

# Safety of ibogaine administration in detoxification of opioid-dependent individuals: a descriptive open-label observational study

Thomas Knuijver<sup>1,2,4</sup> , Arnt Schellekens<sup>2,3</sup> , Maarten Belgers<sup>1,2</sup> , Rogier Donders<sup>5</sup> ,  
Toon van Oosteren<sup>1</sup> , Kees Kramers<sup>4</sup>  & Robbert Verkes<sup>3,6</sup> 

IrisZorg verslavingszorg, Amhem, the Netherlands,<sup>1</sup> Nijmegen Institute for Science Practitioners in Addiction (NISPA), Nijmegen, the Netherlands,<sup>2</sup> Department of Psychiatry, Radboud UMC, Nijmegen, the Netherlands,<sup>3</sup> Department of Pharmacology–Toxicology, Radboud UMC Nijmegen, Nijmegen, the Netherlands,<sup>4</sup> Department for Health Evidence, Radboud UMC Nijmegen, Nijmegen, the Netherlands<sup>5</sup> and Centre of Forensic Psychiatry, Pompe Kliniek, Nijmegen, the Netherlands<sup>6</sup>

## ABSTRACT

**Background and aims** Ibogaine is an indole alkaloid used in rituals of the African Bwiti tribe. It is also used in non-medical settings to treat addiction. However, ibogaine has been linked to several deaths, mainly due to cardiac events called *torsades des pointes* preceded by QTc prolongation as well as other safety concerns. This study aimed to evaluate the cardiac, cerebellar and psychomimetic safety of ibogaine in patients with opioid use disorder. **Design** A descriptive open-label observational study. **Setting** Department of psychiatry in a university medical center, the Netherlands. **Participants** Patients with opioid use disorder ( $n = 14$ ) on opioid maintenance treatment with a lasting wish for abstinence, who failed to reach abstinence with standard care. **Intervention and measurements** After conversion to morphine-sulphate, a single dose of ibogaine-HCl 10 mg/kg was administered and patients were monitored at regular intervals for at least 24 hours assessing QTc, blood pressure and heart rate, scale for the assessment and rating of ataxia (SARA) to assess cerebellar side effects and the delirium observation scale (DOS) to assess psychomimetic effects. **Findings** The maximum QTc (Fridericia) prolongation was on average 95ms (range 29–146ms). Fifty percent of subjects reached a QTc of over 500ms during the observation period. In six out of 14 subjects prolongation above 450ms lasted beyond 24 hours after ingestion of ibogaine. No *torsades des pointes* were observed. Severe transient ataxia with inability to walk without support was seen in all patients. Withdrawal and psychomimetic effects were mostly well-tolerated and manageable (11/14 did not return to morphine within 24 hours, DOS scores remained below threshold). **Conclusions** This open-label observational study found that ibogaine treatment of patients with opioid use disorder can induce a clinically relevant but reversible QTc prolongation, bradycardia, and severe ataxia.

**Keywords** Addiction, cardiac safety, cerebellar toxicity, detoxification, ibogaine, opioid use disorder.

Correspondence to: T. Knuijver, IrisZorg verslavingszorg, 4001 CB Tiel, the Netherlands. E-mail: thomas.knuijver@radboudumc.nl  
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## INTRODUCTION

Ibogaine is an active alkaloid tryptamine found in the root of *Tabernaemontana iboga*, a shrub found in Central Africa [1]. Ibogaine is the main indole alkaloid of the rootbark extract. It is an entheogen, used in traditional coming-of-age rituals by the West African Bwiti tribe [2]. It is also used in non-medical settings by underground providers for the treatment of addiction [3].

Ibogaine has shown some promise in the treatment of addiction, i.e. opioid and cocaine use disorder. Several case–series and small-scale observational studies have been published, showing a variety of effects: diminished

withdrawal, abstinence for varied periods of time, reduction of craving and an increase in overall wellbeing [3–6]. Moreover, a meta-analysis of animal studies showed a reduction in self administration of opiates, cocaine and ethanol and a reduction of place preference after ibogaine administration in rat and mouse models of addiction [7].

Concerns about the safety of ibogaine use have also been reported. Studies have shown ibogaine to be associated with *torsades des pointes* (TdP) after ingestion of ibogaine [8,9]. *In-vitro* studies show that ibogaine prolongs repolarization of cardiomyocytes through human Ether-a-go-go-related gene (hERG) channel inhibition [10,11]. This

induces lengthening of the QT interval on the electrocardiogram and increases the risk of TdP [9,11,12]. Furthermore, ibogaine can reduce heart rate and blood pressure, further increasing the risk for TdP [13].

As well as cardiac risks, ibogaine has been observed to produce reversible ataxia [4]. In rodents this ataxia occurs with cell death of cerebellar purkinje cells [7,14]. Systematic observations on ataxia in humans are lacking. However, neurological examination in three cases of ibogaine treatment confirms the occurrence of transient ataxia [5]. Anecdotal evidence from case reports for other potential adverse effects of ibogaine include seizures [15], mania [16] and hallucinogen persisting perception disorder [17]. Moreover, one case of suicide during ibogaine use under supervision of an underground treatment provider has been published [18].

Despite concerns about the clinical safety of ibogaine and limited evidence for effectiveness, ibogaine treatments are offered widely across the world, often without medical supervision. The aim of the present study was to evaluate clinical safety of ibogaine in the treatment of patients with opioid use disorder (OUD). Specifically, we assessed the cardiac, cerebellar and behavioral effects of a single administration of ibogaine in patients on opioid substitution treatment during opioid detoxification. We hypothesized that treatment with ibogaine reversibly induces (1) QTc prolongation on the electrocardiogram, (2) ataxia and (3) psychomimetic behavioral changes. We also included some observations on withdrawal, to measure potential benefits and durability.

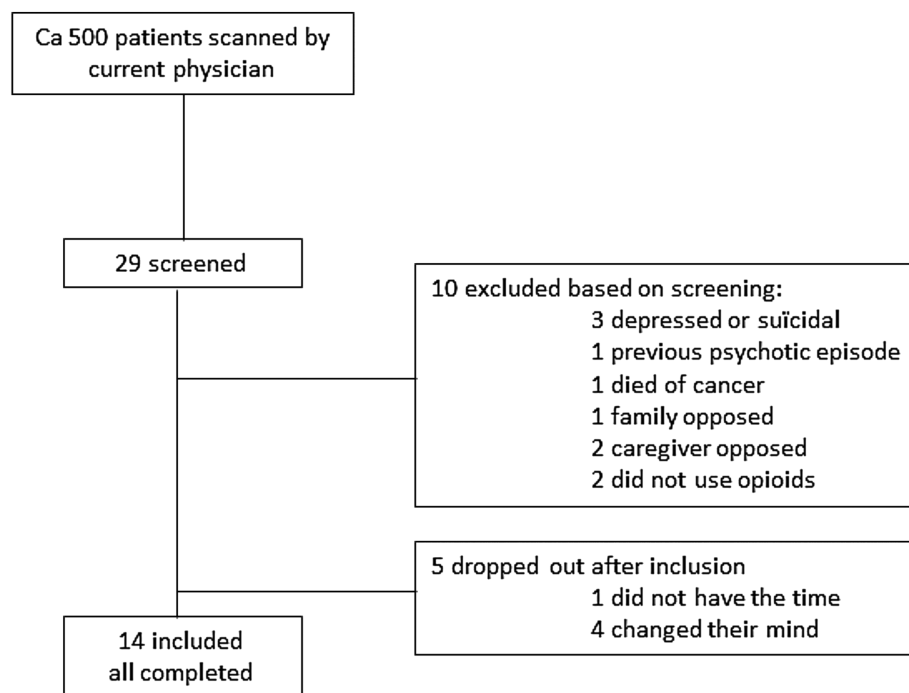
## METHODS

### Study design

To investigate the safety of ibogaine *in vivo* we conducted an open-label observational study in patients with OUD in opioid substitution treatment (OST). The study was approved by the medical ethical review committee region in Arnhem–Nijmegen (CMO ref.no. 2014/081), and all participants provided written informed consent. The study has been registered under EUDRACT Trial Number 2014-000354-11. A data safety monitoring board was installed and consulted after two, seven and 14 patients. Stopping criteria were TdP, death or any other unexpected serious adverse event.

### Participants

All recruited patients were diagnosed with OUD according to the DSM-IV, and were selected from two outpatient addiction clinics (IrisZorg: Arnhem and Nijmegen). Files of 500 outpatients were inspected to approach potential participants. Of these 500 we chose to look into 130 files of patients who were psychosocially stable and on OST. These files were screened for exclusion criteria. Thirty-six patients deemed eligible were approached to participate; 29 patients were willing and were screened (Fig. 1). Inclusion took place between October 2015 and November 2017. We aimed to recruit 15 patients, and succeeded in including 14. A *post-hoc* power analysis showed that with a baseline QTc of 410 (men) and



**Figure 1** Inclusion flow-chart.

420 (women) and an increase of 10% QTc (+ 42 ms, giving 462 ms, which is enough for prolongation) with 10 patients 80% power would be reached ( $\alpha = 0.05$ ,  $\beta = 0.2$ ) (Supporting information) [19]

Inclusion criteria were: 20–60 years of age, a wish for detoxification and abstinence of opioids and prior treatment failure. Exclusion criteria were a history of clinically significant cardiac disease (including ventricular fibrillation, long QT syndrome (LQTS), history of syncope, and ECG abnormalities, including QTc > 450 ms for men and > 470 ms for women), serum potassium > 5.0 mmol/l or < 3.5 mmol/l, severe liver or renal dysfunction (MDRD < 30 ml/min/1.73 m<sup>2</sup>), or pregnancy. Participants were not allowed to use QT prolonging [20] or CYP2D6 [21] affecting medication, except for methadone (see below). Patients with a history of psychotic symptoms, severe major depressive disorder or suicidality were excluded, based on the Mini-International Neuropsychiatric Interview (MINI version 5.0.0 R) [22].

### Intervention

Participants received ibogaine-HCl 10 mg/kg orally, administered in a yoghurt mixture, at 8.30 a.m. This dosage is in the lower bound of the range of doses administered in previous studies [3,4,6,13,23–26]. Ibogaine hydrochloride for human use was purchased from Phytostan enterprises (Montreal, Quebec, Canada), brand name Remogen [27]. Purity was assessed using a validated liquid chromatography assay with ultraviolet detection [high-performance liquid chromatography (HPLC)-UV] by the manufacturer. The purity was confirmed locally by our pharmaceutical laboratory with a validated HPLC-UV assay and an independent reference substance at purity of 102.3%, with an expected value of 98%–102%. Our batch of ibogaine went past its shelf life in December 2017, after the treatment of the last participant. Before ibogaine administration subjects were given 20 mg of metoclopramide to prevent nausea for comfort and to ensure full ingestion [28].

### Outcome measures

#### Sample characteristics

Age, sex and current medication use were recorded. Substance use and addiction severity were assessed using the Addiction Severity Index (ASI) [30–34]. The ASI covers seven domains of addiction (medical, employment/support, drug and alcohol use, legal, family/social, psychiatric) documenting life-time substance use problems and substance use in the past 30 days. It scores the severity of problems experienced as well as a wish/request of the patient for help in these domains, on a scale from 0 to 4 [31–35]. Higher scores indicate more severe problems. Validation in patients with drug and alcohol use disorders

show good internal consistency and reliability [30,31]. Scoring takes approximately 30 minutes by a trained clinician.

#### ECG measures

QTc prolongation was assessed using twelve lead ECG measurements performed with a Philips Healthcare, multi-channel TC50. QT was corrected using Fridericia's formula ( $QTcFr = (QT/(RR/1s)^{1/3})$ ). QT durations were measured manually by two independent researchers (T.K. and A.I.) in order to obtain a reliable estimation of the QT interval by taking the average of the V5 and II leads [36]. The correlation between the QT intervals calculated by the two researchers was moderate ( $r = 0.64$ ). Furthermore, Bland–Altman analysis of the manually corrected QTc measurements showed a mean difference between measurements of researchers T.K. and A.I. of 0.89 ms. This means that the measurements were, on average, the same, and neither researcher systematically over- or underestimated measurements, indicating no measurement bias. The average absolute difference per measurement was 34 ms, or less than 1 mm on the electrocardiogram (ECG) paper. The average QTc-value of the two assessors was used in the analyses.

The Philips Healthcare TC50 also provides an automated calculation of the QTc time. These values were used for medical monitoring during treatment. The correlation between the average QTc interval of the assessors and the TC50 QTc interval was strong ( $r = 0.71$ ,  $p < 0.01$  sig 2-tailed). The Bland–Altman plot showed a non-significant mean difference of + 7 ms for the automatic measurement, with a standard deviation of 26 ms.

#### Heart rate

The heart rate measured on the ECG was used. Blood pressure was measured after each ECG assessment. A heart rate below 60 beats per minute (bpm) and systolic pressure below 90 mmHg were used as cut-off for bradycardia and hypotension [37].

#### Ataxia

Cerebellar ataxia was assessed using the scale for the assessment and rating of ataxia (SARA), a structured clinical assessment applied by a trained physician [38–40]. The SARA indexes severity of ataxia, often related to cerebellar pathologies. It has eight items (maximum score): gait [8], stance [6], sitting [4], speech [6], finger-chase test [4], nose–finger test [4], fast alternating movements [4] and a heel–shin test [4], with a total maximum score of 40. The heel–shin test was performed while standing. Higher scores indicate worse performance [38–41]. The SARA has been found reliable and consistent in several large studies among a range of cerebellar diseases causing ataxia [38–41].

## Delirium

Psychomimetic effects were monitored using the delirium observation screening (DOS) scale, a 13-item observational scale of verbal and non-verbal signs of delirium [42]. A score of 3 or higher is indicative of delirium. Scoring was conducted by a trained clinician. The DOS is a reliable, commonly used instrument in many inpatient settings to check for delirium [42]. Any adverse events were noted.

## Withdrawal

Withdrawal was measured using the clinical opioid withdrawal scale (COWS), a standardized test for measuring opioid withdrawal used world-wide [24,43]. It scores withdrawal on 11 signs and symptoms of withdrawal on a 0–4 or 5 scale. The total scores are translated to a non-severe scale, which we translated as 0–4 for further analyses.

## Study procedures

Before ibogaine treatment, all subjects were admitted to an inpatient clinic and converted from OST to oral morphine sulphate for 8 days, in order to eliminate any QT prolonging effects of methadone and homogenize baseline pharmacotherapy for all participants. Doses of morphine were administered at 4-hourly intervals. Subjects received the last dose of morphine 4 hours prior to ibogaine administration. Withdrawal was expected to commence between 4–6 hours after the last morphine administration. Subjects were detoxified of any other drugs for at least 8 days prior to participating in the study, with the exception of tobacco. Tobacco smoking was allowed up to half an hour pre-ingestion and 4–6 hours after ibogaine ingestion, depending on the ability to walk to a smoking area.

Baseline of all outcomes were measured 30 minutes before administration of ibogaine.  $K^+Ca^{2+}$  and  $Mg^{2+}$  were checked to be within normal ranges prior to ibogaine administration. ECGs were then performed every half hour for the first 12 hours. Thereafter, ECG measurements were performed every hour in case of persistent QTc prolongation ( $> 450$  ms for men;  $> 470$  ms for women) or every 4 hours if automatic QTc time was shortening and below 500 ms. ECG measurements continued for 24 hours after administration. After 24 hours a cardiologist assessed if monitoring needed to continue. If QTc exceeded 500 ms, participants received a magnesium bolus infusion of 2 g in 10 minutes, followed by 2 g of magnesium over the next 10 hours for myocardial stabilization. If necessary, subjects could be transferred to the coronary care unit (CCU) for continuous cardiac monitoring.

The SARA and COWS were assessed at 2, 6, 10 and 24 hours after administration of ibogaine. The DOS scale was assessed every hour for the first 12 hours after administration of ibogaine.

## Statistical analyses

Demographics, type of substitution therapy, current substance use and addiction severity were summarized using descriptive statistics.

Based on the Food and Drug Administration (FDA) guidelines (Guidance for Industry, Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs), we used the following outcome measures: the difference between the QTc before administration and the maximum QTc during the observation period ( $\Delta QTc_{Max}$ ) per subject, the proportion of subjects with a QTc  $> 500$  ms at any given time and the proportion of subjects with a QTc  $> 500$  ms and  $> 450$  ms at each measurement [44]. During the evening and night subjects were left sleeping, if deemed safe, therefore fewer measurements were taken during the night. The measurements t27–t30 (evening), t31–39 (night) and t40–t48 (morning) were pooled and renamed 'evening', 'night' and 'morning'.

The number of subjects developing bradycardia or hypotension and the mean maximum drop in heart rate and blood pressure during the first 12 hours were calculated [37]. The number of magnesium supplementations and adverse events such as TdP, seizures and vomiting were counted. Average total SARA scores and per-item SARA scores were calculated at each time-point. Our intention was to calculate the time to onset of withdrawal. COWS scores remained low, however, so the number of measurements with a non-zero score was summarized.

As 10 participants scored zero and four scored one to two points on the DOS during the observation period, no statistical analyses were performed and psychomimetic effects were reported qualitatively.

All statistical analyses were performed using IBM SPSS statistics version 25 and Microsoft Excel.

## RESULTS

Patient characteristics, medical history, drug use and vitals are summarized in Table 1. Patients scored on average between 0 and 1 on all ASI domains except drug use, reflecting a stable psychosocial situation and a wish for abstinence. All subjects had a history of polysubstance (ab)use. Heart rate, blood pressure and QTc were within the normal range.

### Primary outcomes

#### ECG changes

The main findings are presented in Table 2. The  $\Delta QTc_{Max}$  varied greatly, with a median of a 95 ms (Fig. 2). Half the participants reached a QTc of  $> 500$  ms; the proportion of subjects with a QTc  $> 500$  ms at any given time varied

**Table 1** Subject characteristics and baseline measurements.

Characteristics	n = 14
Sex M/F	12/2
Methadone/buprenorphine	12/2
Age (median; 25th and 75th percentile)	48 (44–51)
ASI <sup>a</sup>	Average (SD)
Physical	0,85 (1,14)
Work	0,46 (0,78)
Alcohol	0,77 (1,48)
Drugs	3,23 (1,83)
Judicial	0,38 (1,12)
Family and social	0,46 (0,52)
Psychological and emotional	1,00 (1,22)
Total	1,02 (1,16)
Drug use <sup>b</sup>	
Alcohol	2/14
Amphetamine	0/14
Benzodiazepines	3/14
Cannabis	4/14
Cocaine	7/14
Heroin	8/14
Tobacco	13/14
Baseline clinical measurements (25th and 75th percentiles)	
Baseline median QTc	411 ms (387–434 ms)
Baseline median HR	70 bpm (63–80 bpm)
Baseline mean diastolic blood pressure	78 mmHg (75–88 mmHg)
Baseline mean systolic blood pressure	129 mmHg (119–146 mmHg)

<sup>a</sup>Addiction severity index scores range from 0 to 4. A score of 0 means that the subject does not consider this domain a problem or needs no help, and a score of 4 means that the subject experiences the domain to be a big problem and would like help; <sup>b</sup>frequency of any drug use 1 month prior to detoxification. SD = standard deviation; bpm = beats per minute; HR = heart rate; M/F = male/female.

between 7–21% (Fig. 3). After 24 hours, QTc was still > 450 ms in 29% of subjects (Fig. 3). No TdP were observed on ECG and no clinical signs of such were seen. QTc prolongation was highly variable over time, showing spikes up and down (Supporting information, Fig. 5). This variation also occurred in the automatic measurements (data not shown).

QTc is known to be slightly longer in women, and measurements up to 470 ms are deemed normal [19]. Both women included in our study had measurements above 500 ms, with baseline measurements of 438 ms and 441 ms. Eight subjects received magnesium infusions, due to QT prolongation over 500 ms on automatic ECG measurements. No seizures occurred.

## Secondary outcomes

### Heart rate, blood pressure and adverse events

During the first 12 hours after administration mild bradycardia (c. 50 bpm) and a decrease in blood pressure

**Table 2** Primary and secondary outcomes.

Outcomes	
$\Delta$ QTcMax <sup>a</sup> (median, SD, range)	102 ms (36 ms; 40–168 ms)
No. of subjects with QTc > 500 ms event	7/14
No. of subjects with QTc > 450 ms after 24 hours	6/14
Magnesium infusions	8/14
No of subjects with bradycardia (< 60 bpm)	7/14
Median maximum decrease in heart rate	9 bpm
No. of subjects with hypotension (systolic < 90 mmHg)	0/14
Median maximum decrease in blood pressure	22 mmHg
Median and average COWS <sup>b</sup> scores	0; 0.08
No. of subjects not on morphine after 24 hours	11/14
Average maximum SARA <sup>c</sup> score	13.7 points
No. of subjects with DOS <sup>d</sup> score > 2	0/14
Subjective duration of ibogaine experience	3–7 hours

<sup>a</sup>The maximum prolongation of QT interval from baseline, corrected for heart rate using Fridericia's formula; <sup>b</sup>clinical opioid withdrawal scale (COWS). The median and average COWS scores were used only if no reversal to morphine; <sup>c</sup>scale for the assessment and rating of ataxia; <sup>d</sup>delirium observation scale (DOS). SD = standard deviation; SARA = assessment and rating of ataxia; bpm = beats per minute.

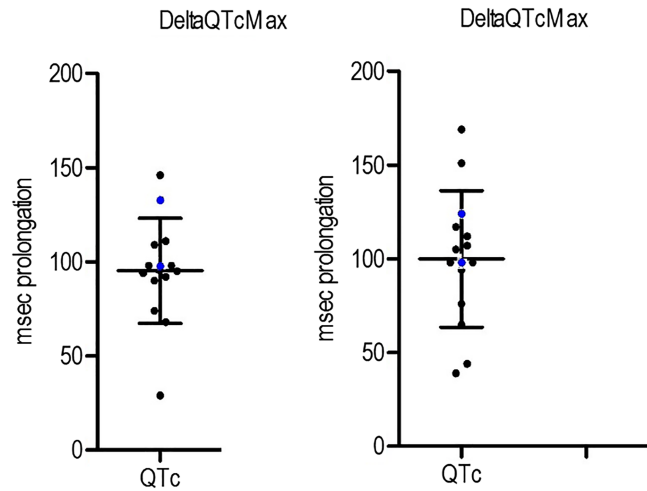
occurred (Table 2). The only observed adverse event was vomiting, observed in two patients more than 2 hours after ibogaine ingestion.

## Ataxia

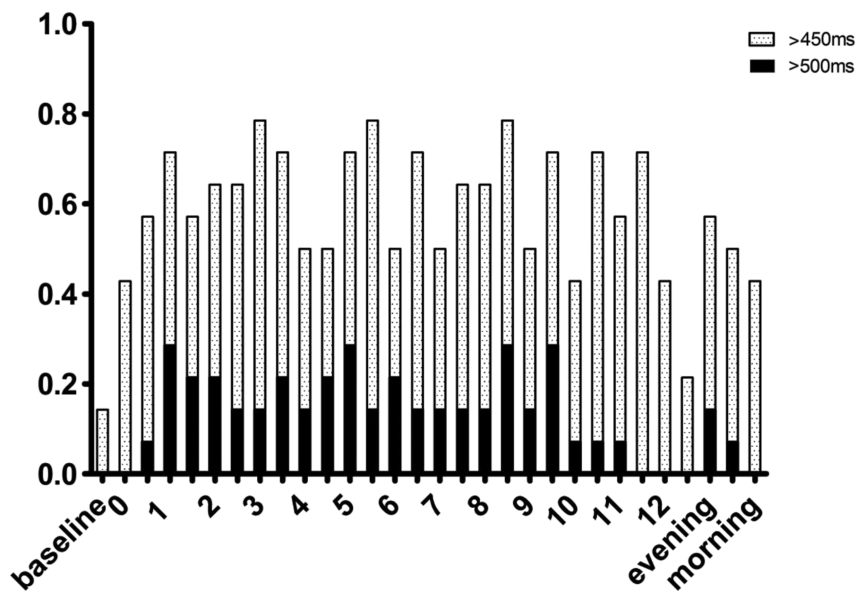
The SARA scores increased from baseline to maximum in 2–6 hours after ingestion (Fig. 4). All subjects developed clinical signs of cerebellar ataxia, with full remission within 24 hours after ibogaine administration. Five patients scored above zero [1,2] after 24 hours; they were tested again 24 hours later, with full remission of ataxia. Signs of ataxia were mainly observed in gait, standing and the heel–shin tests, with subjects needing support by a nurse to go to the bathroom (for scores per item; see Supporting information, Fig. 6).

## Psychomimetic effects

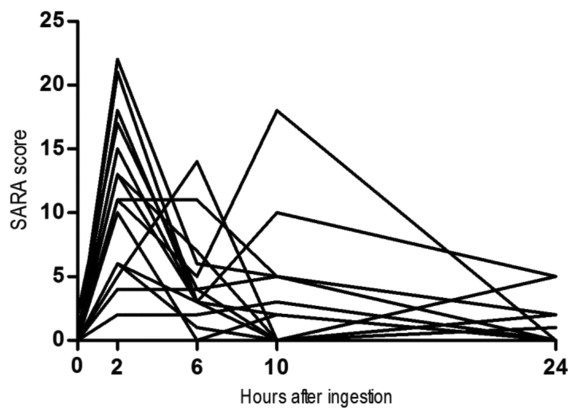
The DOS scores were zero at baseline. In 10 subjects no delirious signs were observed; the other four participants scored one to two points during treatment. Our clinical observation was that all subjects were mostly lying quietly on their beds for c. 4–8 hours. They reported wakeful dreaming and reliving memories. One subject seemingly grabbed at items that were not there and three were not adequately spatially orientated. This experience lasted approximately 3–7 hours.



**Figure 2**  $\Delta$ QTcMax per subject with mean and standard deviation bars (102 ms; 36 ms, females in blue)



**Figure 3** QTc prolongation proportions of subjects with a QTc time exceeding 450 and 500 ms during the first 24 hours. Evening, night-time and morning (24 hours) measurements are grouped into their respective categories



**Figure 4** Scale for the assessment and rating of ataxia (SARA) scores. This shows the progression of SARA scores of all individuals. The highest scores are mainly in the 2–6-hour range

*Withdrawal*

Withdrawal severity remained low during the observation period of 24 hours after ibogaine ingestion for most subjects. Only five measurements gave a score of 1. Three subjects requested a return to morphine substitution based on a subjective feeling of treatment failure. No measurements of COWS or SOWS were done immediately prior to restarting morphine, as this was not part of the procedure and subjects were allowed to return to morphine unconditionally. Resumption of these 3 individuals was at 3.5, 10 and 19.5 hours after ibogaine ingestion.

## DISCUSSION

This study aimed to investigate safety of ibogaine-HCl (10 mg/kg) in patients with OUD in OST undergoing acute opioid withdrawal. All but one patient developed a degree of QTc prolongation, with half of the patients developing a QTc exceeding 500 ms. Although reversible, this QTc prolongation is a clinically relevant cardiac safety risk, including risk of TdP, even after a relatively small dose of ibogaine [26]. Furthermore, bradycardia and decreased blood pressure were observed, as well as transient ataxia. During the first 24 hours, subjects experienced mostly mild withdrawal and transient psychomimetic effects, which were well-tolerated. Three out of fourteen subjects returned to morphine treatment within this timeframe.

The observed QTc prolongation is in agreement with case reports of subjects admitted to emergency departments after ibogaine ingestion. A QTc of > 500 ms is associated with a large increase [odds ratio (OR) = 11.2, 95% confidence interval (CI) = 4.6–27] in the risk of an adverse cardiovascular disorder in patients presenting with a drug overdose to the emergency room (ER) [45]. The patients in these case reports showed a prolonged QTc, together with ventricular fibrillation, TdP or both [9]. Other illicit substances or pre-existing cardiac pathology appeared relevant in some of these patients. Our study shows that in a well-controlled experimental setting, ibogaine produces a clinically relevant QTc-prolongation in patients without pre-existing cardiac abnormalities. This indicates that administration of ibogaine should be restricted to well-controlled settings with strict cardiac monitoring.

*In-vitro* studies strongly suggest that the QTc prolonging effect of ibogaine and its metabolite noribogaine results from inhibition of cardiac hERG-potassium channels [9–11]. As hERG channels are crucial for cardiac repolarization, inhibition of these channels results in prolongation of the action potential with subsequent prolonged depolarization of cardiomyocytes. Our observations show QTc prolongation in a clinical setting, reproducing the *in-vitro* results [9–12]. The observed bradycardia further adds to the risk of TdP [46].

The interindividual variation in the extent, timing and duration of QTc prolongation might result from several interindividual pharmacokinetic and pharmacodynamic differences. For instance, ibogaine is metabolized to noribogaine by CYP2D6, an enzyme of the cytochromeP450, that has strong interindividual variation in activity in humans. Genetic variation in the CYP2D6 genotype results in poor, intermediate, extensive and ultra-rapid metabolizers [47–49]. This variation can cause variation in the first-pass effect, bioavailability, as well as elimination of ibogaine and availability of noribogaine. Although our subjects did not take any medication affecting CYP2D6 activity, such medication is commonly used,

particularly in psychiatry. This might add further risk of cardiotoxicity of ibogaine in clinical practice, with presumably highest risks in poor metabolizers and those taking CYP2D6 inhibiting medication.

Even though none of our participants had QTc times exceeding 500 ms after 24 hours, QTc was still > 450 ms after 24 hours in 29% of subjects. It is important to note that the metabolite noribogaine has also been associated with QTc prolongation, although some suggest noribogaine to be less potent compared to ibogaine itself [29,50]. The half-life of serum ibogaine is 1–6 hours and that of noribogaine is 28–49 hours [29]. This might further add to persistent QTc prolongation, as observed in some individuals [9].

In line with previous observations in animals and humans, transient ataxia occurred after administration of ibogaine [3,7]. Based on the known half-life and Tmax of ibogaine it seems likely that ibogaine itself, and not its metabolites, is responsible for this observation. The transient ataxia resolved long before noribogaine levels peak. It has been suggested that impaired motor control might be due to the oneirogenic experience that occur during ibogaine treatment [3]. However, we hypothesize that an effect of ibogaine on the cerebellum can however not be ruled out. Indeed, cerebellar toxicity of ibogaine is observed in animal models much higher doses are given [51–54]. Translation of these animal data to humans is however complex. The pronounced effects of ibogaine on motor coordination of distal limbs and balance is in accordance with a higher susceptibility of the vermis to toxicity effects as opposed to the cerebellar cortex [55]. This may be because the vermis is closer to the CSE, in which toxins may enter [55]. A human autopsy report on a woman receiving multiple doses of ibogaine did not show cerebellar damage [56]. There are no reports of long lasting neurologic effects of ibogaine treatment. Effects on the human cerebellum need further study, for instance using neuro-imaging techniques. Interestingly, the cerebellum has also been implicated to modulate dopaminergic neurons in the ventral tegmental area (VTA) in the limbic system, and as such might play a role in addictive behaviors [57]. Future studies should investigate whether cerebellar effects of ibogaine play a role in its alleged anti-addictive properties [57].

Despite clear effects, no subjects had substantial increases on the DOS scale. Although no severe behavioral changes occurred in our subjects, they reported having psychomimetic experiences of closed eye visuals and vivid memories. One subject reported visual hallucinations. In the current study, these so-called 'oneirogenic experiences' were generally well-tolerated. However, literature and internet fora suggest that longer-lasting disturbing behavioral changes can occur after ibogaine ingestion [58,59]. As such, ibogaine administration in settings with expertise

in handling people experiencing neurogenic and/or psychotic symptoms is advisable.

Although the mechanism of action of ibogaine is poorly understood, it is known that ibogaine has a high affinity for several receptor sites, including N-methyl-D-aspartate receptor (NMDA),  $\kappa$ - and  $\mu$ -opioid receptors as well as sigma-2 receptor sites [51]. The observed mild withdrawal during the first 24 hours after ingestion in the current study might be related to an effect on opioid receptors, although any mechanistic conclusions cannot be based on the current clinical observations.

Taken together, our findings of serious (cardiac) side effects of ibogaine hamper the clinical utility of ibogaine in the treatment of substance use disorders. Given the limited evidence for effectiveness, the presumed clinical benefits may not outweigh the observed cardiac risks. If the side effects are dose related, an alternative to the single high dose ibogaine treatment regimen might be a repeated low dosing approach, which may produce a more favorable safety profile although accumulation of noribogaine (with a much longer  $t_{1/2}$ ) and subsequent QTc prolongation is a risk. Multiple dosing should only be performed under strict monitoring of QTc and based on CYP2D6 genotyping.

The current findings should be interpreted in the light of several limitations. First, we selected a specific group of subjects with OUD on OST with a wish for abstinence and a stable psychosocial situation, as reflected by their ASI scores. Furthermore, we excluded people with known liver or cardiac disease, which are both common among chronic illicit opioid users. The selection was made to limit the risk of increased exposure to ibogaine, cardiac events and psychosocial destabilization. The safety concerns presented here might thus be even more pertinent for the overall sample of patients with OUD or other addictions, especially those with cardiac pathology.

Secondly, only 14 patients were included in the current study. Although our study shows systematic effects on QTc time (primary outcome measure), the study is underpowered to detect rare, severe adverse events such as TdP, seizures or severe psychosis. As for TdP, our ECG monitoring was not continuous and short episodes may even have been missed. Furthermore, the provided dose of 10 mg/kg is in the lower bound of dosages in previous research settings, potentially contributing to an underestimation of ibogaine's toxic effects. Further studies using higher doses therefore seem superfluous based on the current findings.

Thirdly, all patients received metoclopramide to prevent nausea and vomiting. Both ibogaine and metoclopramide are metabolized by CYP2D6 and *in vitro* findings suggest limited competitive inhibition of metabolism. Yet, it cannot be fully ruled out that this may have had an effect on bioavailability of ibogaine (by limiting the first pass effect) and prolonging the half-life (by limiting metabolism) [60]. However, this interaction has been suggested to only occur

at very high ibogaine plasma levels of above 100uM [60]. Moreover, Metoclopramide is not listed in the Micromedex or upToDate-interaction checker as having a significant interaction with other, well known CYP2D6 substrates, such as tamoxifen and metoprolol [61].

Next, CredibleMeds lists metoclopramide as a QT-prolonging drug [62]. However, little quantitative studies are available. One study found 2 mg of metoclopramide i. v. to have a mild QTc-prolonging effect of about 1%, or 3-4 ms [65]. Another study showed metoclopramide to affect beat-to-beat fluctuations, which may explain some of the interval variation seen in our results [65,66]. As the QT-prolonging effects of metoclopramide are small, we do not deem this to be of major concern regarding the observed impressive QTc-prolongation. Yet, given the lack of a placebo control group, which we consider unethical in this population, any confounding effects of metoclopramide or opioid withdrawal itself cannot be fully ruled out.

Lastly, our washout period for opioid substitution treatment was eight days. No urine samples on drug testing were available during the inpatient study period. It can thus not be fully ruled out that any (residual) methadone was present at the start of ibogaine treatment. However, it is highly unlikely that (residual) methadone had a major contribution to the observed QT-prolongation after ibogaine ingestion. QTc was within normal range during methadone treatment (at screening) and in the IBM Micromedex no interactions of methadone or buprenorphine with ibogaine leading to higher plasma levels are reported, eg based on replacement of protein-binding by these drugs [61]. Taken together, possible drug-drug interactions with metoclopramide, methadone or buprenorphine on metabolism or QT-prolongation will not have a major effect on the massive QT-prolongation observed. If choosing an antiemetic or other concomitant medication with ibogaine treatment both QT-prolonging and CYP2D6 inhibiting effects should be ruled out, and an individual correction formula (QTcI) made in accordance with current FDA (or EMA) guidelines [67].

In our study we focused upon safety outcomes after ibogaine ingestion; however, we observed some promise in alleviating withdrawal [26]. Patients with OUD have limited treatment options, the mainstay being detoxification combined with psychosocial treatments or substitution programs [68]. Any potential beneficial effect of new treatment options are thus worth exploring in a research context, but the risks of ibogaine treatment observed here may not outweigh the potential benefits [51,68]. For future work with ibogaine we strongly advise treatments to take place under careful clinical monitoring to ensure patient safety. Research reports on efficacy of ibogaine should also report on these safety issues.

In conclusion, this open-label observational study in patients with OUD in opioid substitution treatment in



acute withdrawal showed that ibogaine induces a clinically relevant reversible QTc prolongation. Other observed transient adverse effects of ibogaine were bradycardia and severe ataxia. Based on the current findings, the use of ibogaine outside a well-controlled medical context (i.e. by underground providers) should be avoided due to its high cardiac risk profile.

### Clinical trial registration

This study has been registered under EUDRACT trial number 2014-000354-11.

### Declaration of interests

None.

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### Author contributions

**Thomas Knuijver:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; visualization. **Arnt Schellekens:** Conceptualization; data curation; investigation; methodology; resources; supervision. **Maarten Belgers:** Conceptualization; funding acquisition; investigation; methodology; resources. **Rogier Donders:** Data curation; formal analysis; visualization. **Toon Van Oosteren:** Conceptualization; funding acquisition. **Kees Kramers:** Conceptualization; investigation; methodology; resources; supervision. **Robbert Verkes:** Conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision.

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### Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S3** Suggested Bazett-Corrected QTc Values for Diagnosing QT Prolongation.

**Table S4** Ranges of normal serum levels of potassium, calcium and magnesium.

**Figure S5** Manual QTc measurements per subject. The individual measurements of the QTc using Bazett's formula on manual QT measurements during the first 24 hours after ibogaine ingestion.

**Figure S6** Average ataxia scores with standard error bars per item of the SARA. Measurements taken within 24 hours after ibogaine ingestion.