Observational study of the long-term efficacy of ibogaine-assisted therapy in participants with opioid addiction

STUDY PROTOCOL

Purpose and Objectives

This research is an investigator-sponsored observational study investigating the effectiveness of ibogaine therapy in treating people with drug dependence. The purpose of the study is to determine whether individuals suffering from drug dependence (and specifically forms of opioid dependence) will benefit from treatment with ibogaine, and whether the treatment effect will last for a period of over 12 months.

Primary objective:

- to determine the effectiveness of ibogaine-assisted therapy in elimination or reduction of drug usage, craving and withdrawal, and in improving other aspects of life as measured by the Addiction Severity Index Lite (ASI-Lite) composite scores over a period of 12 months following the therapy.

Secondary objectives:

- to assess the severity of withdrawal symptoms following ibogaine treatment as measured by the Subjective Opioid Withdrawal Scale (SOWS), and to assess whether ibogaine treatment reduces the presence of such symptoms;
- to determine the effectiveness of ibogaine-assisted therapy in producing relief from self-reported depression using the Beck Depression Inventory-II (BDI-II);
- to investigate the relationship between Addiction Severity Index composite scores after ibogaine treatment and the subjective effects of the treatment and alteration of consciousness as measured by the States of Consciousness Questionnaire (SCQ)
- to assess the participant's status and well-being using the investigator ratings
- to determine whether the effects of the therapy have met the participants' expectations set before the treatment
- to verify drug use or abstinence using data obtained from urine drug screening

Sample population

People suffering from opioid drug dependence and having independently undergone ibogaine treatment will be enrolled in the study. People who sought but were denied the ibogaine treatment for medical or other reasons but have consequently undergone an at-home detox treatment will comprise a control group. Both groups will be assessed at the same time points using the same measures, unless otherwise specified.

This study has been approved by the Multi-Region Ethics Committee
ref # MEC/11/11/095

A minimum of 20 and a maximum of 30 participants will be enrolled in the study with about five participants constituting a control group. The total number of subjects in the study is based upon examination of how many people may reasonably be enrolled over an 18-month enrollment period.

No participants who withdraw from or drop out of the study will be replaced.

Inclusion criteria:

- A minimum of 18 years old
- Able to communicate in English
- Have already received ibogaine treatment or at-home detox treatment for a primary dependence on opioids
- Able to provide informed consent on own behalf
- Prepared to provide contact information of one or two close affiliates whom researcher may contact for corroborating data
- Must possess a reliable means of contact with the investigators, either through telephone, electronic mail or other electronic means (e.g. Skype)
- Committed to regular contact with investigators for 12-month period after the treatment

Exclusion criteria

- Persons who underwent ibogaine-assisted therapy for any reason other than opioid drug dependence
- Persons who received ibogaine treatment in the past for any reason.
- Persons who, in the opinion of the investigators, have any personal, health, situational, social or other problem that would prevent them from being able to fully comply with the requirements of this study.
- Participants who cannot give adequate informed consent.

Study duration

The study will take 12 months to complete for each participant.

Outcome measures

The Addiction Severity Index Lite (ASI-Lite) is the primary outcome measure to be used in the study. The ASI-Lite will be used to measure subjects' substance use and other associated behaviors and lifestyle (McLellan et al., 1992). It will be administered before the ibogaine administration and afterward at month 1, 3, 6, 9 and 12 follow-ups. The ASI is an assessment instrument designed to be administered as a semi-structured interview. A composite score of addiction severity can be calculated from the participants' responses during this interview. This score will be our primary measure of this variable. Other sub-scores include employment status, medical status, psychiatric status, family/social status, alcohol use, and legal status.

The secondary outcome measures include the States of Consciousness Questionnaire (SCQ), used to gauge the alterations of consciousness and mystical experiences during the ibogaine treatment (Griffith et al. 2006); the

Subjective Opiate Withdrawal Scale (SOWS), a scale for grading the intensity of opioid withdrawal symptoms before and after the treatment (Handelsman et al., 1987); and the Beck Depression Inventory (BDI-II) used to measure baseline depressive symptoms prior to treatment and to track changes after the treatment (Beck et al., 1996). In addition to these published instruments, several other secondary outcome measures, described below, will be used in the study.

The Beck Depression Inventory-II (BDI-II) will be administered before the treatment, again at the post-treatment visit and at month 1, 3, 6, 9 and 12 follow-up visits. The SOWS will be administered before the ibogaine treatment and then once again following ibogaine treatment while the participant is still in residence at the clinic. The SCQ will be administered just once, at the post-treatment visit. Ibogaine treatment subjects will provide a brief description of their experience during treatment.

Control group subjects will not be asked to provide this brief description, or to fill out the SCQ.

The Investigator Ratings of the Subject Status and Well-being will be assigned by the investigator based on the responses provided by the subjects in ASI-Lite (at baseline and month 1, 3, 6, 9, 12 follow-ups) or a subset of ASI-Lite questionnaire (at the rest of the visits). Investigator ratings will be compared with ASI-Lite, BDI-II and SOWS scores.

In addition to these questionnaires and interviews, subjects will undergo two random urine tests and one fixed urine test in the end of the study that will be used as one more measure to determine drug use or abstinence. Urine drug testing can detect drug usage within 1 to 5 days of drug usage. Drug testing will be conducted at a local drug testing service. Urinary drug screens will be analysed by a local laboratory facility.

Before the treatment the subjects will be asked about their expectations from the treatment, and after the treatment the subjects will be asked whether the treatment has met their expectations.

Visit summary

There will be a total of 14 visits or telephone interviews (including one intake interview and one post-treatment survey).

- Intake visit, post-treatment visit and 12 follow-up telephone calls or face-to-face visits (5 to administer outcome measures and 7 short follow-up phone calls) that will take approximately 15 hours total over 12 months.
- Three urine drug screens – two random and one at the final visit – will be done at follow-up evaluations.

Visit descriptions

- Recruitment and informed consent
    - PI communicates with the ibogaine treatment provider(s) to identify potential participants.

  - Ibogaine provider will contact each consecutive patient in their program to see if they are interested to participate.
  - Potential participants will receive consent materials. Only those that sign the informed consent can participate in the study. Informed consent should be signed prior to Visit 1.
  - Subjects are officially enrolled in the study after they have undergone the treatment (ibogaine or at-home detox) but prior to Visit 2.

- Visit 1 (intake; 2 ½ hours; pre-treatment, from 2 weeks before the treatment up to the day of the treatment)
  - Questions about self, drug use, review of previous addiction treatments
  - Complete Beck Depression Inventory-II (BDI-II); Addiction Severity Index Lite (ASI-Lite)
  - Subjective Opiate Withdrawal Scale (SOWS) is administered by the treatment provider at commencement of treatment
  - Investigator Ratings of the Subject's Status and Well-being
  - Subjects' expectations from the treatment are collected
  - Provide researcher with contact details of two affiliates for data corroboration

- Visit 2 (2 hours; 3-5 days post-treatment)
  - Review and make sure that the inclusion and exclusion criteria are still met
  - Subject enrollment
  - Complete States of Consciousness Questionnaire (for ibogaine group only); SOWS; BDI-II;
  - Written description of ibogaine 'experience'(for ibogaine group only)

- Visits 3-14 (1½ hours if ASI-Lite/BDI-II administered, or 15 minutes; 1-12 months post-treatment)
  - Monthly telephone or in-person follow-up visits with the researcher
  - Drug usage data collected
  - Complete BDI-II and ASI-Lite at Visits 3, 5, 8, 11 and 14 (corresponding to 1, 3, 6, 9 and 12 month follow-ups respectively)
  - Investigator rating of subjects' status and well-being at Visits 3, 5, 8, 11 and 14
  - Subjects are asked if their expectations of the treatment were met
  - Three urine drug tests: two scheduled randomly and one - at the final follow-up visit (drug tests should be done from 48 hours before to 24 hours after the administration of ASI- Lite)
  - Data verification with named affiliates

Risks of study participation

There are no foreseeable physical risks to taking part in this observational study.

Study participants may experience psychological discomfort or distress from repeated questions concerning their drug dependence and effects of their addictions on their lives. Responding to measures of the effects of substance addiction, presence of withdrawal symptoms and depression are an essential part of this study and cannot be avoided. The researcher will be available before, during, or after the interviewing process to talk to participants about their concerns, and to facilitate referrals to consultants, other healthcare professionals, or therapists if such a need should arise. All participants will be encouraged to contact the researcher should they need additional support or referral after the interviews.

Potential benefits of study participation

It is not expected that individual participants will gain direct benefits from study participation. If this observational study detects enduring benefits from ibogaine treatment, then findings might assist in developing ibogaine as a treatment to help people with addictions to opioids or other substances.

Adverse effects

Due to the observational nature of the research, it is unlikely that research participants will experience adverse effects as a result of study procedures. All participants will be encouraged to contact the researcher should they experience any unpleasant or disturbing feelings from the study interviews.

Any adverse effects that happen during the study as a result of the ibogaine treatment (and <u>not</u> as a result of participation in this research) will be collected as a part of the participants' medical history.

Data analysis

There are no published controlled or systematic studies of ibogaine treatment for opioid addiction that can be used to estimate statistical power for this study. The study is observational and exploratory. The investigators will compute descriptive statistics for all outcome measures, including ASI-Lite composite scores for all domains, BDI-II, SOWS and SCQ scores, investigator ratings of the participant status and wellbeing, and participant expectations of the treatment. Participant expectations concerning ibogaine or conventional rehabilitative treatment will be collected at the start of the study and at 1, 3, 6, 9 and 12 months post-study. They will collect information on the identity and amount of drug used during each point of contact.

ASI-Lite and BDI-II scores will be compared at baseline and 1, 3, 6, 9 and 12 months post-treatment in both the treatment and the control group respectively. Ibogaine and control participant ASI-Lite scores over these six points in time will be analyzed with a repeated measures analysis of variance with treatment (ibogaine or control) as a between-participants factor and time of measurement (baseline, 1, 3, 6, 9 or 12 months post-treatment) as a repeated measure. The investigator will compute the difference between each baseline ASI-Lite domain scores and ASI-Lite domain score during the

point of final response, either 1, 3, 6, 9 or 12 months post-treatment. An independent t-test will compare each difference score in ibogaine and control participants. ASI-Lite domain scores and BDI-II scores of ibogaine and control participants will also be compared at three months post-treatment.

SOWS scores will be collected and compared at baseline and post-treatment in ibogaine and control participants. SQC scores will be collected post-treatment for treatment group only, and each SCQ scale score will be correlated with ASI-Lite domain scores at 1, 3, 6, 9 and 12 months post-treatment to see whether there is an association between one or more experienced alterations in consciousness and changes in ASI scale scores.

The investigator will rate participant on their state of mind and problem areas related to substance use disorders. The investigator will collect these ratings as Investigator Ratings of the Subject Status and Well-being at month 1, 3, 6, 9 and 12 post-treatment, and descriptive statistics will be computed for such ratings.

Urine test results will be collected to determine presence and degree of drug use and positive results for one or more substance will be noted. Percentage of participant with positive results for each drug tested will be computed for one, two or three urinary tests. The investigators will explore any possible relationships between urinary drug screen results and ASI Lite, BDI-II or Investigator Ratings of the Subject Status and Well-being at one or more time points occurring after the drug screen.

Presence of drug use reported by ibogaine and control participants at each month and, if present, number of occurrences of use and type of substances used will be compared at each month. Self-reported drug use in ibogaine and controls participants at baseline and after treatment will be compared, including comparisons at selected points in time and at final contact.

Participant expectations concerning treatment success will be collected. Descriptive statistics will be computed for ibogaine and control participants. Expectations about treatment success will be compared with ASI-Lite domain scores, BDI-II score and SOWS score in ibogaine participants, control participants and both samples combined.

If at least one measure is completed by a participant during a follow up call or visit, then any missing data will be addressed by the use of the sample average.

Subjects lost to follow-up will be considered relapsed. This will be done for ibogaine treatment and control participants.

Confidentiality

Potential participants' details will only be provided to the researcher once they have expressed interest in the study. All hard copies will be stored in locked filing cabinets in a locked office. All digital (quantitative) data will be

anonymised and password protected. Following storage of digital data, computer systems will be purged of originals. After the study is completed, digital files will be stored on appropriate media (CD) in a locked filing cabinet in a locked building and on a password-protected server.

Access to data will be restricted to the researchers and the personnel monitoring the study. Data used for analysis will not contain participant names or addresses, and will list each participant by the participant identification number or participant only.

Cost and Compensation for Participation in the Study

There will be no costs for the participants associated with participation in the study.

Participants will be compensated with Warehouse vouchers to the value of $10 for each completed phone interview or in-person follow-up, up to a maximum value of $120 for all 12 follow-up phone interviews. Participants will also be compensated for any costs associated with urine drug testing.

References

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Griffiths, R.R., et al., *Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance.* Psychopharmacology (Berl), 2006. **187**(3): p. 268-83; discussion 284-92.

Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987) *Two New Rating Scales for Opioid Withdrawal*. American Journal of Alcohol Abuse, 1987. **13**: p. 293-308.

McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., & Argeriou, M. *The Fifth Edition of the Addiction Severity Index.* Journal of Substance Abuse Treatment, 1992. **9**: p. 199-213.