ICEERS
INTERNATIONAL CENTER FOR ETHNOBOTANICAL EDUCATION RESEARCH & SERVICE

Phase-II Clinical Trial on Preliminary Efficacy and Safety of Ibogaine in the Treatment of Opioid Dependence

ClinicalTrials.gov Identifier: NCT04003948

1. Introduction

Why this study is important

Over the past few years, several countries have been experiencing an "opioid epidemic" that has been linked, in part, to the misuse of prescription medications. In the United States, opioid overdoses increased by 54% in the largest cities of 16 states, reaching a daily rate of 130 lethal overdoses in the whole country.[1] Also in Canada drug overdoses have sky-rocketed.

With the opioid epidemic completely out of control, it is evident that effective treatments for opioid dependency are lacking. The crisis is presenting an opportunity for engaging in clinical research and in policy advocacy to address barriers to conducting research and to providing clinical treatment. Current trends indicate that there is growing interest in the potential of ibogaine for the treatment of drug dependency and that the demand for evidence to support its use is increasing.

In this context, ICEERS is committed to advancing clinical research into ibogaine, one of the alkaloids present in the Central West African shrub *Tabernanthe iboga*. This plant has been traditionally used by the Pygmies and Bwiti in Gabon, Cameroon and Congo for rites of passage and healing ceremonies. Over the past few decades, extensive anecdotal evidence from the medical subculture and observational research illustrates that ibogaine is capable of blocking or seriously reducing opioid dependency and alleviating craving from opioids and other drugs for up to several months. However, there has only been one randomized, placebo-controlled clinical trial[2] in which ibogaine was administered (Glue et al. 2015) to study the pharmacological effects and safety in humans, where researchers provided very small doses of ibogaine (20 mg). No other phase 1 clinical trials (in healthy humans) have been conducted as of yet.

Within the published literature, concerns have been noted regarding the use of high doses of ibogaine and some suggest lower doses need to be explored in terms of safety and efficacy. For example, Schep et al.[3] (2016) suggested that clinical trials should start with 1 mg/kg of ibogaine, slowly increasing this dose in order to determine what dose is optimal. These researchers noted that high doses of ibogaine, commonly used in ibogaine clinics, must be avoided due to the risk of severe adverse reactions. Mash et al.[4] (2018) noted that Ibogaine decreases drug craving and improves depressive symptoms when administered in a range of 500–1000 mg.

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[1] National Institute on Drug Abuse (2019). Opioid overdose crisis. Retrieved from: https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis

[2] Glue, P., Winter, H., Garbe, K., Jakobi, H., Lyudin, A., Lenagh-Glue, Z., & Hung, C.T. (2015). Influence of CYP2D6 activity on the pharmacokinetics and pharmacodynamics of a single 20 mg dose of ibogaine in healthy volunteers. *The Journal of Clinical Pharmacology, 55*(6), 680-687

[3] Schep, L.J., Slaughter, R.J., Galea. S., & Newcombe, D. (2016). Ibogaine for treating drug dependence. What is a safe dose? *Drug and Alcohol Dependence, 166*, 1-5.

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

In order to fill in this important research gap, ICEERS has partnered with Hospital Sant Joan de Reus, in Catalonia (Spain), a hospital recognized for its world-class drug dependency treatment unit. Through this collaboration, we will conduct a Phase-II Randomized Control Trial with 20 participants, testing a novel ibogaine treatment protocol with ascending low doses of ibogaine to support patients to taper off of methadone.

Why methadone?

Methadone is a very long-acting opiate that despite its benefits as an opioid substitution therapy, can result in significant withdrawal symptoms in patients looking to wean from it. Methadone is very difficult to detox from, so if the protocol we will be employing is successful in supporting participants to detox from methadone using ibogaine, this will provide evidence to support its application with shorter acting opioids, such as heroin.

Whereas prescription medications like fentanyl or tramadol and illegal drugs, such as heroin, have played a role in the current opioid crisis, opioids like methadone are being also misused, causing drug-dependence and death. In the US, the number of prescription methadone overdoses increased by 300% between 1999 and 2014, and between 1999 and 2006 the number of deaths related to the use of methadone increased by 600%, although this rate decreased by 39% between 2007 and 2014.[5] In European countries, such as Croatia, Denmark, France, and Ireland, the number of deaths associated with methadone is larger than those due to heroin.[6]

In the Spanish context, the number of people in Methadone Maintenance Programs (MMP) was 58,291 in 2016.[7] Due to the increased number of opiate users in these programs, as well as the increased surveillance of HIV patients in recent decades, a rising number of people are seeking treatments for methadone cessation. The common method of detoxifying from methadone involves gradually reducing the dose, however in many cases the patient does not tolerate this well, which may result in them requesting a dose increase due to anxiety and the appearance of Opiate Withdrawal Syndrome (OWS). Due to this challenge, a patient, once stabilized at a fixed dose, will often need to take methadone for years or for life.

While Spain is not currently experiencing an overdose crisis, as in the US and Canada, following the heroin epidemic in this country in the 1980s, there are many people who remain dependent on methadone. Many have been dependent for 15 years or more, and a number of them are living stable lives (have work, family, housing, etc.) and are experiencing relatively good health. These are the types of patients that will be recruited at Hospital Sant Joan de Reus.

The prestige of the Hospital's drug dependency unit, the relatively low-risk population they are working with in the MMP and use of a novel slower treatment protocol with lower ascending doses offers the ideal context for a first clinical trial with ibogaine that will give new insight into safety as well as efficacy of low to mid-range dosing protocols.

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[5] Faul, M., Bohm, M., Alexander, C. (2017). Methadone prescribing and overdose and the association with Medicaid preferred drug list policies-United States, 2007–2014. MMWR Morb Mortal Wkly Rep, 66, 320–323.

[6] Observatorio Europeo de las Drogas y las Toxicomanías. 2017. Informe Europeo sobre Drogas: Tendencias y novedades. https://goo.gl/U5Z9z1

[7] Observatorio Español de La Droga y las Toxicomanías. INFORME 2016. Situación y tendencias de los problemas de drogas en España. Plan Nacional Sobre Drogas. https://bit.ly/2HoKDvY

2.Methods

Sample

Twenty patients will be recruited through a Methadone Maintenance Program located at the Drug Dependence Services of Sant Joan Hospital, Reus, Spain. Subjects will be selected according to extensive inclusion/exclusion criteria (see Appendix A), which includes a previous unsuccessful attempt to terminate their methadone use.

Treatment

Based on a previously published case-report[8], we will use a standardized protocol consisting in progressively reducing the methadone dose used, while administering low to mid doses of ibogaine in order to treat opiate withdrawal symptoms.

Patients will be split into two randomized groups. Group 1 (n=10) will receive six doses of ibogaine (100 mg each), while Group 2 (n=10) will receive ascending doses of ibogaine, increasing by 100 mg per dose (100-200-300-400-500-600 mg). Ibogaine doses will be administered in a double-blind fashion.

Measures

The main variable for measuring efficacy will be the methadone dose reduction ratio. This measure will be determined by calculating the difference of methadone dose between the start of the study and the dose required at the end of the study.

Psychometric questionnaires assessing psychological variables (Hospital, Anxiety and Depression Scale) and satisfaction with treatment (SATMED-Q questionnaire) will be also administered. The days when ibogaine is administered, urine drug test, blood

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[8] Wilkins, C., dos Santos, R.G., Solá, J., Aixalà, M., Cura, P.,… & Bouso, J.C. (2017). Detoxification from methadone using low, repeated, and increasing doses of ibogaine: A case report. Journal of Psychedelic Studies, 1(1), 29-34.

'Sant Joan' Hospital, Reus, Spain.

pressure, heart rate and EKG will be recorded. The Brief Psychiatry Rating Scale will be used to detect psychiatric symptoms during treatment with ibogaine, and the UKU scale will be used to assess potential adverse events.

At two and six months following the end of the study, patients will be asked about their use of methadone or other opiates and the dose used (if any).

Procedure

Patients will receive a methadone dose 24 hours prior to ibogaine administration. Following ibogaine administration (9:00 am), patients will stay in the hospital for 24 hours. In the first 12 hours following ibogaine administration, EKG tests will be conducted hourly. When symptoms of OWS appear, patients will receive methadone (half the size of the previous dose) over the course of three to five days. During this time, methadone use will be interrupted with the same procedure, and patients will be provided with another dose of ibogaine and reducing the methadone dose by a half (see Appendix B).

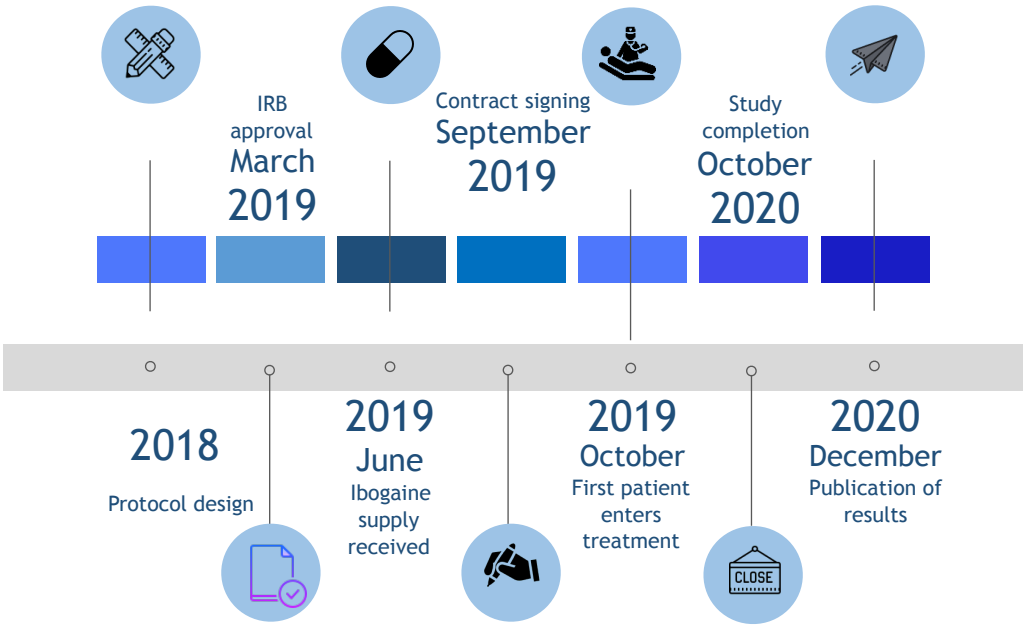
Our hypothesis is that after six doses of ibogaine the symptoms of OWS will subside and that patients will be able to terminate their use of methadone.

Statistical analyses

Data will be obtained through an electronic Data Collection Logbook specifically developed for this study by the Catalan Institute of Pharmacology.

Comparisons between basal and final data regarding dose of methadone used and severity of OWS symptoms will be conducted. Dropouts per group will be registered. All adverse events will be recorded by appearance, frequency, and severity.

3.Timeline



In March 2019, we obtained the Research Ethics Board (IRB) approval for the study (see Appendix C).

In June 2019, we received the ibogaine (27 grams) needed to conduct the study.

Meanwhile we are fundraising for the study and hope to be able to complete fundraising by October of 2019, when (given that funding is secured) the trial can begin.

4.Team

Principal Investigator: José Carlos Bouso, PhD. **Current position and expertise**: Scientific Director at ICEERS. PhD in Pharmacology. Dr. Bouso has decades of experience in conducting clinical trials with psychedelic drugs at various Spanish institutions and in collaboration with research teams in other countries.

Principal Investigator: Tre Borràs, MD. **Current position and expertise**: Head of the Drug Dependence Services at Sant Joan Hospital. Medical Doctor and Psychiatrist. Dr. Borràs has decades of clinical experience in the field of drug dependence and harm reduction strategies.

Coordinator: Genís Oña, MSc, PhD(c). **Current position and expertise**: Research Coordinator at ICEERS. MSc in Pharmacology and PhD candidate in Health, Psychology and Psychiatry. Genís has experience in clinical trials involving the administration of psychedelic and epigenetic drugs.

Collaborating Researcher: Antoni Llort, PhD. **Current position and expertise**: Anthropologist of the Drug Dependence Services of Sant Joan Hospital. PhD in Medical Anthropology. Dr. Llort has experience in working with people with drug dependence and in the field of harm reduction.

Collaborating Researcher:: Maria Teresa Colomina, MD, PhD. **Current position and expertise**: Full Professor of Psychobiology at Rovira i Virgili University, Tarragona, Spain. Dr. Colomina has decades of experience in neuroscience research.

Collaborating Researcher: Eduardo Beas, MSc. **Current position and expertise**: Nurse within the Drug Dependence Services at Sant Joan Hospital.

Collaborating Researcher: Rafael Guimarães dos Santos, PhD. **Current position and expertise**: PhD in Pharmacology. Postdoctoral Fellow in the Department of Neurosciences and Behavior at Ribeirão Preto Medical School.

Collaborating Researcher: Jaime Eduardo Cecilio Hallak, MD, PhD. **Current position and expertise**: Psychiatrist and expert in schizophrenia and psychoactive drugs. Associate Professor at the Ribeirão Preto Medical School of the University of São Paulo.

Collaborating Researcher: Miguel Ángel Alcázar Córcoles, PhD. **Current position and expertise**: Professor of Psychology at Autonomous University of Madrid, Spain.

Collaborating Researcher: Lourdes Rofes Ponce, MD. **Current position and expertise**: Associate Professor at Rovira i Virgili University, Tarragona, Spain.

Collaborating Researcher: Eulàlia Sabater Puig, MD. **Current position and expertise**: Medical Doctor in Drug Dependence Services at Sant Joan Hospital.

Collaborating Researcher: Neus Vilalta Ollé, MD. **Current position and expertise**: Medical Doctor at the Drug Dependence Services at Sant Joan Hospital.

Collaborating Researcher: Andrés Ferreira Gilabert, MSc. C**urrent position and expertise**: Nurse of the Drug Dependence Services at Sant Joan Hospital.

Collaborating Researcher: Josep Maria Alegret, MD. **Current position and expertise**: Professor of Cardiology at Rovira i Virgili University, Tarragona, Spain. Vice-president of the Spanish Society of Cardiology.

Collaborating Researcher: Carmen Ligero, MD. **Current position and expertise**: Professor of Cardiology at the Rovira i Virgili University, Tarragona, Spain.

5.Budget

Specification	Participant	Days / Unit	Price / Unit	Total
Study design				**€ 4.832,00**
Protocol design				€ 3.332,00
Translation costs Spanish - English				€ 1.500,00
Development				**€ 23.070,71**
Research Ethics Committee fee				€ 2.044,50
Purchase Ibogaine	20	1,69	€ 150,00	€ 5.070,00
Database development and hosting				€ 6.000,00
Participant recruitment	20	2	€ 156,024	€ 6.240,96
Insurance Clinical Trial				€ 3.715,25
ICEERS Staff				**€ 55.800,00**
Supervision				€ 21.600,00
Ph.D. candidate researcher				€ 24.000,00
Research Assistant				€ 9.000,00
Travel		30	€ 40,00	€ 1.200,00
Hospital costs				**€ 75.522,82**
Nurse				€ 9.146,56
M.D.				€ 17.467,46
Reus General Supervision & Coordination	20	6	€ 174,24	€ 20.908,80
Reus Hospitalization	20	6	€ 150,00	€ 18.000,00
Cardiology Department Services				€ 10.000,00
Laboratory analysis				**€ 14.600,00**
Biochemical	20	2	€ 86,00	€ 3.440,00
Hematological	20	2	€ 117,00	€ 4.680,00
Urine analysis	20	2	€ 37,00	€ 1.480,00
Serology	20	2	€ 75,00	€ 3.000,00

Extra analysis (rejected study volunteers)	10	1	€ 200,00	€ 2.000,00
Urine PH acetone				€ 68,00
Drug tests				€ 200,00
Alcohol meter				€ 105,00
Nicotine chewingum				€ 65,00
Tablet				€ 139,00
ECG				€ 1.500,00
Publication & Promotion				**€ 5.200,00**
Translation publications				€ 1.200,00
Publication costs Journals				€ 4.000,00
Subtotal				**€ 179.025,53**
Total (incl. overhead)				**€ 215.657,56**

total cost trial: €215,658 - $239,380 - £182,202

Appendix A

Study Inclusion & Exclusion Criteria

Inclusion criteria:

1. Between 18 and 60 years of age.
2. Body weight in normal range (BMI of 19-27).
3. Clinical history and physical examination in normal ranges (according to hospital criteria).
4. No presence of organic diseases, based on clinical examination and laboratory tests.
5. Normal EKG values (PR < 240 ms, QRS < 110 ms, and QTc < 430 ms in men and QTc < 450 in women. Heart rate > 50, and normal ST wave.
6. Laboratory tests (blood count, biochemical and urine analysis) in normal values, according to hospital reference levels.
7. Blood pressure, Heart Rate, Respiratory Rate, Body temperature and EKG in normal ranges, according to hospital reference levels.
8. No participation in other clinical trials during the previous two months prior to the start of the study.
9. Consent to participate in the study, including written consent.

Exclusion criteria:

1. Allergy or hypersensitivities to other drugs.
2. Use of prescription or drugs of abuse that could produce contraindications in the 15 days prior to the start of the study.
3. Intake of any food, supplement or plant mixture (infusion, extract or capsules) that could affect the CYP2D6 enzyme in 7 days before the start of the study.
4. Positive test for Hepatitis B, Hepatitis C, or HIV.
5. History or present evidence of cardiac, respiratory, renal, hepatic, endocrine, gastrointestinal, hematologic, neurologic or chronic disease.
6. One or more psychiatric disorders registered by MINI interview, such as psychosis, bipolar disorder, or dissociative disorders. High score obtained in the screening test for assessing the risk of developing psychotic/bipolar disorders will be considered.
7. Current risk of suicide.
8. Major surgery 6 months prior to the study.
9. Positive result in urine drug screening for ethanol, cocaine, amphetamines, or benzodiazepines.
10. Subjects who do not understand the nature and consequences of the study or some of the methods used.
11. Abnormalities in the EKG (PR > 240 ms, QRS > 110 ms, or QTc > 430 ms in men and QTc > 450 ms in women), bradycardia (HR < 50 bpm) or minor but clinically significant changes in ST wave.
12. Positive result in pregnancy test, in case of women.
13. Not understanding the informed consent.

Appendix B

Study Diagram

GROUP 1 n=10	GROUP 2 n=10
Methadone interruption	Methadone interruption
↓	↓
Ibogaine session (100mg)	Ibogaine session (100mg)
↓	↓
Methadone (1/2 basal dose)	Methadone (1/2 basal dose)
↓	↓
Ibogaine session (100mg)	Ibogaine session (200mg)
↓	↓
Methadone (1/2 last dose)	Methadone (1/2 last dose)
↓	↓
Ibogaine session (100mg)	Ibogaine session (300mg)
↓	↓
Methadone (1/2 last dose)	Methadone (1/2 last dose)
↓	↓
Ibogaine session (100mg)	Ibogaine session (400mg)
↓	↓
Methadone (1/2 last dose)	Methadone (1/2 last dose)
↓	↓
Ibogaine session (100mg)	Ibogaine session (500mg)
↓	↓
Methadone (1/2 last dose)	Methadone (1/2 last dose)
↓	↓
Ibogaine session (100mg)	Ibogaine session (600mg)

Appendix C

IRB Approval Notification

IISPV
INSTITUT D'INVESTIGACIÓ SANITÀRIA PERE VIRGILI

DE: SRA. ELISABET GALVE AIXA - **SECRETARIA DEL CEIm**
A: Dra. Tre Borràs Cabacés - **H. Universitari Sant Joan de Reus**

Assumpte: IBO-METAD-001
Ref. CEIm: 038/2019

Benvolguda,

Li comunico que amb data 28/02/2019, el CEIm ha avaluat l'estudio titulat **"Estudio piloto de eficacia preliminar y seguridad de la ibogaína en el tratamiento de la deshabituación de la metadona"**

El dictamen del CEIm respecte a l'anomenat projecte en el format actual és **favorable.**

Cordialment,

78582502N ELISABET GALVE (R: G43814045)

Firmado digitalmente por 78582502N ELISABET GALVE (R: G43814045)
Fecha: 2019.03.18 13:39:21 +01'00'

Sra. Elisabet Galve Aixa
Secretaria Comitè Ètic d'Investigació amb medicaments
Institut d'Investigació Sanitària Pere Virgili

Registre de Fundacions de la Generalitat de Catalunya, núm. inscripció 1.206, NIF G43814045