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Ketamine in the treatment of cocaine use disorders

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ABSTRACT

Introduction: ketamine is a dissociative anesthetic and, recently, its antidepressant properties has been described. Besides, its safety has been proven in the treatment of Stimulant Use Disorders. Objective: to evaluate the use of ketamine in the treatment of Stimulant Use Disorders (specially cocaine and its byproducts). Methods: patient's motivation for change was measured by URICA scale and psychiatric symptoms by EAS-40 score, both before and after the intervention. Results: it was verified, after the comparison between the Readiness Score means, an increase in the motivation for change after ketamine's single administration, when compared to the moments before and after the intervention. Analyzing the Global Severity Index before and after ketamine administration, by EAS-40 score, we noticed a slight reduction of the psychiatric symptoms before and after the intervention. Conclusion: it was proven that ketamine's single administration led to a quick and lasting improvement on the user's motivation without worsening the mental health status.
Keywords: Cocaine treatment; Ketamine; Motivation; URICA; EAS-40

1 INTROUCTION

Ketamine is a selective NMDA receptor antagonist, and an indirect activator of the AMPA receptor signaling cascade. It is among the World Health Organization's List of Essential Medicines (WHO, 2015), where are the most effective and safe medicines for the needs of a health care system. It is used as a dissociative anesthetic in an attack dose

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range of 1 to 5 mg/kg, and 0.1-0.5 mg/min for maintenance. In the last decades, na antidepressant effect of ketamine was identified when used in subanesthetic doses (0.1-0.75 mg/kg), due to its action in the glutamatergic pathway, with a rapid and incisive action in the treatment of suicidal ideation and anhedonia (ZANOS *et al.*, 2016). In addition, it has proven its safety for use in the recommended doses for the treatment of psychiatric disorders (PERRY *et al.*, 2007).

Cocaine and its byproducts or mixtures (derived from base paste or with additives such as oxy, merla, and crack) are consumed by 0.3% of the world's population and most of its users are concentrated in the Americas, some studies citing a total of up to 70% of the entire world share. Its behavioral effects mainly cause increased alertness, euphoria and relief of dysphoric symptoms; when ceased, they are replaced by feelings of melancholy, hopelessness and sadness, contributing to the recurrence of use in a short time. To date, there is no formal indication of any specific drug that has shown to be especially effective in relieving withdrawal symptoms in cases of cocaine or its byproducts dependence. The therapeutic action aims to medicate the presented symptoms, provide clinical support in cases of medical complications and orient the patient to multidisciplinary approaches (GIGLIOTTI A, MALBERGIER A, MARQUES ACPR, MARQUES R; ANDRADA NC, LARANJEIRA R, BUZZINI RF, 2016).

The usual models to categorize the stages or levels of addiction in which each patient is included, correlates the substance use disorder and the individual's motivation for change. These levels of motivation for change are defined in five stages: pre-contemplation (when the user ignores the possibility for change), contemplation (the user demonstrates insight and begins to consider the change), determination or preparation (the user defines his plans for the change), action (the user initiates the change), maintenance (stabilization of the change itself). After a relapse (which can occur even from the contemplation phase), the user returns to any of the previous motivation levels. (PROCHASKA; DiCLEMENTE; NORCROSS, 1992; PROCHASKA *et al.*, 1994).

Several studies have identified cocaine-induced neuroadaptations in glutamatergic transmission and the importance of this mechanism in the genesis of addiction and abstinence syndromes (SCHMIDT; PIERCE, 2010; LALUMIERE, 2008).

It has been described that the potential mechanisms of action of ketamine, in the treatment of drug addictions, are mainly due to its effect on neuroplasticity, neurogenesis and synaptogenesis; directed disruption of established functional neural networks (such as connectivity between the medial prefrontal cortex and the Default Mode Network); in the reconsolidation of memories (reward and learning mechanisms); and its rapid antidepressant effect (common symptom in addiction and abstinence syndromes) (IVAN EZQUERRA-ROMANO *et al.*, 2018).

Previous investigations evaluating the use of subanesthetic doses of ketamine in cocaine-dependent individuals demonstrated a promising effect increasing the motivation of cocaine users to abstain from use, and also in the relief of withdrawal symptoms of cocaine symptoms (DAKWAR, ELIAS *et al.*, 2014), (DAKWAR, E. *et al.*, 2016), (DAKWAR, E. *et al.*, 2018). Previous clinical trials with up to two years of follow-up were conducted with similar methodology and efficacy for drugs such as alcohol and even heroin (KOLP *et al.*, 2009), (KRUPITSKY, EVGENY M; PH; GRINENKO, 1998), (KRUPITSKY, EVGENY *et al.*, 2002) (KRUPITSKY, EVGENY *et al.*, 2002); and studies in animal models have demonstrated efficacy even in nicotine dependence (REZVANI *et al.*, 2018).

This study evaluated the use of ketamine in the treatment of cocaine (and its byproducts) use disorders, monitoring the participants' motivation to abstain from drugs and also the evolution of their psychiatric symptoms in the moments before and after the intervention. This evaluation was made using University of Rhode Island Change Assessment (URICA)- Brazilian version assembled by Szupszynski *et al.* (2008), and Symptom Assessment Scale (EAS-40), (LALONI, 2001). Subsequently, we evaluated the parameters evolution after a single dose of ketamine (0.5mg/kg, subcutaneously) in order to estimate the frequency of administrations required to sustain the therapeutic improvements in a stable and lasting way. Especially in Brazil, this would be the first study

to specifically evaluate the therapeutic effects of ketamine in the treatment of cocaine related disorders.

2 METHODOLOGY

2.1 Type of Research

This is an uncontrolled, before-after, interventional study, which is justified by the fact that it was possible to evaluate the efficacy of ketamine as a therapeutic tool for the treatment of substance use disorder (specifically cocaine and its byproducts), history of harmful use, dependence or abstinence, according to the DSM-5 criteria.

2.2 Participants

A sample formed by 26 volunteer participants, from treatment services (CAPS-AD, therapeutic communities, outpatient from psychiatric clinics, among others) and/or referred to psychiatric beds of a general hospital in the Zona da Mata of Minas Gerais. All of them met the diagnostic criteria of the DSM-V for Stimulant Use Disorder, cocaine and/or its byproducts, without perceptual disturbances (AMERICAN PSYCHIATRIC ASSOCIATION, 2013).

All users were abstaining from illicit substances or alcohol at the time of the study. Tobacco use was not ruled out, considering that there was no unanimity about the interruption of smoking among the health services from which the users came. Medicaments already in use were kept, so we didn't change previous therapies.

2.3 Inclusion and exclusion criteria

This study included volunteers over 18 (eighteen) years old who met the diagnostic criteria of DSM-V for Stimulant Use Disorders, without perceptual disturbances, specifically

cocaine and/or byproducts (derived from the base paste or with additives such as oxy, merla, and crack), because these are the cocaine presentations most commonly used in Brazil (ABDALLA *et al.*, 2014). Patients who did not agree with the free and informed consent form, those under 18 (eighteen) years old, and those with Systemic Arterial Hypertension, patients with schizophrenia spectrum disorders, intellectual disability, patients with current diagnosis of acute psychotic disorders, acute intoxication or neurocognitive disorder; were excluded from the study, because these conditions could bias the data collection.

2.4 Therapeutic approach

The sample was initially submitted to a clinical and psychiatric evaluation, on the first day, to be admitted according to the inclusion and exclusion criteria of this research. After explaining the research details and the free and informed consent form, we collected the fist data (phase D0A) according to the objectives of this study. We used the Assessment Form for the social and individual data of each participant; the URICA assessment, which provides the Readiness Score (RS) for future analysis of the motivation for change of each participant; and the EAS-40 scale, which allow us to calculate the Global Severity Index (GSI) for future analysis of the psychiatric symptoms of each volunteer. The assessments and forms were read and monitored by the same examiner to avoid interpretation and communication mistakes (SZUPSZYNSKI; OLIVEIRA, 2008), (BANDEIRA *et al.*, 2011), (LALONI, 2001).

Then, the participants were submitted to ketamine administration at the therapeutic dose of 0.5mg/Kg subcutaneously (single dose). This is a therapeutic regimen based on reports from previous studies on the psychoactive potency and tolerability of subanesthetic doses of ketamine, comparable to the antidepressant dose. (PERRY EB. *et al.* 2007). Sixty minutes after the administration (D0D), the volunteers were submitted to a new evaluation though EAS-40 and URICA scales.

The day after the intervention (D1) we did a new assessment with EAS-40 and URICA scales. Subsequently, they were reevaluated with the same protocol at day 7 (D7), on the 15th day (D15) and on the 30th day (D30).

There was no psychotherapeutic approach in the participants before, during or after the intervention.

2.5 Data Collection and Analysis

The following data were collected: type of drug(s) of abuse (cocaine or specified byproduct), usage time, estimated dose of drug(s) used weekly; the main symptoms and adverse effects presented before, during and after the intervention; and the motivation for change after the ketamine treatment (Assessment Form, URICA and EAS-40 assessment scales).

The collected data were tabulated in Microsoft Excel 2016 and processed in SPSS Statistics (IBM) 23.0, considering a significance level of 5%. For descriptive analysis, the quantitative variables of the study were presented by the mean, standard deviation, median and their minimum and maximum values, according to parametric or nonparametric distributions, which was verified through the Shapiro-Wilk test. For the analysis of parametric variables, the paired Student's t-test was used for the dependent samples, and for the analysis of nonparametric variables, we use the Wilcoxon test.

The study was developed respecting ethical aspects according to Resolution 466/2012 of the National Health Council and approved by the Ethics Committee on Research with Human Beings of the Federal University of Viçosa (CAAE: 03062518.0.0000.5153).

3 RESULTS

About the sample (n=26), the age ranged from 18 to 59 years old, most of them men (88.46% men and 11.54% women), self-declared brown, unemployed (or temporary away from work due to health and treatment reasons), with low scholarship (1 illiterate, 14 with

elementary school, 10 with high school and only 1 with academic degree), religiously active (with most of them becoming religious by the beginning of their treatment), with family income below two minimum wages (only 6 patients were above two minimum wages and, among these, 2 patients with family income above 4 minimum wages). Most claimed to live with their families; 1 patient lived alone and 1 patient claimed to be "homeless" (traveler from another state, with an undefined family situation).

All participants reported a history of recent cocaine use and, among the other substances, marijuana and/or alcohol were the most common (for 16 and 15 of the participants, respectively). Cocaine byproducts (merla, oxi or crack) were used at least once by 8 patients. In addition, all participants were at a motivational stage equal to or higher than the “determination or preparation” stage.

Among the medications already in use, the most used class was benzodiazepines (only 1 patient did not use it; 17 used clonazepam, 7 diazepam and 1 alprazolam); and the other classes were: antipsychotics (chlorpromazine, quetiapine or risperidone), antidepressants (amitriptyline or fluoxetine), and several others (omeprazole, AAS).

Twenty-six individuals were submitted to the intervention and were followed up until D30. When analyzing the motivation for change, the URICA Scale variables (Readiness Scores) showed a normal distribution, as detailed in Table 1.

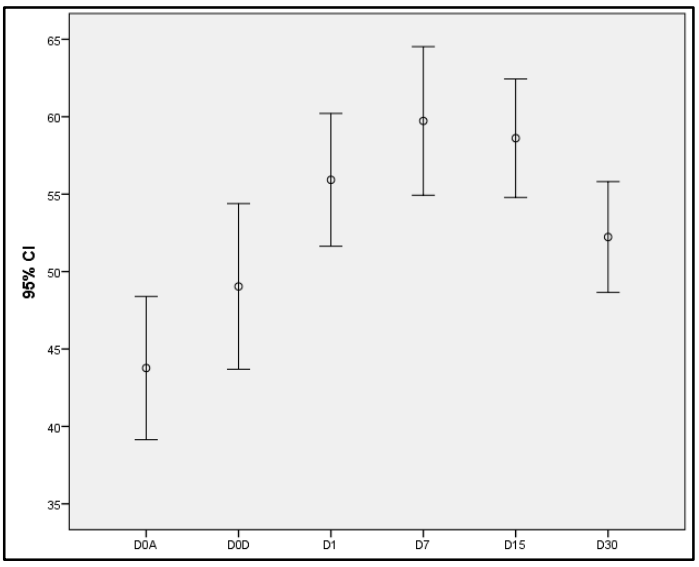
Table 1 – Means of Readiness Scores (RS) obtained through URICA assessment, according to each evaluation moment

Day	Average	IC95%
D0A	43,77	39,14 - 48,40
D0D	49,04	43,68 – 54,39
D1	55,92	51,64 – 60,21
D7	59,73	54,93 – 64,53
D15	58,61	54,79 – 62,44
D30	52,23	48,65 – 55,81

Source: Authors (2020)
In were: D0A: Day 0 before administration; D0D: Day 0 after administration; D1: 1 day after administration; D7: 7 days after administration; D15: 15 days after administration; D30: 30 days after administration.

Comparing the means of the Readiness Scores of each moment, we find that there was an increase in the motivation for change ($p<0.05$) after the intervention with a single administration of ketamine, when we compared the moment before the administration (D0A) with the following moments (D0D, D1, D7, D15 and D30). There was a decline in the means from D15, but the motivation for change was still statistically higher than the moment before the intervention, as shown in Table 2 and Figure 1.

Figure 1 – Comparison of the means between the moments before and after ketamine administration



Source: Authors (2020)

Table 2 – Comparison between the Readiness Scores (RS) means of the moment before the administration of the single dose of ketamine and the later moments

Moments	Average	Standard Deviation	P-value
D0A	43,77	11,46	0,001
D0D	49,04	13,25	
D0A	43,77	11,46	0.001
D1	55,92	10,61	
D0A	43,77	11,46	0.001
D7	59,73	11,88	
D0A	43,77	11,46	0.001
D15	58,61	9,47	
D0A	43,77	11,46	0.001
D30	52,23	8,86	

Source: Authors (2020)

In were: D0A: Day 0 before administration; D0D: Day 0 after administration; D1: 1 day after administration; D7: 7 days after administration; D15: 15 days after administration; D30: 30 days after administration.

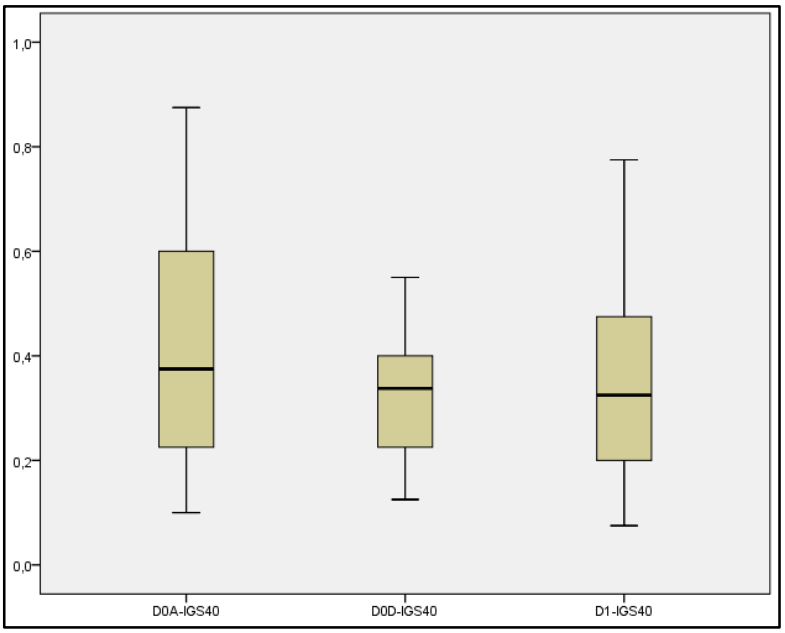
Analyzing the Global Severity Indices (GSI) before and after the ketamine administration, measured with the EAS-40 Scale, there was no difference in the participants' scores between the moments before the intervention (D0A) and after the intervention (D0D); as well as between the moments before (D0A) and 1 day after the intervention (D1), both with statistical significance (respectively p=0.021 and p=0.005). However, the comparison between the GSI after the intervention (D0D) and 1 day after an intervention (D1), we observed that there was a decrease in the score, but without statistical significance (p=0.864), as shown in the Table 3 and Figure 2.

Table 3 – Comparison between the medians of the Global Severity Index (SGA) of psychiatric symptoms at different times, according to the EAS-40 scale

Moments	Medians	Minimum-maximum value	P-value
D0A/	0,375	0,100 – 0,875	0,021
D0D	0,337	0,125 – 0,550	
D0D/	0,337	0,125 – 0,550	0,864
D1	0,325	0,075 – 0,700	
D0A/	0,375	0,100 – 0,875	0,005
D1	0,325	0,075 – 0,700	

Source: Authors (2020)
In were: D0A: Day 0 before administration; D0D: Day 0 after administration; D1: 1 day after administration; D7: 7 days after administration; D15: 15 days after administration; D30: 30 days after administration.

Figure 2 – Comparison of GSI medians at different times



Source: Authors (2020)

Interpreting the data from the statistical analysis of the GSI, it was verified that a single dose of ketamine promoted a decrease in the median of the sample scores at all times. Comparing these results, we can conclude that the medication was able to reduce the psychiatric symptoms of the participants quickly (in 60 minutes after administration), which lasted for at least 24 hours (time of the last measurement). The point is that the therapeutic effect found one day after the intervention was similar to that found already just in the first 60 minutes after the medication.

4 DISCUSSION

This study aimed to evaluate the therapeutic effects of ketamine on the motivation for change (search and maintenance of abstinence) in patients with Stimulant Use Disorder, cocaine and/or its byproducts, without perceptual disturbances) and possible changes in their psychiatric symptoms.

The evaluated sample was composed of cocaine drug addicts and/or byproducts in different motivational stages, belonging to different health services (each one with its own peculiarities of therapeutic approach) and of different age groups. There are distinct characteristics in the groups, but the patients share a common diagnosis, for which the

medication under study showed a rapid, robust, and statistically effective therapeutic response.

The serial comparison of the sample GSI sample, which reflects the patient perception of his psychiatric symptoms, concluded that after the intervention there was no worsening in the mental health status of the participants, but rather the opposite: the sample had a slight improvement of its GSI when compared to the scores performed before the intervention.

We found that, through the use of ketamine in a single dose and serial data collection at different times, it was possible to prove that the intervention led to a rapid and lasting improvement in the motivation for change of the participants (measured by their average RS). Even at the moments we observed a slight decrease in the sample average motivation (15th and 30th day), these levels (including that on the 30th day) remained statistically better than before the intervention. For this reason, it was not possible to evaluate the duration of the therapeutic effect of a single dose of ketamine, since the improvement in the Readiness Score (RS) of the sample verified even at the last moment of the study (30th day) did not return to a level close to the found before the intervention.

Thus, we could not accurately imply the frequency of ketamine administrations, in order to obtain a stable therapeutic result over time. Therefore, further studies will be needed to evaluate this pattern of evolution throughout a sufficiently longer time, allowing the correct estimate of this result.

As verified, the mean RS of the sample reflected an improvement in the motivation for the change of the participants already in the first 60 minutes after the intervention. Even with the decrease in the mean scores observed from the 15th day, this improvement continued to be higher than the first measure (before the intervention) including in the 30th day of follow-up ($p \leq 0.001$). Regarding the evolution of psychiatric symptoms (measured by the GSI), there was no worsening in the clinical-psychiatric pattern of the sample after ketamine administration. In contrast, the statistical analysis revealed that

there was even a slight improvement of the GSI between the moment before the intervention and after it.

The therapeutic approach focused on the drug addiction of cocaine and its byproducts, based on the modulation of glutamatergic excitatory pathways, specifically with ketamine, presents promising results. As evidenced by Dakwar *et al.* (2016), these results demonstrate that ketamine is an alternative medication that has shown, perhaps, an even more robust action than the dopamine agonists already used in the treatment of cocaine disorders. Comparing other drugs also used for the treatment of cocaine addiction, Dakwar *et al.* (2016) confirmed the superiority of ketamine over midazolam in improving the motivation of cocaine users to abstain from the drug. Similarly, it was also superior to lorazepam in its ability to optimize the patient RS, sustaining this effect for at least 4 weeks of observation (DAKWAR *et al.*, 2014).

In addition, we have seen that ketamine has been tested for the treatment of depressive disorders in the last decades. Its action can promote fast and substantial improvement on patient's depressive mood, including fast remission of suicidal ideation; whose effects lasted for days and even for weeks. Berman *et al.* (2000), in their double-blind, placebo-controlled clinical trial, reported that a single administration of ketamine at a dose of 0.5mg/kg resulted in rapid antidepressant effects. Knowing that depressive symptoms are an important risk factor for relapses in patients with dependence or abstinence syndromes due to cocaine and/or its byproducts use, we can conclude that the controlled administration of ketamine is capable of reversing the glutamatergic changes associated with depression and, consequently, remitting the symptoms and reversing the psychopathological dynamics of drug addictions (IVAN EZQUERRA-ROMANO *et al.*, 2018).

Previous studies have proved that ketamine in subanesthetic doses promotes substantial effects in cocaine addicts, including an increase in motivation for change, a reduced desire for cocaine use and finally, a decrease in consumption rates of the drug (DAKWAR *et al.*, 2019). The anxiety related to the drug abuse, the general demotivation of the patient, and a high behavioral reactivity are recognized as compromising factors that worsen the chances of modifying the drug-related behavior, which negatively impacts in

the treatment engagement. In their study, Ivan Ezquerra-Romano *et al.* (2018) also proved that ketamine is capable of promoting a significant reduction of the eager for cocaine use, in addition to effectively decrease the impulse and the hyper-reactivity of drug-addicted patients up to 48 hours after the administration of the medication, which is essential to avoid future relapses.

Other design of interventions using ketamine obtained similar results. In a randomized double-blind trial using ketamine associated with psychotherapy, Krupitsky *et al.* (2002) found effective changes in patients with heroin use disorder already under treatment, verifying that, after the intervention, patients began to adopt positive attitudes aimed at the abstinence promotion.

The mechanisms involving the dynamics of cocaine-induced dysfunctional neuroadaptations in glutamatergic transmission are of fundamental importance in the genesis of disorders of cocaine and/or it's byproducts use (SCHMIDT; PIERCE, 2010). Regarding to the neurobiological patterns involving reward mechanisms in chemical dependence, it is also known that there are genetic characteristics that directly affect negative neuroadaptive changes that may arise after the exposure to drugs (either after a single exposure, repeatedly or with prolonged use).

In drug addictions, one of the main objects of study are the changes in the dopaminergic dynamics of the mesolimbic pathway, as they affect the reward and learning functions; which even explains the so-called "gateway effect", referring to the capacity of a drug to lead an individual to its continued use or even to the abuse of other drugs (DUNN *et al.*, 2019). Ketamine's most relevant mechanisms of action to the approach based on the neurobiological patterns of drug addictions are mainly due to its effect on the direct disruption of established dysfunctional neural networks (such as connectivity between the medial prefrontal cortex and the "Default Mode Network"); the reconsolidation of memories (reward and learning mechanisms); the neuroplasticity, synaptogenesis and neurogenesis; and also on its rapid antidepressant effect (a common symptom in cocaine dependence and withdrawal syndromes).

In a research about the action of subanesthetic doses of ketamine and neurological mechanisms involving the use of nicotine, Rezvani *et al.* (2018) reported that the role of glutamatergic transmission in the regulation of the mesolimbic system is closely related to the reward mechanisms involved in the psychodynamics of drug addictions; and, through their study design, concluded that the antagonism of NMDA glutamatergic receptors promoted by ketamine may also be effective against nicotine dependence. Similarly, Li *et al.* (2014) showed that modulating the pathways related to the neurobiology of drug addictions reducing glutamatergic transmission by blocking the post-synaptic glutamate receptors, or activating presynaptic inhibitors, or increasing the inhibitory activity of GABAergic transmissions, may inhibit reward and conditioning mechanisms related to nicotine use.

Thus, ketamine is capable of promoting the interaction between brain structures associated with cognitive information processing (frontal cortex) and involved structures in the processes of emotions, motivation, memory, and subconscious experiences and perceptions (limbic structures) (KRUPITSKY, EVGENY *et al.* 1997).

Therefore, we can imply that the therapeutic effects of ketamine on Stimulant Use Disorders, specifically cocaine and/or its byproducts (without perceptual disturbances), are able to promote a higher rate of abstinence, similar to the effects of other NMDA receptor ligands, such as acamprosate and ibogaine.

5 CONCLUSION

Ketamine showed positive therapeutic effects according to the expected outcome, and without causing worsening of psychiatric symptoms in the sample. However, even reaching a sample number higher than some theoretical references used, clinical trials are still needed to expand these results and evaluate the efficacy of this intervention in a larger sample.

In the future, this research may encourage the production of new theoretical-scientific foundations to the creation of practical protocols, eventually. Regarding the

reality of many patients with cocaine and its byproducts related disorders, which lives in social vulnerability conditions, a safe therapeutic option, of very low cost, with fast, lasting and effective action, as evaluated by ours and other studies, may represent a new form of access to a specific treatment.

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