, et al., 2015; Koenig & Hilber, 2015; Lotsof & Alexander, 2001; Mash et al., 1998; Meisner et al., 2016). However, sudden deaths and fatalities with unknown causes have also been reported, and ibogaine should be administered only after a complete medical screening and with a rigorous cardiovascular monitoring (Alper, 2001; Alper et al., 2012; Brown, 2013; Koenig & Hilber, 2015; Litjens & Brunt, 2016; Meisner et al., 2016).

Animal studies showed that ibogaine is neither reinforcing nor aversive, and that this alkaloid reduces opiate/opioid (morphine and heroin), cocaine, and ethanol self-administration (Alper, 2001; Alper et al., 2008; Belgers et al., 2016; Brown, 2013; Donnelly, 2011; Frenken, 2001; Lotsof & Alexander, 2001; Mash et al., 1998). Animal studies also reported that noribogaine reduces nicotine and amphetamine self-administration (Alper, 2001; Alper et al., 2008; Belgers et al., 2016; Brown, 2013; Donnelly, 2011; Frenken, 2001; Lotsof & Alexander, 2001; Mash et al., 1998). A recent meta-analysis of animal studies reported that the most significant effects of ibogaine in reducing drug self-administration were observed in the first 24 hr after its administration, and these effects were sustained for more than 72 hr (Belgers et al., 2016). Moreover, several case reports described significant reductions in drug (mostly heroin, methadone, and cocaine) craving and withdrawal

symptoms within 1–2 hr after oral administration of single or few doses of ibogaine, followed by complete cessation of the opiate/opioid withdrawal syndrome within 24–48 hr and significant reductions or even total cessation of substance use weeks to months (or longer) following ibogaine intake (Alper, 2001; Alper et al., 2008; Brown, 2013; Donnelly, 2011; Frenken, 2001; Lotsof & Alexander, 2001; Mash et al., 1998). These data from human case reports are in line with animal studies (Belgers et al., 2016).

Although some reviews analyzing the antiaddictive effects of ibogaine in humans were published, these were narrative and non-systematic reviews (Alper, 2001; Alper et al., 2008; Brown, 2013; Donnelly, 2011; Mash et al., 1998), and the most recent of them was published 3 years ago (Brown, 2013). To the best of our knowledge, no systematic review analyzing the antiaddictive effects of ibogaine in humans was previously performed. Therefore, considering the apparent increase in ibogaine use and its possible toxic and therapeutic effects (Alper et al., 2008), this study aimed to conduct a systematic literature review of human studies that investigated the antiaddictive effects of ibogaine or of its main active metabolite, noribogaine.

METHODS

Data for this systematic review were collected in accordance with the Systematic Reviews and Meta-Analyses guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009).

Data acquisition

We attempted to identify all human studies available to review up to July 2, 2016 in which the antiaddictive effect of ibogaine or noribogaine was analyzed.

Search strategy

Electronic searches were performed using PubMed, LILACS, and SciELO 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 up to July 2, 2016 were included without any language restriction.

Eligibility criteria

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

Article type

Case reports and clinical studies published in peer-reviewed journals were included. Books and book chapters indexed in the above-cited databases were also included. Preclinical studies (*in vitro* and *in vivo*), reviews, abstracts and letters, comments, and editorials were excluded.

Study design

The review included case reports and clinical studies of ibogaine administration that assessed dependence/abuse symptoms.

Participants/sample

Subjects with a diagnosis of drug abuse/dependence were included.

Interventions

All designs evaluating the effect of ibogaine on abuse/dependence measures were included.

Comparisons

The main comparator considered was pre-treatment abuse/dependence symptoms.

Outcomes

Studies investigating the effect of ibogaine on abuse/dependence symptoms were included.

Data extraction

All studies were screened by two independent reviewers 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), characteristics of the participants (sample size, age, and gender), response criteria (antiaddictive effect), type of intervention (dose), and type of outcome measure (abuse/dependence symptoms).

RESULTS

Study selection

A flow diagram illustrating the different phases of the systematic review is presented in Figure 1.

The literature search yielded 259 separate references, all from PubMed. These citations were reviewed for abstract screening, and seven potentially relevant references were identified (Alper, 2001; Alper, Lotsof, Frenken, Luciano, & Bastiaans, 1999; Luciano, 1998; Mash et al., 2000, 2001; Schenberg, de Castro Comis, Chaves, & Da Silveira, 2014; Sheppard, 1994). Full-text reports of these citations were obtained for more detailed evaluation. One more citation (Glue, Cape, Tunnicliff, Lockhart, Lam, Hung, et al., 2016) was found after handsearching the bibliography of one of the references used in the Introduction section (Forsyth et al., 2016). This citation was not indexed at any of the databases used at the time of preparation of the manuscript, and the paper was obtained directly from the authors. Following detailed examination of the reports, all citations were included. The studies included comprised seven case series involving the administration of ibogaine (Alper, 2001;
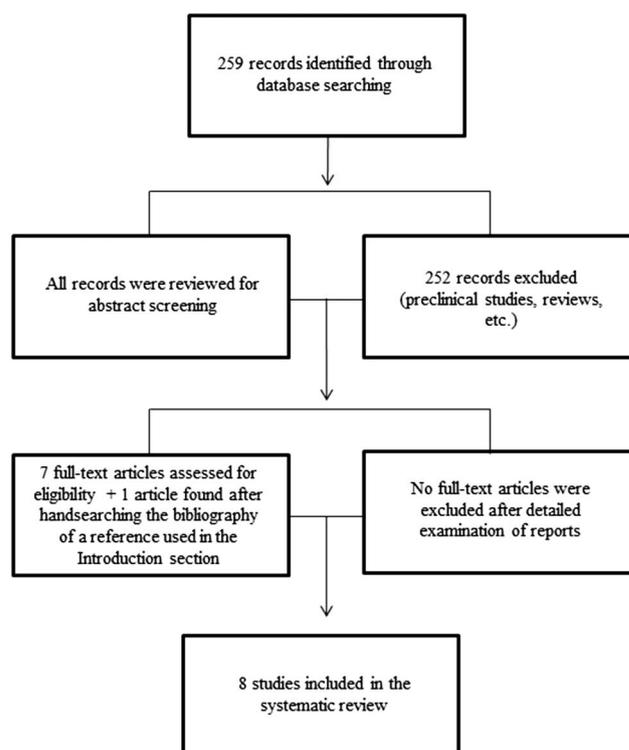
Figure 1. Flow diagram illustrating the different phases of the systematic review

Alper et al., 1999; Luciano, 1998; Mash et al., 2000, 2001; Schenberg et al., 2014; Sheppard, 1994) and one randomized, placebo-controlled clinical trial with noribogaine (Glue, Cape, Tunnicliff, Lockhart, Lam, Hung, et al., 2016). Table 1 shows the main information of each study.

Case series

In an open-label study performed in non-medical settings in Amsterdam, The Netherlands, seven opiate-dependent individuals (five men; mean age 29.28 years; six individuals were dependent on heroin, two on ethanol, and one on codeine) were treated with single oral doses of 700–1800 mg (11.7–25.0 mg/kg) ibogaine HCl (Sheppard, 1994). Treatments occurred between October 1989 and August 1990, and the researchers documented the immediate and long-term (up to 14 weeks) effects of ibogaine. Subjects were administered a trial dose of 100–200 mg ibogaine, followed 1–2 hr later by the remainder of the dose. None of the subjects showed significant opiate withdrawal symptoms 24–38 hr after ibogaine administration. Two subjects who received the lowest dose (700 mg) relapsed to opiate usage within 2 days after ibogaine administration, two subjects who received >1,000 mg relapsed after a number of weeks, one subject who received >1,000 mg reverted to intermittent heroin use, and three subjects who received >1,000 mg remained drug-free for >14 weeks after treatment. Ibogaine administration was also associated with increased energy, appetite, and reduced sleep for several weeks after drug intake. Ibogaine was well tolerated, and adverse effects reported included sensitivity to light and sound, ataxia, diarrhea, and nausea and vomiting. Interestingly, ibogaine

Table 1. Open-label case series and clinical trials describing the antiaddictive effects of ibogaine

References	Design/setting	Subjects	Dose	Main results	Safety
Sheppard (1994)[a]	Open-label Non-medical Amsterdam, The Netherland	7 (heroin, methadone, codeine, and ethanol) 5 men, mean age 29.28 years	Single doses 11.7–25 mg/kg	Absence of withdrawal symptoms after 24–38 hr for all subjects, two relapsed within 48 hr, two after several weeks, one reverted to intermittent heroin use, and three remained drug-free >14 weeks	No medical screening or monitoring No serious adverse reactions
Luciano (1998)	Open-label Setting (?)	3 (cocaine, opiates/opioids, and ethanol) Gender, age (?)	Single doses 20–25 mg/kg	Absence of withdrawal and craving symptoms after 24 hr for all subjects Abstinence (?)	Medical screening and monitoring No serious adverse reactions
Alper et al. (1999)[a]	Open-label Non-medical United States and The Netherlands	33 (heroin, methadone, and cocaine) 22 men, mean age 27.3 years	Single doses 6–29 mg/kg	Absence of withdrawal symptoms and drug use for 25 (76%) subjects after 72 hr, four did not report symptoms but used drugs in <72 hr, two reported attenuated symptoms and no drug use in <72 hr, and one reported absence of effects	Medical screening and monitoring one fatality, probably caused by concomitant heroin use
Mash et al. (2000)[b]	Open-label Private clinic St. Kitts, West Indies	27 (heroin, methadone [?] and cocaine) 23 men, mean age 34.6 (opiates/opioids) and 37.5 (cocaine) years	Single doses 500, 600, and 800 mg	Significant ($p < .005$) reductions in all HCQN-29 subscales[c] and in two CCQN-45 subscales[d] after 36 hr and 14 days, and significant ($p < .0005$) reductions in BDI scores after one month Abstinence (?)	Medical screening and monitoring No serious adverse reactions
Mash et al. (2001)[b]	Open-label Private clinic St. Kitts, West Indies	32 (heroin and methadone) 23 men, mean age 33.6 years	Single dose 800 mg	Significant ($p < .05$) reductions in OOWS scores after 12–24 hr and in OP-SCL scores after <72 hr and 6–9 days, and months of abstinence in many subjects (although data were not presented)	Medical screening and monitoring No serious adverse reactions
Alper (2001)[a]	Open-label Non-medical United States and The Netherlands	41 (heroin. methadone, cocaine, sedatives, ethanol) Gender, age (?)	Single doses 6–29 mg/kg	15 (29%) subjects reported abstinence for <2 months, 15 (29%) for ≥2 months/<6 months, 7 (13%) for ≥6 months/<1 year, 10 (19%) for >1 year, and 5 (10%) the outcomes could not be determined	Medical screening and monitoring No serious adverse reactions
Schenberg et al. (2014)	Open-label Private hospital Santa Cruz do Rio Pardo, Brazil	75 (ethanol, cannabis, cocaine, and crack-cocaine) 67 men and 8 women, mean age 34.16 (men) and 29.50 (women) years	Single and multiple doses; mean number of sessions 3.83 (men) and 5.40 (women) 17–20 mg/kg	Significant ($p < .001$) increases in abstinence duration, and 61% of subjects were abstinent after single (median 5.5 months) and multiple (median 8.4 months) doses	Medical screening and monitoring No serious adverse reactions
Glue, Cape, Tunnicliff, Lockhart, Lam, Gray, et al. (2016)	Randomized, double-blind, placebo-controlled, single ascending-dose clinical trial Research unit Dunedin, New Zealand	27 (methadone) 21 men, mean age 41.2 years	Single doses (noribogaine) 60, 120, and 180 mg	Non-significant effects on SOWS, OOWS, COWS, and time to resumption of MST	Medical screening and monitoring No serious adverse reactions Significant QT interval prolongation

Note. BDI, Beck Depression Inventory; CCQN-45, Cocaine Craving Questionnaire; COWS, Clinical Opioid Withdrawal Scale; HCQN-29, Heroin Craving Questionnaire; OOWS, Objective Opiate Withdrawal Scale; OP-SCL, Opiate-Symptom Checklist; MST, methadone substitution treatment; SOWS, Subjective Opioid Withdrawal Scale. Interrogation: not informed.
[a]Included subjects from the same sample.
[b]Included subjects from the same sample.
[c]Desire to Use, Intention to Use, Anticipation of Positive Outcomes, Relief of Negative States, and Lack of Control.
[d]Relief of Negative States and Lack of Control.

administration was not associated with a reduction in cannabis use. Importantly, there is no control of drug use prior, during, or after treatment was performed, and some subjects used drugs (mostly heroin) in the days immediately before/after treatment. Moreover, no medical or psychiatric screening was described in the report. Careful analysis of this report, other citations, and handsearching the bibliography of the references showed that this study described a full sample of previous treatments published in non-scientific reports (Frenken, 2001).

A report from an unidentified city/country (probably Amsterdam, The Netherlands) and apparently of an open-label design reported three cases of subjects treated with ibogaine HCl (20–25 mg/kg) for cocaine dependence (one subject was also dependent on heroin and two were also dependent on ethanol) (Luciano, 1998). No information regarding age or gender of the participants was given in the report. Subjects were included after medical and psychiatric screening, laboratory exams, electrocardiogram (ECG), electroencephalogram (EEG), and magnetic resonance. Medical monitoring was continuous, and neurologic/EEG assessments were performed intermittently over 24 hr. All subjects showed transient cerebellar dysfunction (nystagmus, tremor, and ataxia) 2 hr after ibogaine intake, and these symptoms improved 8 hr after drug administration. Visual alterations with eyes closed were observed in only one subject, reality testing remained normal in all of them, and no anxiety symptoms or thought disorder were observed. EEG assessments were normal in all participants during and after treatment, and no medical or ECG abnormalities were observed during the treatment. Twenty-four hours after ibogaine administration, all subjects reported an absence of subjective or objective signs of withdrawal or craving, and all neurologic/EEG examinations were normal.

A larger retrospective report described a group of 33 subjects (22 men, mean age 27.3 ± 4.7 years) that were treated with ibogaine HCl (average dose: 19.3 ± 6.9 mg/kg, range 6–29 mg/kg) for opiate/opioid dependence (mostly heroin, primarily by the i.v. route; all met DSM-IV criteria for opiate/opioid dependence) in non-medical settings under open-label conditions between 1962 and 1993 (Alper et al., 1999). Eight subjects were also using methadone and eight were using cocaine on a daily basis. Seven treatments were carried out in the United States between 1962 and 1963, and the other 26 treatments were carried out in The Netherlands between 1989 and 1993 [including patients from a previous report (Sheppard, 1994)]. Treatments occurred 8–10 hr after the subjects made their last use of heroin (24 hr in the case of the subjects using methadone), and they were monitored for 72 hr. Twenty-four hours after ibogaine administration, 25 subjects (76%) reported complete resolution of opiate/opioid withdrawal without drug-seeking behavior, and these effects were sustained for 72 hr. Four subjects did not report withdrawal signs but used opiates/opioids within 72 hr after ibogaine administration, and the other two subjects reported attenuated signs of withdrawal but remained drug-free. Only one participant reported an absence of effect of ibogaine on withdrawal symptoms. But the report does not specify whether the subjects with less effect of ibogaine on withdrawal symptoms were the methadone users or not. One fatality was reported: a 24-year-old female treated in The

Netherlands, in 1993, died 19 hr after ibogaine administration. Apparently, this fatality was due to heroin use in the first few hours after treatment.

In a conventional research setting (clinic) in St. Kitts, West Indies, more than 150 drug-dependent subjects were treated with single doses of 500–800 mg ibogaine HCl under open-label conditions (Mash et al., 2000, 2001). Baseline screening included physical and psychiatric examinations, ECG, and blood/hematological tests, and adverse effects were assessed by clinician ratings and self-reports. Ibogaine was safely administered based on cardiorespiratory measures, blood cell tests, and measures of hepatic enzymes. The most frequent adverse effects were transient nausea and mild tremor during the acute effects of ibogaine.

A subset of 27 opiate/opioid- and cocaine-dependent (DSM-IV criteria) subjects (23 men, mean age 34.6 ± 1.9 years for the opiate/opioid group and 37.5 ± 2.9 years for the cocaine group) participated in a 2-week inpatient Phase I dose-escalation study to assess ibogaine safety and efficacy for treating drug dependence symptoms (Mash et al., 2000). Subjects were randomly assigned to receive single fixed doses of 500, 600, or 800 mg ibogaine HCl under open-label conditions and completed structured self-reports relating to depression symptoms (Beck Depression Inventory, BDI) and craving [heroin (HCQN-29) or cocaine (Craving Questionnaire, CCQN-45); 1 hr before drug intake, and 36 hr and 14 days after drug intake]. The BDI was also applied 1 month after ibogaine administration. Ibogaine administration was associated with significant reductions in all five subscales of the HCQN-29 (*Desire to Use*, *Intention to Use*, *Anticipation of Positive Outcomes*, *Relief of Negative States*, and *Lack of Control*; for all subscales $p < .0001$) 36 hr and 14 days after drug intake, suggesting decreased craving for opiates/opioids. Ibogaine intake was also associated with significant reductions in two subscales of the CCQN-45 (*Relief of Negative States*, $p < .0005$; *Lack of Control*, $p < .002$) 36 hr and 14 days after drug administration, suggesting decreased craving for cocaine. Ibogaine administration was also associated with significant reductions in BDI scores ($p < .0005$) 1 month after drug intake, suggesting sustained reductions in depressive symptoms. Again, the study did not clarify if (or which) the subjects were under methadone treatment and if this interfered somehow with the results.

Another subset of 32 patients from the original sample (23 men, mean age 33.6 years), all opiate/opioid dependent (heroin or methadone, DSM-IV criteria), received a single 800 mg of dose, and withdrawal and craving symptoms were assessed with the physician-rated Objective Opiate Withdrawal Scale (OOWS) and with the Opiate-Symptom Checklist (OP-SCL, self-rated) (Mash et al., 2001). Data were collected 1 hr before drug intake (12 hr after last opiate/opioid dose) and 12 and 24 hr after drug intake (24 and 36 hr after last opiate/opioid dose, respectively). The OP-SCL was also used 6–9 days after ibogaine intake. Compared with baseline values, OOWS scores were significantly ($p < .05$) reduced 12 and 24 hr after ibogaine administration, and OP-SCL scores were significantly ($p < .05$) decreased <72 hr and 6–9 days after drug intake. The only information provided regarding drug abstinence stated vaguely that many subjects "...were able to maintain abstinence

from illicit opiates and methadone over the months following detoxification (data not shown)." Again, authors did not differentiate subjects regarding previous methadone use.

A retrospective report assessed the long-term effects of ibogaine in 41 individuals treated in non-medical settings under open-label conditions between 1962 and 1993, in the United States and in The Netherlands, mainly for opiate/opioid or stimulant dependence (Alper, 2001), including patients from previous studies (Alper et al., 1999; Sheppard, 1994). Fifteen (29%) reported abstinence of less than 2 months, 15 (29%) for at least 2 months and less than 6 months, seven (13%) for at least 6 months and less than 1 year, and 10 (19%) for more than 1 year. In five cases (10%), the outcomes could not be determined. Again, authors failed to identify subjects under methadone treatment.

In another retrospective study conducted in a private hospital in Santa Cruz do Rio Pardo, Brazil, the safety and efficacy of an open-label ibogaine treatment combining the administration of the drug with cognitive behavioral therapy were analyzed using data from 75 drug-dependent (DSM-IV criteria) patients (67 males and 8 females; mean ages 34.16 $\pm$ 8.33 and 29.50 $\pm$ 5.31 years, respectively) (Schenberg et al., 2014). Seventy-two percent of the subjects were Brazilian polydrug users (ethanol, cannabis, cocaine, and crack cocaine), with only one European patient having a history of opiate/opioid use. Subjects underwent a total of 134 ibogaine sessions (mean number of sessions for male and female participants was 3.83 $\pm$ 3.31 and 5.40 $\pm$ 0.91, respectively). Patients were required to stay abstinent for 30–60 days prior to ibogaine administration at their homes, or for at least 24 hr as a residential patient at the clinic. Subjects received oral doses of 17–20 mg/kg ibogaine HCl, preceded 30–45 min before by 20 mg of the dopamine $D_{2/3}$ receptor antagonist domperidone, to reduce nausea. If a patient reported a weak response to ibogaine after the initial dose, an additional 100–200 mg of dose was administered. Blood pressure, cardiac frequency, and oxygen saturation were measured every 25–30 min for 10 hr, and subjects were dismissed after 24–48 hr, returning for psychological therapy/follow-up. Single and multiple doses of ibogaine were associated with significant ($p < .001$) increases in abstinence duration, and 61% of participants were abstinent after ibogaine treatment (single dose, median 5.5 months; multiple doses, median 8.4 months). Acute adverse effects included transient nausea, ataxia, vomiting, tremors, headaches, and mental confusion. No serious adverse reactions such as cardiac arrhythmias or fatalities were observed.

Clinical trials

In a randomized, double-blind, placebo-controlled, single ascending-dose study, 27 patients (21 men, mean age 41.2 years) on methadone substitution therapy received noribogaine doses of 60, 120, or 180 mg (Glue, Cape, Tunnicliff, Lockhart, Lam, Hung, et al., 2016). Subjects were selected based on medical history, physical examination, safety laboratory tests, vital signs, ECG, and switched to morphine treatment a week before study participation. The effects of noribogaine on withdrawal symptoms and as a possible agonist of µ-opioid receptors were assessed by pupillometry

(baseline to 144 hr later), and oximetry and capnography (baseline to 72 hr later). Withdrawal symptoms were also analyzed by measuring the time to resumption of methadone treatment (mean time between last morphine dose given 2 hr prior to treatment and time to resumption of methadone treatment) and by the Subjective, Objective, and Clinical Opioid Withdrawal Scales (SOWS, OOWS, and COWS; baseline to 144 hr later, at the time of resumption of methadone treatment, and 2 hr afterward). Safety and tolerability measures (physical examinations, adverse events, laboratory tests, vital signs, and continuous ECG recordings) were assessed from baseline to 144 hr after noribogaine/placebo administration, and outpatient and telephone assessments were performed until 35 days later.

Noribogaine was well tolerated: no significant changes were observed in vital signs, safety laboratory tests, oximetry or capnography, respiratory rate, or physical examinations, and there were no deaths or serious adverse effects. The most frequent adverse effects were transient changes in light perception (light brighter than usual), headache, and nausea, and no hallucinogenic effects were reported. However, noribogaine induced significant dose- and concentration-dependent QT interval prolongation (a risk factor for cardiac arrhythmias and sudden death), which reached clinically concerning levels with the 180 mg of dose. Opiate/opioid withdrawal symptoms increased 1–2 hr before resumption of methadone treatment as well as pupil diameter. Noribogaine did not produce significant reductions on subjective and objective rating scales measuring opiate/opioid withdrawal symptoms (SOWS, OOWS, and COWS) and also failed to induce significant increases in the time to resumption of methadone treatment, which was very similar between the placebo and noribogaine groups. Surprisingly, the 120-mg dose group experienced the longest time to resumption of methadone treatment, which was supported with the lowest scores on opiate/opioid withdrawal symptoms.

DISCUSSION

In this systematic review, eight studies suitable for inclusion regarding the investigation of the antiaddictive effects of ibogaine in humans were identified. Despite the small number of studies, the open-label nature of most citations (seven), the high degree of heterogeneity among them, and the results reported in the case series suggest that ibogaine/noribogaine significantly reduced opiate/opioid withdrawal symptoms and that many subjects remained drug-free for several days after treatment. However, the only clinical trial performed, using noribogaine, failed to find significant reductions on opiate/opioid withdrawal symptoms. Therefore, the antiaddictive effects of ibogaine/noribogaine should be interpreted with caution.

The absence of effects of noribogaine could be related to several factors. First, the equivalence between therapeutic doses of ibogaine and noribogaine is not well known, so the lack of effects could be related to the administration of low doses of noribogaine, which would not be enough to achieve anti-withdrawal effects. In fact, based on their studies involving the administration of ibogaine and noribogaine

to healthy volunteers (Glue, Lockhart, et al., 2015; Glue, Winter, et al., 2015), the authors predicted that an ibogaine dose of 286 mg would lead to noribogaine C_{max} values comparable to a 180-mg dose of noribogaine, and there are no reports in the bibliography, where such a low dose of ibogaine has been administered to opiate-/opioid-dependent subjects. Second, the case series described the treatments of subjects mostly dependent on heroin, with fewer patients reporting the use of methadone, and most of the reports did not differentiate between heroin/methadone users. Methadone has a longer half-life than heroin (Argoff & Silvershein, 2009). In another paper, Glue, Cape, Tunnicliff, Lockhart, Lam, Gray, et al. (2016) detailed how they did the patient's switching from methadone to morphine in 6 days and explained that at that time 91% of methadone was cleared. They also found a mean elimination half-life of 59 hr. Furthermore, subjective reports of methadone dependents suggest that they may suffer withdrawal symptoms for more than a month. Thus, the absence of significant reductions in opiate/opioid withdrawal, as the authors acknowledge, may need repetitive doses of ibogaine/noribogaine if the propose is to detoxify from methadone.

The most important limitation of the reviewed studies is that seven of the eight citations are open-label case series. The lack of control groups and placebo in these studies does not allow to suggest causation, especially considering that most treatments were performed in non-medical and unsupervised contexts with no standardized protocols. Therefore, it is not possible to affirm that ibogaine/noribogaine are effective treatments for drug dependence. Moreover, the only clinical trial performed with noribogaine did not find significant reductions on opiate/opioid withdrawal symptoms, suggesting that the results reporting antiaddictive effects of ibogaine/noribogaine should be interpreted with caution.

However, animal studies consistently show that ibogaine significantly reduces opiate/opioid and cocaine self-administration (Alper, 2001; Alper et al., 2008; Belgers et al., 2016; Brown, 2013; Donnelly, 2011; Frenken, 2001; Lotsof & Alexander, 2001; Mash et al., 1998), and the pattern of results observed in all case series – including the duration of the therapeutic effects of ibogaine – is very similar (from 24 hr to days/weeks). However, as exposed above, the only clinical trial found in the review reported that noribogaine failed to reduce opiate/opioid withdrawal symptoms (Glue, Cape, Tunnicliff, Lockhart, Lam, Hung, et al., 2016).

Some researchers have been speculated that the therapeutic effects of ibogaine seem to be related to the pharmacokinetics of its main metabolite, noribogaine, which is longer lasting, and to the multiple receptor profile of both compounds (Alper, 2001; Alper et al., 2008; Brown, 2013; Donnelly, 2011; Frenken, 2001; Kolp et al., 2007; Lotsof & Alexander, 2001; Mash et al., 1998, 2000, 2001). The neurochemical effects of ibogaine/noribogaine are not completely understood and may include antagonism of the NMDA glutamatergic and α3β4 adrenergic receptors, inhibition of 5-HT reuptake transporter and of dopamine release in the nucleus accumbens and other brain areas, agonism of the σ_2, κ-opioid, and 5-HT$_{2A}$ receptors, and enhancement of GDNF (Alper, 2001; Alper et al., 2008; Brown, 2013; Mash

et al., 1998). Antagonism of the NMDA receptor is shared with the anesthetic hallucinogen ketamine, which has been reported to show anxiolytic (Kolp et al., 2007), antidepressive (Luckenbaugh et al., 2014; Sos et al., 2013), and antiaddictive (Dakwar, Levin, Foltin, Nunes, & Hart, 2014; Krupitsky et al., 2007) effects. Agonism of the κ-opioid receptor is shared with the plant hallucinogen salvinorin A, which has potential effects in the treatment of stimulant-related disorders (Dos Santos, Crippa, Machado-de-Sousa, & Hallak, 2014). Agonism of the 5-HT$_{2A}$ receptor is shared with classic serotonergic hallucinogens such as LSD, psilocybin, and ayahuasca/DMT, which has anxiolytic, antidepressive, and antiaddictive properties (Dos Santos, Osório, Crippa, & Hallak, 2016; Dos Santos, Osório, Crippa, Riba, et al., 2016; Nunes et al., 2016).

An important limitation to the clinical use of ibogaine/noribogaine is the possible toxicity of these alkaloids, which include fatalities, cardiac arrhythmias, psychosis, mania, and seizures (Alper, 2001; Alper et al., 2012; Breuer et al., 2015; Brown, 2013; Forsyth et al., 2016; Glue, Lockhart, et al., 2015; Glue, Winter, et al., 2015; Houenou et al., 2011; Koenig & Hilber, 2015; Litjens & Brunt, 2016; Marta et al., 2015; Meisner et al., 2016). Moreover, the clinical trial with noribogaine reported a significant dose-dependent increase in QT interval prolongation, which is a risk factor for cardiac arrhythmias and sudden death. Thus, a clear and firm warning of the cardiovascular dangers of ibogaine/noribogaine should be provided to patients, who must also be informed of the risks of using drugs – in particular opiates/opioids – during or immediately after ibogaine/noribogaine intake, which may potentiate the effects of these alkaloids or of the opiates/opioids, thus increasing the risk of an overdose. This is especially important considering that many ibogaine treatments are performed under non-medical/unsupervised conditions using extracts of unknown purity sold in the black market. The absence of proper medical screening and monitoring increases the possibility of hazardous situations (Alper, 2001; Alper et al., 2012; Breuer et al., 2015; Brown, 2013; Forsyth et al., 2016; Glue, Lockhart et al., 2015; Glue, Winter, et al., 2015; Houenou et al., 2011; Koenig & Hilber, 2015; Litjens & Brunt, 2016; Marta et al., 2015; Meisner et al., 2016).

In summary, the results of this systematic review suggest that ibogaine/noribogaine have antiaddictive properties. Although these results are supported by animal studies, no controlled clinical trials have been performed with ibogaine, and the only clinical trial assessing the antiaddictive potentials of noribogaine failed to find significant results. These results suggest a more cautious interpretation of the antiaddictive effects of ibogaine/noribogaine.

The use of heroin and synthetic opiates has reached an alarming level in Europe (EMCDDA, 2016), and only in the United States, 44 people die every day from overdose of prescription painkillers (SAMHSA, 2016). Moreover, there are no proper medications for treating withdrawal symptoms associated with methadone use in the case of patients that use this drug for treating dependence on other opiates/opioids, such as heroin. In this sense, the investigation of ibogaine/noribogaine could provide new pharmacological treatments

with fast-acting and sustained beneficial effects for patients suffering drug dependence, especially to opiates/opioids and cocaine. Controlled studies are needed to replicate these findings.

Conflict of interest: The authors declare that they have no conflict of interest.

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