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INTEGRATIVE REVIEW ARTICLE

# MEDICINE TREATMENT OF CRAVING IN USERS OF COCAINE/CRACK: INTEGRATIVE REVIEW

## TRATAMENTO MEDICAMENTOSO DO CRAVING EM USUÁRIOS DE COCAÍNA/CRACK: REVISÃO INTEGRATIVA

## TRATAMEINTO MEDICAMENTOSO DEL CRAVING EN USUARIOS DE COCAÍNA/CRACK: REVISIÓN INTEGRADORA

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**ABSTRACT**

***Objective***: to analyze the knowledge about the positive outcomes of medicine treatment for craving for crack/cocaine users. ***Method***: integrative review aimed at answering the question << What are the studies that using drug treatment showed positive effect on craving in users of cocaine/crack?>>. The search was conducted in CINAHL databases, Scopus, Medline and Cochrane in June 2014 using the non-indexed keyword "Craving" and the indexed keywords "Crack Cocaine", "Drug Therapy" and "Treatment Outcome". ***Results***: of the 902 records retrieved, only eight studies showed treatment regimens with positive effects for the craving of cocaine. There were nine different drugs used. The drugs had a positive influence in reducing cocaine levels in urine and craving; behaviors considered antisocial and crime associated with the abuse of crack/cocaine. ***Conclusion***: The results are in agreement with the need to develop new research on the action of the drugs and the specific pharmacological interventions. ***Descriptors***: Mental Health; Disorders Related to Substance Use; Drug Treatment; Crack; Cocaine.

**RESUMO**

***Objetivo*:** analisar o conhecimento sobre o resultado positivo do tratamento medicamentoso para o *craving* em usuários de crack/cocaína. ***Método:*** revisão integrativa com vistas a responder à questão <<Quais estudos usando tratamento medicamentoso evidenciaram efeito positivo no *craving* em usuários de cocaína/crack? >>. Foi realizada a busca nas bases de dados CINAHL, Scopus, Medline e Cochrane no mês de junho de 2014 empregando o descritor não-indexado "Craving" e os indexados "Crack Cocaine", "Drug Therapy" e "Treatment Outcome". ***Resultados:*** dos 902 registros recuperados, apenas oito estudos apresentaram esquemas terapêuticos com efeitos positivos para o *craving* da cocaína. Utilizaram-se nove drogas diferentes. Os medicamentos influenciaram positivamente na diminuição dos níveis de cocaína na urina e do *craving*, de condutas consideradas antissociais e na criminalidade associada ao abuso do crack/cocaína. ***Conclusão:*** os resultados são concordantes com a necessidade de desenvolvimento de novas pesquisas sobre a ação dos fármacos e as intervenções medicamentosas específicas. ***Descritores:*** Saúde Mental; Transtornos Relacionados ao Uso de Substâncias; Tratamento Medicamentoso; Cocaína; Crack.

**RESUMEN**

***Objetivo*:** analizar el conocimiento sobre el resultado positivo del tratamiento medicamentoso para el *craving* en usuarios de crack/cocaína. ***Método:*** revisión integradora para responder la pregunta << ¿Cuáles estudios usando tratamiento medicamentoso evidenciaron efecto positivo en *craving* en usuarios de cocaína/crack? >>. Fue realizada la búsqueda en las bases de datos CINAHL, Scopus, Medline y Cochrane en el mes de junio de 2014 empleando el descriptor no-indexado "Craving" y los indexados "Crack Cocaine", "Drug Therapy" y "Treatment Outcome". ***Resultados:*** de los 902 registros recuperados, apenas ocho estudios presentaron esquemas terapéuticos con efectos positivos para el *craving* de cocaína. Se utilizaron nueve drogas diferentes. Los medicamentos influyeron positivamente en la disminución de los niveles de cocaína en la orina y del *craving*, de conductas consideradas antisociales y en la criminalidad asociada al abuso del crack/cocaína. ***Conclusión:*** los resultados son concordantes con la necesidad de desarrollo de nuevas investigaciones sobre la acción de los fármacos y las intervenciones medicamentosas específicas. ***Descriptores:*** Salud Mental; Trastornos Relacionados al Uso de Sustancias; Tratamiento Medicamentoso; Cocaína; Crack.

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## INTRODUCTION

The abuse of alcohol and other drugs is a globally important problem in public health, worrying all segments of society. The global report about drugs is highlighted for the abuse as harmful to economic and social development of the population, as well as finance crime and violence, and to encourage the spread of diseases like HIV and hepatitis.[1]

It is estimated that there are 230 million people worldwide, 5% of the adult population (15-64 years old) have used a drug at least once in life. Since then, there were no significant changes in the global status of drug use, production and consequences for health.[1] It is noteworthy that the drugs most used in Brazil are marijuana and cocaine, including crack, and Brazil is the world´s largest market.[2]

The crack as a cocaine byproduct goes through different processes to reach a solid state (stone). Procedurally toxic substances are blended with cocaine such as calcium bicarbonate, talc, glass powder, among others.[3] Crack and its harmful consequences have achieved prominence in the media and scientific journals, with little progress regarding the treatment of this dependence compared to the traditional models of treatment.[4]

The treatment of cocaine dependence until the mid-1970s had a focus exclusively on non-pharmacological methods. Therefore, studies conducted by researchers showed that chronic abuse of cocaine led to neurophysiological changes,[5] proving that cocaine use causes an increase neurotransmission of dopamine and serotonin, which are largely responsible for the pleasurable and enhancer effects of the drug. Deregulation of these neurotransmitters during withdrawal syndrome caused by cocaine and its derivatives has an important role in the development of craving.[6]

In recent years, there is an increase in research. Many studies focus on the treatment of addiction users of crack/cocaine, using various medications such as buspirone,[7] topiramate,[8] biperiden.[9] However, there is no medication approved by psychoactive substances regulatory for the treatment of addiction to crack/cocaine. In this sense of incomplete regulation, several drugs have been tested in an attempt to alleviate symptoms related to the use and abstinence from cocaine. It is agreed that the convergence of the findings from this study may contribute to a better understanding of the pharmacological mechanisms and relevance of drug treatment in reducing the craving for crack/cocaine users.

## OBJECTIVE

- To analyze the knowledge about the positive outcomes of drug treatment for craving for crack/cocaine users.

## METHOD

It is a study of integrative review, following the steps outlined in the literature,[10] They are the establishment of the questions and objectives of the integrative review; apply the inclusion and exclusion criteria of articles; definition of databases and extracting the relevant information from the selected articles; analyzing the results; discussion of the data and, finally, the synthesis of the review.

The guiding question of the study was “What studies using drug treatment showed positive effect on craving in cocaine/crack users?”

The inclusion criteria were complete articles available free in selected databases that addressed the result, drug treatment for the craving for crack/cocaine users, published in Portuguese, Spanish or English. Exclusion criteria of the study were articles published in editorial format; letters to the editor; other types of reviews; articles to submit the treatment performed in crack/cocaine users together with other drugs.

Regarding the period, all publications available in every database were taken through the month of June 2014 without previous limit, providing a wider selection of studies. Theses, dissertations, monographs and articles that after reading the summary did not converge with the proposed subject matter were excluded, in addition to the publications that were repeated in the databases.

The selection of articles took place from 23 to 28 June 2014 in the following databases: CINAHL (Cumulative Index to Nursing and Allied Health Literature), Scopus, Medline, and Cochrane.

It is worth mentioning that each database has been accessed in one day by three researchers concurrently on different computers to ensure reliability in the selection of articles eligible for the study.

For the survey of articles in the databases, it was defined the non-indexed descriptor: “Craving” and indexed in Mesh (Medical Subject Headings): “Crack Cocaine”, “Drug Therapy”, “Treatment Outcome”. The choice of indexed descriptors ensures a controlled

search. As a result, there was the crossing of the descriptors as follows: “Craving” [and] “Crack Cocaine” [and] “Treatment Outcome”; “Craving” [and] “Crack Cocaine” [and] “Drug Therapy”; “Craving” [and] “Crack Cocaine” [and] “Treatment Outcome” [and] “Drug Therapy”.

During the research sampling, applying the intersections of descriptors, there were: “Craving” [and] “Crack Cocaine” [and] “Treatment Outcome” (CINAHL=34; SCOPUS=532; Medline=317; Cochrane=19); “Craving” [and] “Crack Cocaine” [and] “Drug Therapy” (CINAHL=33; SCOPUS=479; Medline=301; Cochrane=22; “Craving” [and] “Crack Cocaine” [and] “Treatment Outcome” [and] “Drug Therapy” (CINAHL=14; SCOPUS=362; Medline=227; Cochrane=0). After the completion of the initial data collection stage and applied the inclusion and exclusion criteria by reading each article, the sample consisted of eight articles indexed, one of CINAHL, foru of Scopus, and three of Medline.

To meet the objective and research question, the review was from a data collection instrument with the following routing: identification of the article; year of publication; site of research development; authorship; goals; study design; evidence level of drug used for the treatment of craving in crack/cocaine; positive result of drug treatment for craving of crack/cocaine.

The results were presented descriptively and the studies were initially classified according to the level of evidence presented in Figure 1.

| Level of Scientific Evidence by Type of Study | | | |
|---|---|---|---|
| Degree of Recommendation | Level of Evidence | Treatment/Prevention - Ethiology | Diagnosis |
| A | 1A | Systematic review (with homogeneity) of Randomized and Controlled Trials. | Systematic review (with homogeneity) of Level 1 Diagnostic Criteria Studies.<br>Diagnostic in studies level 1B in different clinical centers. |
| | 1B | Randomized and Controlled Clinical Trial with Narrow Confidence Interval. | Cohort valid, with good reference standard of Diagnostic Criteria, tested on a single clinical center. |
| | 1C | Therapeutic results of the “all or nothing”. | Sensitivity and specificity near 100%. |
| B | 2A | Systematic review (with homogeneity) of Cohort Studies. | Systematic review (with homogeneity) level diagnostic studies> 2. |
| | 2B | Cohort study (including Lower Quality Randomized Clinical Trial). | Exploratory cohort with good standard Reference Diagnostic Criteria derivatived or validated in fragmented samples or database. |
| | 2C | Therapeutic observation results (outcomes research) Ecological Study. | |
| | 3A | Systematic review (with homogeneity) of Case-control Studies. | Systematic review (with homogeneity) level diagnostic studies> 3B. |
| | 3B | Case-control Study. | Selecting non-consecutive cases or little consistent reference standard applied. |
| C | 4 | Case reports (including lower quality cohort or case-control). | Case-control study; or poor or not independent reference standard. |
| D | 5 | Opinion without critical evaluation or based on basic materials (physiological study or study with animals). | |

Figure 1: Levels of evidence applied in the description of publications.

Source: *Adaptation of OCEBM.*[11]

## RESULTS

As results of the integrative review, there are eight articles meeting the inclusion and exclusion criteria previously established. Figure 2 shows the characterization of the selected studies.

| Year | Place. | Reference | Leel | Degree | Objectives | Method |
|---|---|---|---|---|---|---|
| 2014 | US | Dakwar et al. The Effects of Subanesthetic Ketamine Infusions on Motivation to Quit and Cue-Induced Craving in Cocaine-Dependent Research Volunteers. Biological Psychiatry. 2014; 76(1):40–46. | 1B | A | To investigate ketamine infusion effects on motivation to stop using cocaine and craving for cocaine addicts. | Randomized, double-blind study. |
| 2013 | US | Bankole A. Johnson, et al, Topiramate for the Treatment of Cocaine Addiction. JAMA Psychiatry. 2013; 70(12):1338-1346. | 1B | A | To determine the efficacy of topiramate in placebo and treatment of addiction to cocaine. | Randomized, double-blind study. |
| 2013 | US | Saladin, M.E., A double blind, placebo-controlled study of the effects of postretrieval propranolol on reconsolidation of memory for craving and cue reactivity in cocaine dependent humans. Psychopharmacology (Berl). 2013 April; 226(4): 721-737. | 1B | A | To examine the effects of Propranolol compared to placebo applied immediately after an active search session. | Randomized, double-blind study. |
| 2012 | US | Winhusen T et al. Evaluation of Buspirone for relapse-prevention in adults with cocaine dependence: an efficacy trial conducted in the real world. Contemporary Clinical Trials. 2012; 33(5):993–1002. | 1B | A | To evaluate the effect of aspirin in controlling cocaine addiction. | Randomized, double-blind study. |
| 2009 | US | Mooney ME. *et al*. Effects of Oral Methamphetamine on Cocaine Use: A Randomized, Double-Blind, Placebo-Controlled Trial. Drug Alcohol Depend. 2009; 101(1-2): 34–41. | 1B | A | To evaluate the safety, tolerability and efficacy of methamphetamine as a treatment for cocaine addiction. | Randomized, double-blind study. |
| 2006 | US | LaRowe, S.D, et al. Safety and Tolerability of N-Acetylcysteine in Cocaine-Dependent Individuals. Am J Addict. 2006; 15:105–110. | 1B | A | To evaluate the safety and tolerability of N-Acetylcysteine in cocaine-dependent patients. | Double-blind, controlled study, crossover. |
| 2003 | Australia | Shearer, J *et al*. Pilot, randomized double blind placebo-controlled study of dexamphetamine for cocaine dependence. Society for the Study of Addiction to Alcohol and Other Drugs. Addiction. 2003; 98:1137–1141. | 1B | A | To establish the feasibility of conducting a clinical paper controlled by dexamphetamine replacement therapy placebo for cocaine dependence and obtain preliminary data. | Randomized, double-blind study. |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2003 | US | Campbell, J *et al*. Comparison of Desipramine or Carbamazepine to Placebo for Crack Cocaine-Dependent. Am J Addict. 2003; 12(2):122-136. | 1B | A | To compare the effects of desipramine or carbamazepine over placebo in an intensive program of cocaine abuse. | Randomized clinical paper, double-blind. |

Figure 2.– characterization of selected studies.

As noted above, the publications of the selected studies obey the interval between the years 2001 and 2014, covering a larger number of disclosures from 2009. There was the predominance of international production, especially the United States (7 studies), and Australia (1 study). As noted, all studies are experimental, derived from randomized, double-blind clinical papers that fall within the 1B level of evidence, considered strong. The selection results of the studies are only provided for the treatment of cocaine craving.

For a better view, the data in Figure 3 were organized with two items: drug used to treat craving of crack/cocaine and outcome of drug treatment for craving of crack/cocaine.

| Drug used to treat craving of crack/cocaine | Result of drug treatment for craving of crack/cocaine |
|---|---|
| Desipramine and Carbamazepine | It shows improvements in self-evaluation over time related to craving. |
| Dexamphetamine | The percentage of cocaine-positive urine samples detected in the treatment group decreased from 94% to 56% as compared to no change in the placebo group (79% positive). Although improvements were not significant between groups, analysis within the group revealed that the treatment group had a decrease in self-reported use of cocaine (p=0.02) reduced the criminal activity (p=0.04), the reduced desires (p<0.01) and the reduced severity of cocaine dependence (p <0.01), without improvement in the placebo group. |
| N-Acetylcysteine (NAC) | The results suggest that the use of MAC is safe and decreased symptoms of craving. |
| Oral methamphetamine | The long-acting methamphetamine showed consistently lower rates of positive urine samples for cocaine and reported a reduction in the desire to consume cocaine. Methamphetamine prolonged action was associated with decreased sleep and increased weight loss. |
| Buspirone | The study showed that aspirin has a beneficial effect in reducing relapse and compulsion to use the drug. |
| Propranolol | The study presented evidence that Propranolol can modulate memory in cocaine craving. |
| Topiramate | Topiramate was more effective than placebo in increasing days of non-use and in reducing craving. |
| Ketamine | Ketamine has shown promising effects on motivation to quit cocaine and craving. |

Figure 3. Characterization of selected articles referring to the type of drug used medication and treatment outcome.

The selected studies for the treatment of cocaine craving used 09 different drugs. The more recent study [12] was the double-blind crossover type and conducted with eight volunteers presenting active addiction to cocaine and who were not in treatment or abstinent. Three intravenous infusions of 52 minutes of Ketamine or Lorazepam were given. The infusions were separated by 48 hours and evaluations were performed at baseline and after 24 hours of each infusion. Ketamine has shown promising effects on motivation to quit cocaine and craving.

The clinical paper with topiramate 13 consists of a double-blind, randomized, placebo-controlled study of 12 weeks with 142 cocaine-dependent adults (n=71) or placebo (n=71) in increasing doses of 50 mg/d to target maintenance dose of 300 mg/d, and combined with weekly cognitive-behavioral treatment. The results show that topiramate was more effective than placebo in increasing days of non-use and in reducing craving.

The study using Propranolol[14] followed 50 cocaine-dependent individuals, who received 40 mg of the drug or placebo immediately following a session of "recovery" exposure to cocaine stimuli. The study presented evidence that Propranolol can modulate memory operating in cocaine craving.

Another drug tested was the Buspirone[15], evaluating its effects in preventing relapse in cocaine users. Two clinical studies were conducted, a pilot (N=60) and other of large scale (Estimated N=264). Both practices were placebo controlled, randomized, double-blind. It was concluded that use of this drug has a beneficial effect on reducing cocaine craving.

Methaphetamine was evaluated by a double-blind, randomized, placebo-controlled

study,[16] considering treatment conditions in 82 individuals addicted to cocaine: (1) placebo (0 mg of 6×/day; n=27) (2) , immediate release (IR) methamphetamine (5 mg, 6×/day, n=30), (3) prolonged release (PR) methamphetamine (30mg first tablet, 1×/ day; 0 mg of 5×/day , n=25). The study used a sequential of two-step (that is, four weeks of medication and counseling followed by four weeks of medication/advice and a contingency management procedure). The results demonstrated the account of reduction of cocaine craving.

Also in this perspective, a Phase I cross-type, double-blind, placebo-controlled study was designed to evaluate the safety and tolerability of N-acetylcysteine (NAC) in healthy people, cocaine dependents.[17] In the practice, 13 participants remained in hospitalization for three days in those receiving placebo or NAC. The subjects were crossed over to receive the opposite medication condition during a second hospitalization of three days, which occurred in the following week. The results showed a reduction of craving for cocaine.

A double-blind, randomized placebo-controlled study was developed for 30 users dependent of injecting drugs cocaine dependentes to accomplish dexamphetamine replacement for cocaine dependence.[18] Participants were randomly assigned to receive 60 mg/day dexamphetamine (n=16) or placebo (n=14) for 14 weeks. The results enabled to identify, through self-report, reducing the craving.

With a similar goal, a double-blind, controlled study was conducted comparing the effects of Desipramine, of Carbamazepine and placebo.[19] There were 146 individuals participating in a study lasting 08 weeks. The results showed improvements in the self-assessments over time related to craving.

## DISCUSSION

It is estimated that cocaine and crack are consumed by 0.5% of the world´s population and most users - 70% - are concentrated in Americas.[1] Thus, it shows great need for developing studies in several countries since dependence on crack/cocaine is a problem that affects the whole world, endangering the lives of many people.

This fact concerns the whole society because the use of crack/cocaine is related to an inter-sectoral vision and associated with a wide range of psychiatric and social problems for the individual and population problems.[20] The interest in seeking alternatives to overcome drug dependence is emerging and necessary in the current context, given the associated problems, as previously mentioned.

In the last decade, some studies were conducted to search for a suitable drug for the treatment of craving crack/cocaine, which showed little significant positive results. A review by Vocci and Elkashef[21] shows that several pharmacological interventions were surveyed, including Disulfiram and GABAergic agents as Topiramate, Modafinil, and naltrexone. The review reveals that there is no evidence on the effectiveness of drugs for the treatment of cocaine dependence.

Given the absence of evidence-based medicines for the treatment of addiction, this study shows that in the United States almost all dependent patients receive standard treatment with psychosocial approach. However, this treatment has shown modest results, mainly due to the low adherence of dependents.[21]

However, there are some test results[12-19] that have had beneficial effects related to symptoms arising from cocaine removal. However, the scarcity of these results indicates the need to carry out further studies to subsidize them.

Most of the tests carried out show mixed results for each type of drug used. Another possibility of variation of results occurs with the combination of medication and behavioral therapies.[12-19] Studies with positive effects showed results as: reducing cocaine levels in urine, craving, behaviors considered antisocial and crime associated with the abuse of crack/cocaine.

It is essential to observe that in the search conducted for this review, there was no study designed to drug treatment for crack cocaine craving. Scientific evidence shows that the urgency for drug use and intensity of craving effects have the risk associated with drug use as a health public world problem.[5]

The relevance of craving is mainly due to the predisposition to violence and sexual behaviors associated risk, which trigger imbalances of social and health requirements for the user and their context[22]. Violence and sexual risk behavior affect society as a whole and not only crack users, increasing the spread of sexually transmitted diseases and insecurity of the population. This statement only reinforces the need to expand the performance of studies addressing drug treatment, to support the results observed in the available literature as well as increase the visibility of the problem, which has global dimension.

## CONCLUSION

The results of drug treatments with positive effects in this study were limited to the craving of cocaine. Eight studies have nine drugs tested positive for cocaine craving. It was observed that the drug therapy should join the assertions therapies that the isolated use of these not expected to produce the same positive effect. It is concluded, and it is considered that the analysis of studies suggests a potential role for pharmacotherapy in this scenario, especially for the craving of cocaine. The results of this review are consistent with the hypothesis of the need to develop new research that can improve the understanding of the mechanism of action of drugs and more specific drug interventions, and help confirm or reformulate proposed theories, through the results obtained.

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