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Letter to Editor

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Homeopathy on the integrative care of cocaine-related disorders (Cocacrack-3 Study)

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Abstract

Background: An effective pharmacotherapy for cocaine use disorder is still needed. Previous results showed a clinically significant difference between the effects of fifty- millesimal homeopathic potencies of *Opium and Erythroxylum coca* compared to placebo in reducing cocaine/crack use. Due to the high dropout rate and risk of bias, further research is required, specifically focusing on strategies to increase patient retention. To further investigate the fifty-millesimal homeopathic potencies of *Opium* and *Erythroxylum coca* on the integrative care of cocaine-related disorders, we had elaborated a study protocol - Cocacrack-3 study protocol, benefiting from the strengths of primary health care to improve treatment adhesion. However, due to the Covid-19 pandemic, the primary focus of primary care shifted to monitoring individuals in home isolation and addressing other health needs that had previously been suspended as the death rate began to decline. Due to these circumstances, we were required to revise the study protocol. We will conduct Cocacrack-3 Study in specialized facilities, using a network support and telemedicine follow-up approach to enhance adherence.

Objectives: 1) To assess the effectiveness and safety of a sequential administration of homeopathic fifty-millesimal potencies (LM2, LM4, and LM6) of *Opium* and *Erythroxylum coca* in reducing cocaine use among participants. 2) To evaluate the effectiveness of telemedicine and a support network, whether family or otherwise, in enhancing treatment retention rates among individuals with crack cocaine use disorder.

Setting: Psychosocial Attention Centers for Alcohol and other Drugs (CAPS-AD) located in Florianópolis (both on the island and mainland), São José, and Palhoça, cities part of the greater Florianópolis area in the state of Santa Catarina, Brazil. The study center is the Research Laboratory for the History of Nursing and Health Knowledge at the Federal University of Santa Catarina.

Methods design: A randomized, placebo-controlled, double-blind, crossover clinical trial, with six weeks duration per participant.

Hypothesis: H0: There is no clinically significant difference between the effects of fifty-millesimal homeopathic potencies of *Opium* and *Erythroxylum coca* compared to placebo in reducing cocaine use (null hypothesis). H1: There is a clinically significant difference between the effects of fifty-millesimal homeopathic potencies of *Opium* and *Erythroxylum coca* compared to placebo in reducing cocaine use (alternative hypothesis).

Inclusion criteria: men and women between the ages of 18 and 70 who are patients at a participating CAPS-AD, receiving treatment for cocaine use disorder, and having a support network, whether it be family or otherwise.

Exclusion criteria: remission of cocaine use lasting more than two weeks and inability or unavailability to participate in research in a virtual environment, even with the support of family or others.

Sample size and crossover sequences: 120 participants will be enrolled and randomized in a 1:1 ratio to one of two sequences - verum for three weeks followed by placebo for three weeks, or vice versa. Randomization, allocation concealment, and blinding remain unchanged from the original protocol. Interventions: the verum sequence will consist of LM2, LM4, and LM6 homeopathic potencies of *Opium* and *Erythroxylum coca*, used for one week each in ascending order. *Opium* will be given in a sucrose globule dissolved on the tongue in the morning, while *Erythroxylum coca* will be administered in a sucrose globule dissolved on the tongue in the afternoon and evening, plus an additional globule repeated every hour for six hours in the event of craving. The placebo treatment will consist of sucrose globules administered in the same dose. Participation in Cocacrack-3 Study will not interfere with the CAPS-AD treatment routine, and all participants, clinical investigators, CAPS-AD teams, monitors, and statisticians will remain blinded to the study treatments until data analysis is complete.

Primary measure: The percentage of days of cocaine use at week 3, as recorded through telemedicine using a timeline follow-back methodology.

Secondary measures (recorded weekly by telemedicine): The percentage of the reported number of cocaine-using days during participation in the study; change in participant's cocaine craving measured through the Cocaine Craving Questionnaire scale - brief; participant's progression assessed by the Clinical Global Impressions Scale; use of concomitant medications; occurrence of adverse events; assessment of treatment adherence by the Measure Treatment Adherence scale ; evaluation of participant retention by the number of participants at weeks 3 and 6; evaluation of study medication use by vial weight at weeks 3 and 6. The effectiveness measures will be assessed by psychiatrists affiliated with the Federal University of Ceará through telemedicine consultations.

Ethical approval and registration: Cocacrack-3 Study protocol was approved by the Ethics Committee on Human Research at the Federal University of Santa Catarina. Due to the shift in study implementation from Primary Care, we revised the title to "Homeopathy on Integrative Care for Cocaine-Related Disorders (Cocacrack-3 Study). After updating the study registry (UMIN Clinical Trials Registry - ID: UMIN000040161), we have scheduled appointments with the study population (patients and families) and will commence recruitment in early June 2023.

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Dear Editors,

We are writing to inform you of changes to the study protocol for our clinical trial entitled "Homeopathy for Cocaine-Related Disorders: Implementing a Study Protocol in Primary Care (Cocacrack-3 Study Protocol)." We published the protocol for this study in Journal of Addiction Science on June 20, 2020 [1], with plans to include the first participant in September 2020.

Unfortunately, we have encountered an unexpected obstacle in the form of the Covid-19 pandemic. On August 26, 2020, the municipality of Itajaí (Santa Catarina, Brazil), where the study was to be conducted, suspended all elective activities in Primary Care [2]. One year later, Primary Health Care was still inaccessible.

We had held meetings for several months with the Family Health Care teams who were supposed to participate in the study, with the invaluable support of the Health Secretariat and the Mayor of Itajaí. However, due to the pandemic, the primary focus of primary care shifted to monitoring individuals in home isolation and addressing other health needs that had previously been suspended as the death rate began to decline.

As a result of these changes, combined with the turnover in health team personnel, the training we had conducted became lost. Additionally, the delay in obtaining a definition of what would happen in Primary Care led to the expiration of the Benzoylecgonine urine tests donated by the municipal laboratory of Itajaí. Due to these circumstances, we were required to revise the study protocol.

Cocacrack-3 Study aims to explore the following objectives: 1) To assess the effectiveness and safety of a sequential administration of homeopathic fifty-millesimal potencies (LM2, LM4, and LM6) of *Opium* and *Erythroxylum coca* in reducing cocaine use among participants. 2) To evaluate the effectiveness of telemedicine and a support network, whether family or otherwise in enhancing treatment retention rates among individuals with crack cocaine use disorder.

The hypotheses to be investigated remain unchanged as follows:

H0: There is no clinically significant difference between the effects of fifty-millesimal homeopathic potencies of *Opium* and *Erythroxylum coca* compared to placebo in reducing cocaine use (null hypothesis).

H1: There is a clinically significant difference between the effects of fifty-millesimal homeopathic potencies of *Opium* and *Erythroxylum coca* compared to placebo in reducing cocaine use (alternative hypothesis).

The study design remains a randomized, placebo-controlled, double-blind, crossover clinical trial, but with a reduced duration of six weeks per participant instead of twelve weeks. This modification was necessary because we were no longer able to rely on the Primary Care home visits strategy, which we had intended to use to improve participant retention. Instead, we implemented a network support and telemedicine follow-up approach to enhance adherence to the study procedures. We leveraged the benefits of telemedicine, a technology that has been enhanced and regulated in Brazil during the pandemic [3 4].

We will conduct this study in specialized facilities, specifically the Psychosocial Attention Centers for Alcohol and Other Drugs (CAPS-AD) located in Florianópolis (both on the island and mainland), São José, and Palhoça. These cities are all part of the greater Florianópolis area in the state of Santa Catarina, Brazil. The Research Laboratory for the History of Nursing and Health Knowledge at the Federal University of Santa Catarina serves as the center for Cocacrack-3 Study.

Regarding inclusion criteria, we are recruiting men and women between the ages of 18 and 70 who are patients at a participating CAPS-AD, receiving treatment for cocaine use disorder, and having a support network, whether it be family or otherwise. Exclusion criteria are remission of cocaine use lasting more than two weeks and inability or unavailability to participate in research in a virtual environment, even with the support of family or others.

A total of 120 participants will be enrolled and randomized in a 1:1 ratio to one of two sequences

- *verum* for three weeks followed by placebo for three weeks, or vice versa. Randomization, allocation concealment, and blinding remain unchanged from the original protocol.

The *verum* sequence will consist of LM2, LM4, and LM6 homeopathic potencies of *Opium* and *Erythroxylum coca*, used for one week each in ascending order. *Opium* will be given in a sucrose globule dissolved on the tongue in the morning, while *Erythroxylum coca* will be administered in a sucrose globule dissolved on the tongue in the afternoon and evening, plus an additional globule repeated every hour for six hours in the event of craving. The placebo treatment will consist of sucrose globules administered in the same dose.

Figure 1 illustrates possible treatment sequences throughout the study.

Participation in Cocacrack-3 Study will not interfere with the

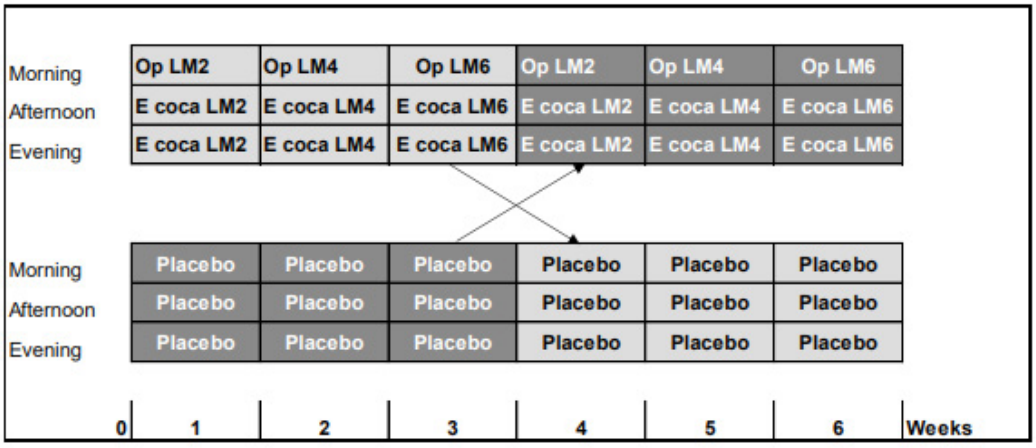

Figure 1: Crossover treatment sequences.

CAPS-AD treatment routine, and all participants, clinical investigators, CAPS-AD teams, monitors, and statisticians will remain blinded to the study treatments until data analysis is complete.

The primary measure is the percentage of days of cocaine use at week 3, as recorded through telemedicine using a timeline follow-back methodology. Secondary measures (recorded weekly by telemedicine): the percentage of the reported number of cocaine-using days during participation in the study; change in participant's cocaine craving measured through the Cocaine Craving Questionnaire scale – brief [5]; participant's progression assessed by the Clinical Global Impressions Scale [6] ; use of concomitant medications; occurrence of adverse events; assessment of treatment adherence by the Measure Treatment Adherence scale [7]; evaluation of participant retention by the number of participants at weeks 3 and 6; evaluation of study medication use by vial weight at weeks 3 and 6.

The effectiveness measures will be assessed by psychiatrists affiliated with the Federal University of Ceará through telemedicine consultations. The pharmacotherapy monitoring will encompass evaluating the occurrence of adverse events, concomitant medication use, and treatment adherence. Furthermore, the study center will closely assess the utilization of study medication by measuring vial weight, and consistently track participant retention throughout the study duration.

We presented the study to the teams of the four CAPS-AD and obtained the necessary administrative authorization and ethical approval from the Ethics Committee on Human Research at the Federal University of Santa Catarina [8]. Due to the shift in study implementation from Primary Care, we revised the title to "Homeopathy on Integrative Care for Cocaine-Related Disorders (Cocacrack-3 Study). After updating the study registry [9], we scheduled appointments with the study population (patients and families) and commenced recruitment in early June 2023.

We remain committed to investigating homeopathic approaches that could aid individuals who use cocaine, particularly crack-cocaine, in overcoming craving and regaining their health.

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