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Homeopathy for Cocaine-Related Disorders: Implementing a Study Protocol in Primary Care (Cocacrack-3 Study Protocol)

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Abstract

Introduction: Previous results showed a significant decrease in cocaine-using days among cocaine users treated homeopathic fifty-millesimal (LM) potencies of *Opium* and *Erythroxylum coca*, as compared to placebo. Those results might have been biased by low adhesion of crack-cocaine users to treatment, trend that has been observed in clinical trials and practice, usually performed in specialized services.

Objectives: to investigate 1) the effectiveness and tolerability of LM-potencies of *Opium* and *Erythroxylum coca* for cocaine-related disorders and 2) the effectiveness of a qualified primary care setting in increasing treatment attendance and retention.

Methods: A randomized, placebo-controlled, double-blind, crossover clinical trial with twelve-week study duration per patient will be performed. 120 participants aged between 18 and 60 years, with Assist score for cocaine between 4 and 26 will be included. Exclusion criterion: urinary benzoylecgonine < 150 ng/mL. Participants will receive verum for 6 weeks followed by placebo for 6 weeks, or vice-versa. Primary endpoint: percentage of reported number of cocaine using days at week 6. Secondary endpoints: percentage of reported number of cocaine using days during participation in the study; percentage of positive benzoylecgonine samples; cocaine craving score, daily craving episodes number, craving episodes mean duration, patient perception of medication action favoring craving reduction (assessed by Minnesota Cocaine Craving Scale); Assist score for cocaine; treatment attendance; retention in treatment; Adverse Events.

Discussion: For the first time, this study utilizes a primary care setting as a platform to increase treatment adhesion of cocaine users and assess the effectiveness of homeopathy for cocaine-related disorders.

Keywords

Cocaine-related disorders, unified health system, primary health care, homeopathy

Introduction

Crack-cocaine use emerged in São Paulo, Brazil, in the early nineties [1, 2]. According to observers of that milieu, the pleasurable sensations produced by crack-smoking, its low price and availability concurred to the widespread use of cocaine over the space of a few years [3]. Two decades later (2012), solely in 27 Brazilian cities (state capitals and federal district), crack users added up to 370 thousand Bastos and Bertoni, 2014) [4], and Brazil ranked among the top cocaine consuming countries [5].

As an effective pharmacotherapy for cocaine use disorder is still needed [6], nonconventional alternatives gain space in the research scenario. For instance, auricular acupuncture [7], and transcranial magnetic stimulation [8] have been tested, so far with ineffective results.

Homeopathy, which is a medical specialty in Brazil [9], has been studied in randomized controlled clinical trials (RCTs). Homeopathic fifty-millesimal potencies of *Opium* and *Erythroxylum coca* have been tested for the integrative treatment of cocaine craving, based on the hypothesis that the endogenous opioid system, which plays a key role in regulating reward and addiction mechanisms [10] might be homeopathically modulated by *Opium* potencies, and that *E. coca* potencies might induce a "substitution-like effect" for cocaine dependence.

The first study on homeopathy for cocaine-crack dependence (Cocacrack) was conducted at Reference Center for Alcohol, Tobacco and Other Drugs (CRATOD), located in the city of Sao Paulo, in the area of the so-called "Cracolândia", the city's oldest open drug scene [11]. Cocacrack was interrupted due to insufficient recruitment, and an exploratory analysis showed no significant between-group differences regarding efficacy or adverse events. However, only within the homeopathy group, the results (compared to baseline) suggested an increased sensation that the medicine had contributed to the reduction of craving [12].

The second study (Cocacrack-2) was conducted at the Psychosocial Attention Center for alcohol and other drugs (CAPS-ad) of São Carlos (a city of 250 thousand inhabitants in the interior of the state of São Paulo). Cocacrack-2 study population comprised 54 patients, who attended at least one post-baseline assessment, out of the 104 cocaine-dependent subjects (ICD10: F14.2) enrolled. The main outcome measure was the percentage of cocaine-using days. Results showed 18.1% of cocaine-using days in the homeopathy group, with a standard deviation (SD) of 22.3%, compared to 29.8% (SD: 30.6%) in the placebo group - $P < 0.01$ [13]. Due to the high dropout rate and risk of bias, further research is required to confirm Cocacrack-2 findings, with a specific focus on strategies to increase patient retention.

Low adhesion of crack-cocaine users has been observed in clinical practice and clinical trials, usually performed in secondary, specialized services. In theory, the great capillarity of primary health care could favor retention, however, care for illicit drug users in Brazilian primary care remains a main challenge [14], as professionals are usually not trained to respond to substance users' needs, may not have the time, capacity, or motivation to provide the attention needed [15], and do not feel prepared to work in mental health [16]. Cocacrack-3 study aims at further investigating the effectiveness and tolerability of homeopathic fifty-millesimal potencies of *Opium* and *Erythroxylum coca* for cocaine-related disorders, overcoming the limitations and benefiting from the strengths of primary health care to improve treatment adhesion.

Objectives

To investigate: 1) the effectiveness and tolerability of homeopathic Q-potencies of *Opium* and *Erythroxylum coca* for cocaine-related disorders in a qualified primary care setting and 2) the effectiveness of a qualified primary care setting in increasing treatment attendance and retention among cocaine-crack users.

Methods

Study design

A randomized, placebo-controlled, double-blind, crossover clinical trial with a twelve-week study duration per patient will be performed to test the following hypotheses:

H0: homeopathic medicines = placebo (null hypothesis) *vs*.

H1: homeopathic medicines ≠ placebo (alternative hypothesis).

Cocacrack-3 study follows Good Clinical Practice (ICH, 2019) [17] and CONSORT (*Consolidated Standards of Reporting Trials*) guidelines for reporting data on homeopathic treatments [18].

Setting

Focusing on real-world conditions, Cocacrack-3 study will be performed in a qualified primary care setting - Itajaí, a city of the southern Brazilian state of Santa Catarina, with a population of 200,000. Itajaí offers 100% primary health care coverage, mainly from the Family Health Strategy (FHS), the core primary care approach of the Brazilian Unified Health System – SUS [19]. Each FHS team includes a physician, a nurse, a nurse assistant, and four to six full-time community health agents, being organized geographically to cover populations of up to 1000 households and to provide responses to most health problems. Agents (and/or other team members) visit each household within their micro-area to collect data and perform, as required, health promotion activities and basic clinical care [20].

Six FHS units of Itajaí will host study procedures in collaboration with the Family Health Support Nucleus (NASF), Psychosocial Attention Center for alcohol and other drugs (CAPS-ad) of Itajaí and inthe "Consultório na Rua" (Outdoor Clinic) - a health team that should go to the user wherever he/she is [21]. Cocacrack-3 study is a technical cooperation between the Itajaí City Hall, the Federal Council of Pharmacy, University of Itajaí Valley (UNIVALI) and the

Brazilian Association of Homeopathic Pharmacists. The study organization chart is hierarchized in figure 1.

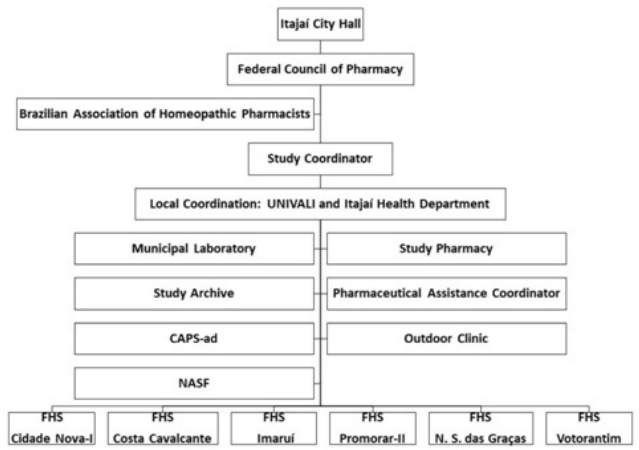

Figure 1: Cocacrack-3 organization chart.

Regulatory approval

Technical Cooperation Term signed by the Mayor of Itajaí, the President of the Federal Council of Pharmacy, the President of UNIVALI, the President of the Brazilian Association of Homeopathic Pharmacists on May 16, 2018.

Trial registration

University hospital Medical Information Network (UMIN).

Unique ID issued by UMIN: UMIN000040161 (https://www.umin.ac.jp/ctr/index.htm)

Ethics

Cocacrack-3 study will be carried out following The Code of Ethics of the World Medical Association - Declaration of Helsinki [22]. The study Presentation Certificate for Ethical Appreciation (CAAE) number is 00705218.2.0000.0120, which was approved by the Brazilian National Research Ethics Commission in March 2019 (report # 3.219.174).

Qualified primary care setting

To face the challenge of improving the quality of care for cocaine-crack users, teams attended pre-inclusion meetings with the study's local and general coordination. Those meetings were held mainly in the second semester of 2019 and discussed the agenda summarized below.

Prejudice towards cocaine/crack users

Reflection on prejudice, on society trends toward seeing "the crack user based on the user's virtual image, disregarding his/her real image, i.e., it does not see him/her as a singular person, with a life history, feelings, desires, learning, gains, and losses. A stigmatizing identity of marginals, bums, and violent persons predominates, creating the idea of non-citizens, without a social place, the ones who should be excluded" [23]. Therefore, "reducing stigma related to drug use may help encourage users to seek necessary care" [24].

Qualification in screening and brief intervention (BI)

Screening and BI aim to identify current or potential problems with substance use and motivate those at risk to change their substance use behavior [25]. Screening provides patients with personal feedback about their substance use risks which may be used as a gateway to Brief Intervention, as Feedback, Responsibility, Advice, Menu of options, Empathy, and Self efficacy (FRAMES) summarizes BI process.

Involving the family in healthcare

"Fear of the dealer" was a subject brought up by the teams at the meetings. FHS personnel, especially the community health agents may be reluctant to identify cocaine-crack users since they live in the same neighborhood and could suffer reprisals from drug dealers. During an extended group meeting, we had the opportunity to address that well-founded fear. Community health agents should not point out neighbors who use cocaine. Instead, FHS teams should promote the protagonism of the family in the care of crack/cocaine users, enhancing bonds between the user, team, and family [26].

Differing from other Brazilian cities or country regions, where families seem "weary of exposing their drug user-related issues" [27], in the southern city of Itajaí families may be reluctant to expose those issues, according to FHS teams' reports. Therefore, we plan to announce the Cocacrack-3 study within the six FHS territories and offer scheduled appointments. Interested users and/or their families will be welcomed with discretion. Families will be asked to act as a mediator between cocaine users and FHS teams. Cocacrack-3 study procedures will be presented and discussed as a Singular Therapeutic Project, "guided by a relation among professionals-person-family that empowers and serves to consolidate the bond and commitment among them" [28].

Participants

Male and female patients aged between 18 and 60 years with an Assist [29] score for cocaine between 4 and 26 will be included. Capability and willingness to give informed consent and to comply with the study procedures will also be required. Exclusion criterion: negative urinary benzoylecgonine detection (< 150 ng/mL).

Sample size

As mentioned above [13], previous (Cocacrack-2) results suggest that 54/104 participants had enough statistical power to detect significant differences. A sample size of 104 participants would correspond to an effect size of 0.5, type 1 error of 5%, and 80% of power (G*Power 3.1.9.2). As Cocacrack-2 results might have been biased by the high dropout rate, Cocacrack-3 protocol will work with a 15% larger sample size (120 participants), changing the setting to primary care as the main strategy to improve attendance and retention.

Study medications

Homeopathic medicines are produced through sequential agitated dilutions in Decimal (D), Centesimal (C), Fifty-

millesimal, or Quinquagintamillesimal (LM or Q) potencies. The fifty-millesimal potencies of *Opium* and *Erythroxylum coca* that have been tested in Cocacrack studies do not pose a risk of intoxication, given that Q-potencies are prepared by grinding of the raw material (in three 1:100 steps), followed by consecutive 1:50,000 agitated dilutions. Therefore, a LM1 potency corresponds to $5x10^{-10}$ fraction of the raw material (LM2 = 2.5×10^{-15}, LM3 = 1.25×10^{-20}, LM4 = 6.25×10^{-24} etc.).

Homeopathic matrices of *Opium* and *Erythroxylum coca* were kindly given to the study coordinator at the beginning of the 1990s by the independent German researcher Peter Barthel [30], who at that time used to carry out grinding of fresh plants. Sucrose globules impregnated with Q-potencies and sucrose placebo-globules for placebo have already been kindly provided by HN-Cristiano Homeopatia (www.homeopatiahncristiano.com.br), which manufactures Q-potencies (identified as standardized LM potencies) according to the methodology described by Hahnemann [31]

Posology and potencies

Fifty millesimal potencies of *Opium* will be administered in the form of sucrose globules, 1 oral globule once daily, in the morning. Fifty millesimal potencies of *Erythroxylum coca* will be administered in the form of sucrose globules, 1 oral globule, in the afternoon, and at night. The patient may repeat the dose hourly, in case of acute craving. Placebo will consist of indistinguishable sucrose globules, provided in indistinguishable vials as verum and taken in the same posology.

Treatment sequences

After inclusion, 60 patients will be randomly allocated to use homeopathy for six weeks, followed by six weeks of placebo and 60 patients will be randomly assigned to the reverse sequence. During the 6 weeks of allocation to homeopathic treatment, patients will receive LM2, LM4, and LM6 potencies of *Opium* and *Erythroxylum coca* in ascendant order, each potency for 2 weeks (Figure 2).

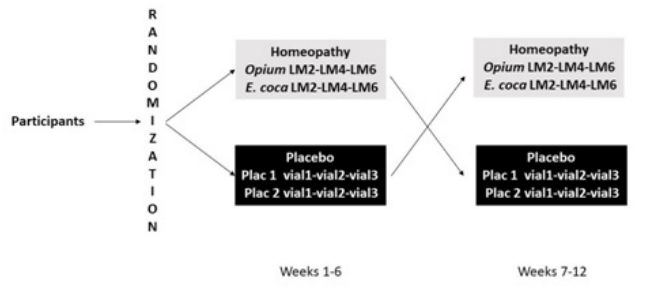

Figure 2: Cocacrack-3 flow-diagram.

Outcomes

The primary endpoint is the percentage of the reported number of cocaine using days at week 6, registered through a timeline follow-back methodology.

The secondary endpoints are: the percentage of the reported number of cocaine using days during participation in the study; the percentage of positive benzoylecgonine samples; cocaine craving score, daily craving episodes number, craving episodes mean duration, patient perception of medication action favoring craving reduction, assessed by Minnesota Cocaine Craving Scale [32]; Assist score for cocaine; treatment attendance (number of attended visits/scheduled visits, including home visits); retention in treatment (period elapsed between treatment intake and dropout [33], i.e., last attendance to a Family Health Strategy team visit or the end of treatment); Adverse Events.

Data management

Data management will be performed by the local coordination, following the ICH-Guidelines for Good Clinical Practice. Information will be recorded, handled, and stored in the Central Archive of UNIVALI, using participants' Inclusion Number – i.e., the randomization-envelope number). The confidentiality of records that could identify subjects will be protected in the local coordinator office (UNIVALI).

Data Analysis

Statistical analysis will be based on an intention-to-treat (ITT) sample, defined as all voluntaries who took at least one dose of homeopathic medicines or placebo. The ratio between days of cocaine use and days recorded (the primary outcome) will be compared between groups by random-effects models [34]. When considered binary secondary outcomes (as cocaine detection in urine), the random-effects model introduced by Ezzet and Whitehead [35] will be used for comparisons between groups. Measures that are expressed as discrete variables (as the daily number of craving episodes) will be analyzed by adequate random-effects models based on discrete distributions, as the model proposed by Layard and Arysen [36] for variables following a Poisson distribution [37]. These models are specific for data from crossover clinical trials and they are also useful to compare baseline characteristics between groups and to test the significance of carryover (residual) effects. Under the assumption of missing completely at random (MCAR), the random-effects model is able to deal with dropouts without further imputation. MCAR refers to a situation where there is no relationship between the missingness of the data and any values, missing or previously observed. Situations where this assumption does not seem appropriate will be clinically discussed and the respective case can be removed from the analysis. All analyzes will be performed using the SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA). The significance level will be set to 0.05.

Randomization, Allocation Concealment and Blinding

Randomization

In December 2019:

– the study statistician generated a randomization list using a 1:1 ratio of the two sequence groups (denoted as **A** and **B**) and a web-based tool [37] and sent it to an Administrative Technician of UNIVALI Pharmacy Course;

– the Administrative Technician wrote down each randomization result (A or B) on an identification card placed it in sequentially numbered, sealed opaque envelopes and handed them over to the Pharmaceutical Assistance Coordinator of the Health Department of Itajaí;

– The General Secretary of the Federal Pharmacy Council decided the study code, i.e., whether A or B corresponded to sequence homeopathy - placebo or vice versa and reported that decision on the Pharmaceutical Assistance Coordinator.

The Pharmaceutical Assistance Coordinator will be the only study collaborator to know the sequence (**A** or **B**) registered on the card of each envelope, as well as the **code**, defining whether A or B of the randomization list corresponds to one or the other treatment sequence.

Allocation concealment

FHS unity "Y" will inform the local Coordination that patient "Z" has been enrolled and confirm that the urine specimen has been collected. The local Coordination will provide the transport (via Health Department, Itajaí) of the urine sample to the Municipal Laboratory, which will perform the benzoylecgonine detection and provide feedback to the local Coordinator.

The local coordinator will include all consecutive eligible patients (urinary benzoylecgonine ≥ 150 ng/mL) in order of presentation, with the corresponding Inclusion Number. She will inform the Pharmaceutical Assistance Coordinator that participant Inclusion Number "X" has been included.

The Pharmaceutical Assistance Coordinator will open the envelope number "X" and assign the participant with the Inclusion Number "X" to designated study sequence A or B (homeopathy-placebo or placebo-homeopathy), according to identification card (A or B) placed in the envelope and the study code provided by the General Secretary of the Federal Pharmacy Council. She will send a prescription to the Study Pharmacy, informing the participant's Inclusion Number and the sequence group: homeopathy-placebo or placebo-homeopathy.

Blinding

The Study Pharmacist will dispense 12 vials per participant: 6 labeled – Inclusion Number X *morning weeks 1-2*; *morning weeks 3-4; … morning weeks 11-12*; and 6 labeled Inclusion Number X *afternoon/evening weeks 1-2*; *afternoon/evening weeks 3-4; … afternoon/evening weeks 11-12*. She will inform the local Coordination when the medication is ready to transport.

The local Coordinator will provide the transport (via Health Department, Itajaí) of study medication from the Study Pharmacy to the FHS unity "Y" and inform the FHS team that participant Inclusion Number "X" corresponds to the patient name "Z".

During scheduled home visits, the FHS team will deliver the medication with Inclusion Number "X" to patient Z every two weeks, as labeled (weeks 1-2 vials, weeks 3-4 vials etc.).

Participants, FHS teams, study personnel (including the statistician) will remain blinded to intervention sequence until the end of data analysis. Figure 3 illustrates enrollment, inclusion, randomization and allocation process.

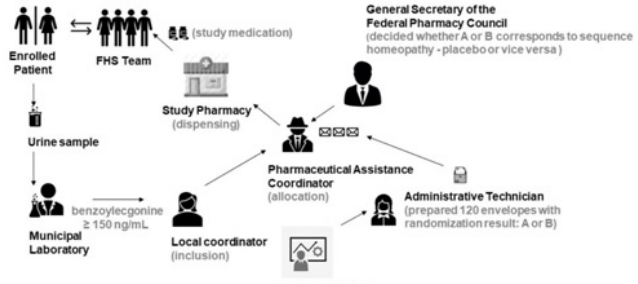

Figure 3: Enrollment, inclusion, randomization and allocation process.

Discussion

This study has pragmatic features with focus on effectiveness. Its general objective is to contribute to the treatment of cocaine users in primary care. Specifically, we aim to confirm if homeopathic Q-potencies of *Opium* and *Erythroxylum coca* are effective for cocaine-related disorders.

When planning the study, we chose the crossover design to offer the verum intervention to all participants and to lessen confounding effects. Anticipating some degree of low adhesion, a washout period was not included, so as not to prolong the duration of the study. Considering possible carry-over effects, the primary endpoint was set at week 6, i.e., before the crossover.

Low treatment retention is a known characteristic of crack-cocaine users. According to the study "Profile of cocaine and crack users in Brazil":

"Among all addicts of psychoactive drugs, cocaine and crack users have the highest treatment drop-out rates… Crack users appear to be more prone to abandoning treatment than users of intranasal cocaine [38].

A strategy that has been used to deal with low adhesion is "contingency management" (CM), i.e., incentives when participants demonstrate target behaviors, as abstinence or treatment adhesion. Results from a 12-week RCT (with 3 sessions/week) conducted in a Specialized Medical Outpatient Clinic for Alcohol and Drug Treatment, in the city of São Paulo, Brazil showed that the mean number of sessions attended was higher in the CM group than in the "standard treatment alone" (STA) group: 19.5/36 (SD = 14.9) versus 3.7/36 (SD = 5.9; $p < 0.01$). The CM group was retained for a mean of 7.7/12 (SD = 5.2) weeks in comparison to 3.0/12 (SD = 4.0) weeks in the STA group -P < 0.01. Notwithstanding these interesting results, the practical implementation of contingency management is still limited [39], as CM is not incorporated by SUS and leads to post-treatment challenges

when monetary reinforcers are removed, and relapse to substance use is common [40].

A qualified primary care setting is our strategy to be closer to cocaine-crack users and their families and thus, improve adhesion. For the first time, this study utilizes a primary care setting as a platform to assess the effectiveness of homeopathic medicines for cocaine-related disorders and to increase treatment attendance and retention of cocaine-crack users.

We do expect a reduction in crack-cocaine using days during homeopathic treatment, as compared to placebo. We also expect that FHS teams, in collaboration with users' families, to be effective in increasing participants' attendance and retention. Nevertheless, the regular use of cocaine, especially in the form of crack, is a complex psychosocial problem and, as such, has no simple solution. Problematic childhood, low education, traumatic life events, vulnerabilities in the family environment mark the user's path that often comes to a street situation [41]. Finally, we expect that primary care and homeopathy will integrate potentialities and help to change that pathway.

If the results meet our expectations, Cocacrack-3 study will provide evidence for the adoption of homeopathic Q-potencies of *Opium* and *Erythroxylum coca* by Brazilian public health authorities, and for investments in primary care to embrace cocaine and crack users.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Benzoylecgonine urine tests will be provided by the Municipal Laboratory – Health Department, Itajaí – SC, Brazil, which will also provide the logistics for the transportation of urine samples and study medication. Study medication (homeopathic medicines and placebo globules) has been kindly provided by HN-Cristiano Homeopatia – Sao Paulo, SP, Brazil.

Conflict of Interest

Dra. Amarilys de Toledo Cesar is co-owner of HN-Cristiano Homeopatia, the pharmacy that has donated the study medication, however, homeopathic potencies of Erythroxylon coca and Opium have been in use for over 150 years and are not patentable.

References

1. Nappo SA, Galduróz JC, Noto AR. 1996. Crack use in São Paulo. *Subst Use Misuse* 31(5): 565-579. https://doi.org/10.3109/10826089609045827
2. Dunn J, Laranjeira RR, Da Silveira DX, Formigoni ML, Ferri CP. 1996. Crack cocaine: an increase in use among patients attending clinics in São Paulo: 1990-1993. *Subst Use Misuse* 31(4): 519-527. https://doi.org/10.3109/10826089609045824
3. Nappo SA, Galduróz JC, Raymundo M, Carlini EA, 2001. Changes in cocaine use as viewed by key informants: a qualitative study carried out in 1994 and 1999 in São Paulo, Brazil. *J Psychoactive Drug*s 33(3): 241-53. https://doi.org/10.1080/02791072.2001.10400571
4. Bastos FI, Bertoni N, 2014. Pesquisa Nacional sobre o uso de crack: quem são os usuários de crack e/ou similares do Brasil? Quantos são nas capitais brasileiras? ICICT/FIOCRUZ, Rio de Janeiro, RJ, Brasil.
5. Abdalla RR, Madruga CS, Ribeiro M, Pinsky I, Caetano R, et al. 2014. Prevalence of cocaine use in Brazil: data from the II Brazilian national alcohol and drugs survey (BNADS). *Addict Behav* 39(1): 297-301. https://doi.org/10.1016/j.addbeh.2013.10.019
6. Chan B, Kondo K, Freeman M, Ayers C, Montgomery J, et al. 2019. Pharmacotherapy for cocaine use disorder-a systematic review and meta-analysis. *J Gen Intern Med* 34(12): 2858-2873. https://doi.org/10.1007/s11606-019-05074-8
7. Gates S, Smith LA, Foxcroft DR. 2006. Auricular acupuncture for cocaine dependence. *Cochrane Database Syst Rev* 25(1): CD005192. https://doi.org/10.1002/14651858.CD005192.pub2
8. Bolloni C, Badas P, Corona G, Diana M, 2018. Transcranial magnetic stimulation for the treatment of cocaine addiction: evidence to date. *Subst Abuse Rehabil* 21(9): 11-21. https://doi.org/10.2147/SAR.S161206
9. Conselho Federal de Medicina. 2002. RESOLUÇÃO CFM nº 1634/2002.
10. Yoo JH, Kitchen I, Bailey A. 2012. The endogenous opioid system in cocaine addiction: what lessons have opioid peptide and receptor knockout mice taught us? *Br J Pharmacol* 166(7): 1993-2014. https://doi.org/10.1111/j.1476-5381.2012.01952.x
11. Ribeiro M, Duailibi S, Frajzinger R, Alonso AL, Marchetti L, et al. 2016. The Brazilian 'Cracolândia' open drug scene and the challenge of implementing a comprehensive and effective drug policy. *Addiction* 111(4): 571-573. https://doi.org/10.1111/add.13151
12. Adler UC, Saraiva IBG, Almeida MF, Jezierski M, Cesar AT, et al., 2013. Homeopathy in crack-cocaine craving: randomized, placebo-controlled, double-blind study (COCACRACK study). *Rev Psiq Clin* 40(6): 241-242. https://doi.org/10.1590/S0101-60832013000600006
13. Adler UC, Acorinte AC, Calzavara FO, da Silva AA, de Toledo Cesar A, et al. 2018. Double-blind evaluation of homeopathy on cocaine craving: a randomized controlled pilot study. *J Integr Med* 16(3): 178-184. https://doi.org/10.1016/j.joim.2018.03.004
14. Arantes LJ, Shimizu HE, Merchán-Hamann E, 2016. The benefits and challenges of the Family Health Strategy in Brazilian primary health care: a literature review. *Cien Saude Colet* 21(5): 1499-1510. https://doi.org/10.1590/1413-81232015215.19602015
15. Krawczyk N, Kerrigan D, Bastos FI. 2017. The quest to extend health services to vulnerable substance users in Rio de Janeiro, Brazil in the context of an unfolding economic crisis. *Int J Health Serv* 47(3): 477-488. https://doi.org/10.1177/0020731416679351
16. Gerbaldo TB, Arruda AT, Horta BL, Garnelo L, 2018. Evaluation of the organization of care in mental health in primary health care in Brazil. 16(3): 1079-1094.
17. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) ICH-GCP International Conference on Harmonisation - Good Clinical Practice - E6(R2). [Accessed May 30, 2020]
18. Dean ME, Coulter MK, Fisher P, Jobst K, Walach H. 2006. Reporting data on homeopathic treatments (RedHot): a supplement to CONSORT. *J Altern Complement Med* 13(6): 368-371. https://doi.org/10.1159/000097073
19. Castro MC, Massuda A, Almeida G, Menezes-Filho NA, Andrade MV, et al. 2019. Brazil's unified health system: the first 30 years and prospects for the future. *Lancet* 27: 394(10195): 345-356. https://doi.org/10.1016/S0140-6736(19)31243-7
20. Macinko J, Harris MJ. 2015. Brazil's family health strategy--delivering community-based primary care in a universal health system. *N Engl J Med* 372(23): 2177-2181. https://doi.org/10.1056/NEJMp1501140
21. Simões TRBA, Couto MCV, Miranda L, Delgado PGG, 2017. Mission and effectiveness of outdoor clinics (Consultórios na Rua): an

experience of consensus production. *Saúde em Debate* 41(114): 963-974. https://doi.org/10.1590/0103-1104201711423

22. World Medical Association. 2018. Declaration of Helsinki - Ethical principles for medical research involving human subjects. [Accessed May 30, 2020].
23. Bard ND, Antunes B, Roos CM, Olschowsky A, de Pinho LB, 2016. Stigma and prejudice: the experience of crack users. *Rev Lat Am Enfermagem* 24: e2680. https://doi.org/10.1590/1518-8345.0852.2680
24. Krawczyk N, Filho CL, Bastos FI. 2015. The interplay between drug-use behaviors, settings, and access to care: a qualitative study exploring attitudes and experiences of crack cocaine users in Rio de Janeiro and São Paulo, Brazil. *Harm Reduct J* 12: 24. https://doi.org/10.1186/s12954-015-0059-9
25. Henry-Edwards S, Humeniuk R, Ali R, Monteiro M, Poznyak V. 2003. Brief intervention for substance use: a manual for use in Primary Care. (Draft Version 1.1 for Field Testing). World Health Organization, Geneva. [Accessed May 30, 2020].
26. Duarte MLC, Pereira LP, Olschowsky A, Carvalho J. 2019. Fourth generation evaluation: assisting family members of crack cocaine users. *Rev Enferm UFSM* 9: 1-19. https://doi.org/10.5902/2179769229057
27. Paula ML, Jorge MSB, Vasconcelos MGF, Albuquerque RA. 2014. Assistance to the drug user in the primary health care. *Psicologia em Estudo* 19(2): 223-33. https://doi.org/10.1590/1413-737222025006
28. Silva AI, Loccioni MFL, Orlandini RF, Rodrigues J, Peres GM, et al. 2016. Singular therapeutic project for professionals in the family health strategy. *Cogitare Enferm* 21(3): 01-08.
29. WHO ASSIST Working Group. 2010. World Health Organization. 2010. The Alcohol, Smoking and Substance Involvement Screening Test.
30. Adler UC, Cesar AT, Adler MS, Padula AE, Garozzo EN, et al. 2010. Da padronização farmacêutica à pesquisa clínica: 20 anos de experiência com diluições cinquenta-milesimais. *Revista de Homeopatia* 73(1/2): 57-67.
31. Hahnemann S. 1921. Organon der Heilkunst: aude sapere, 6. ed. Posthumous publication by Richard Haehl. Haug, Heidelberg, Germany.
32. Halikas JA, Kuhn KL, Crosby R, Carlson G, Crea F. 1991. The measurement of craving in cocaine patients using the Minnesota cocaine craving scale. *Compr Psychiatry* 32(1): 22-27. https://doi.org/10.1016/0010-440x(91)90066-l
33. Miguel AQ, Madruga CS, Cogo-Moreira H, Yamauchi R, Simões V, et al. 2016. Contingency management is effective in promoting abstinence and retention in treatment among crack cocaine users in Brazil: a randomized controlled trial. *Psychol Addict Behav* 30(5): 536-543. https://doi.org/10.1037/adb0000192
34. Lui KJ. 2016. Crossover designs: testing, estimation, and sample size. John Wiley & Sons, New York, USA.
35. Ezzet F, Whitehead J. 1992. A random effects model for binary data from crossover clinical trials. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 41(1): 117-126. https://doi.org/10.2307/2347622
36. Layard MWJ, Arvesen JN. 1978. Analysis of poisson data in crossover experimental designs. *Biometrics* 34(3): 421-428.
37. Randomness and Integrity Services Ltd. [https://www.random.org/lists/] [Accessed on May 30, 2020].
38. Duailibi LB, Ribeiro M, Laranjeira R. 2008. Profile of cocaine and crack users in Brazil. *Cad Saude Publica* 24(4): 545-557. https://doi.org/10.1590/s0102-311x2008001600007
39. Rash CJ, Stitzer M, Weinstock J. 2017. Contingency Management: new directions and remaining challenges for an evidence-based intervention. *J Subst Abuse Treat* 72: 10-18. https://doi.org/10.1016/j.jsat.2016.09.008
40. Fazzino TL, Bjorlie K, Lejuez CW. 2019. A systematic review of reinforcement-based interventions for substance use: efficacy, mechanisms of action, and moderators of treatment effects. *J Subst Abuse Treat* 104: 83-96. https://doi.org/10.1016/j.jsat.2019.06.016
41. Seleghim MR, Galera SAF. 2019. The trajectory of crack users to the street situation in the perspective of family members. *Invest Educ Enferm* 37(2): 1-14. https://doi.org/10.17533/udea.iee.v37n2e03