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Use Of Passiflora Incarnata L. Herba In The Treatment Of Cocaine Use Disorders: The Experience Of An Addiction Center In Monza, Italy.

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ABSTRACT

The authors report a real-world experience on the treatment of cocaine use disorders (craving) in outpatient treatment subjects at the addiction centre in Monza (MB, Italy). 38 patients with Substance Use Disorder (Cocaine) were enrolled over one year for substance craving treatment with Passiflora Incarnata L Herba at a dose of 600 mg/day for a period of two months. All patients were assessed with two craving measurement scales and two clinical scales: one measuring anxiety and one depression. The assessments were carried out before treatment (To), after the first month (T1) and after the second month (T2) of Passiflora treatment. 16 patients finished the first month of treatment and only 9 completed the two months. This high attrition in the patient sample is usual in outpatient addiction treatment centres. There were no significant age differences between patients discontinuing treatment and those completing the two months of treatment. The scales administered show that patients completing two months of treatment have a significant reduction in both cocaine craving and anxiety and depression. In particular, it is reported that the most significant improvement is seen in anxiety and the dimension of craving related to it. Further and larger studies are needed to confirm the efficacy of Passiflora Incarnata L Herba in reducing cocaine craving at least for those DUS patients who have the constancy to take it regularly for at least two months.

INTRODUCTION

Craving symptoms are a fundamental characteristic of Cocaine Use Disorder (CUD) and remain a significant challenge in terms of treatment. Craving is pivotal in addiction processes, acting both as a cause and a consequence of chronic drug use. Consequently, numerous recommendations suggest that craving should be included as a standard outcome in the treatment of substance use disorders [1;2]. Craving is highly significant for addicts, as it is often described as an obstacle to quitting drug use [3]. For this reason, there is evidence that craving itself can be a predictor of relapse [4;5]. Treatments for drug use can influence craving levels, making it an important therapeutic target given its close correlation with withdrawal symptoms and relapse prevention. Indeed, many FDA-approved medications for various forms of drug dependence have been shown to reduce craving [6;7;8].

Although various pharmacotherapies have been tested to reduce craving in cocaine use disorder [9], the Food and Drug Administration (FDA) currently does not recognise specific pharmacological treatments for cocaine-related disorders [10].

Passiflora (P.) incarnata Linnaeus, commonly known as passionflower, has a long history of use as a traditional herbal medicine. It belongs to the Passifloraceae family, which consists of 16 genera and includes more than 600 species, most of which are indigenous to the tropics and subtropics of the New World [11]. Most Passiflora species are used in the pharmaceutical, food, and cosmetics industries. Recently, it has been discovered that P. incarnata extract can reduce tension, restlessness, and nervous irritability, making it beneficial

Journal of Psychiatry Research (ISSN 2995-6439)

for alleviating insomnia and anxiety. Previous studies have demonstrated the potential effects of P. incarnata on anxiety, insomnia, attention deficit hyperactivity disorder, opioid withdrawal symptoms, and menopausal symptoms [12;13]. The dysfunction of the GABA system is implicated in anxiety and depressive disorders. Extracts of P. incarnata have been shown to act on the GABA (gamma-aminobutyric acid) system, suggesting that the plant's sedative activity may derive from positive modulation of GABA receptors [14]. The pharmacological effects of P. incarnata are thought to be mediated through the modulation of the GABA system, including affinity for GABA(A) and GABA(B) receptors as well as GABA uptake [15].

The rationale for this study is grounded in the multifaceted nature of craving and the pressing need for alternative treatments in CUD. Given the promising anxiolytic and sedative properties of P. incarnata, its potential to address both the psychological and physical components of craving warrants thorough investigation. This study aims to provide a structured approach to evaluating the potential benefits of P. incarnata L. in reducing cocaine craving symptoms. By doing so, it hopes to contribute to the broader understanding of alternative treatments for cocaine use disorder and pave the way for larger, controlled studies to confirm these initial findings.

MATERIALS AND METHODS

Study population

A total of 38 patients of both sexes (33 males and 5 females), aged over 18 years (mean age 39.45 ± 9.66), with an active diagnosis of cocaine use disorder (CUD) according to DSM-5-TR criteria, were recruited from the Addiction Service (SerT) of Monza, Italy. The recruitment took place over one year (from December 2022 to December 2023). All participants experienced craving symptoms and provided informed consent to be treated with P. incarnata L. herba for a period of at least two months. The assessment of patients undergoing naturalistic treatment for cocaine craving was performed using the following scales: Cocaine Craving Questionnaire-Brief (CCQ-B), Cocaine Selective Severity Assessment (CSSA), Beck Anxiety Inventory (BAI), and Beck Depression Inventory (BDI). Assessments were scheduled at baseline (T0), and after one month (T1) and two months (T2) from the start of the treatment.

Treatment

The enrolled patients, after signing informed consent, were prescribed therapy with P. incarnata L. herba at a dose of 200 mg tablets: three tablets per day, totaling 600 mg daily. This drug was approved in Italy by AIFA (Agenzia Italiana del FArmaco) as a medical product since November 2020 (commercial name "Tractana"). During follow-up visits, based on the clinical course and patient response to therapy, the dosage was adjusted for two patients. One patient had their dosage increased to four tablets per day (800 mg), while another patient requested a reduction to two tablets per day (400 mg) after the first four weeks. For all other patients there were no issues with taking P. incarnata L. herba at the dosage of 600 mg per day.

Study Design

To monitor the severity of craving, several assessments were conducted over a period of two months. An initial baseline evaluation was performed at time zero (T0), followed by follow-up visits every four weeks, for a total duration of eight weeks. During the first visit and subsequent follow-ups, four clinical scales were administered to evaluate and analyze the clinical presentation of withdrawal symptoms and any changes observed over time as a result of the therapy with P. incarnata L. herba. All patients were administered two scales for the assessment of craving (Cocaine Craving Questionnaire Brief and the Cocaine Selective Severity Assessment) and the two Beck scales for the assessment of anxiety (Beck Anxiety Inventory) and depression (Beck Depression Inventory).

Statistical Analysis

For the statistical analysis of the data, SPSS 29 software was used. Continuous variables were analyzed using repeated measures analysis of variance, while nominal and ordinal variables were analyzed using chi-square statistics.

RESULTS

Sample Analysis

Out of the initial cohort of 38 patients in the study (T0), 16 continued their medication regimen for four weeks, undergoing the first follow-up assessment (T1), while 9 persisted for eight weeks, also completing the second scheduled evaluation (T2).

The study comprised 38 patients of both genders, with 5 females (13,2%). The mean age was 39± 10 years. Among the participants, the majority were single 16 (42%), with 11 (29%) being married, and 11 (29 %) separated or divorced. Seventeen (45%) were parents, and 22 (58%) were employed. Three individuals (8%) were homeless. Additionally, eleven (29%) had a psychiatric diagnosis, including: 7 with personality disorders, 3 with psychoses, and 1 with bipolar disorder; while 6 (16%) had an alcohol use disorder. For a more detailed insight into the demographic characteristics of the patients at different evaluation times (**Table 1**)

Journal of Psychiatry Research (ISSN 2995-6439)

Table 1. Demographic data of the enrolled study population.

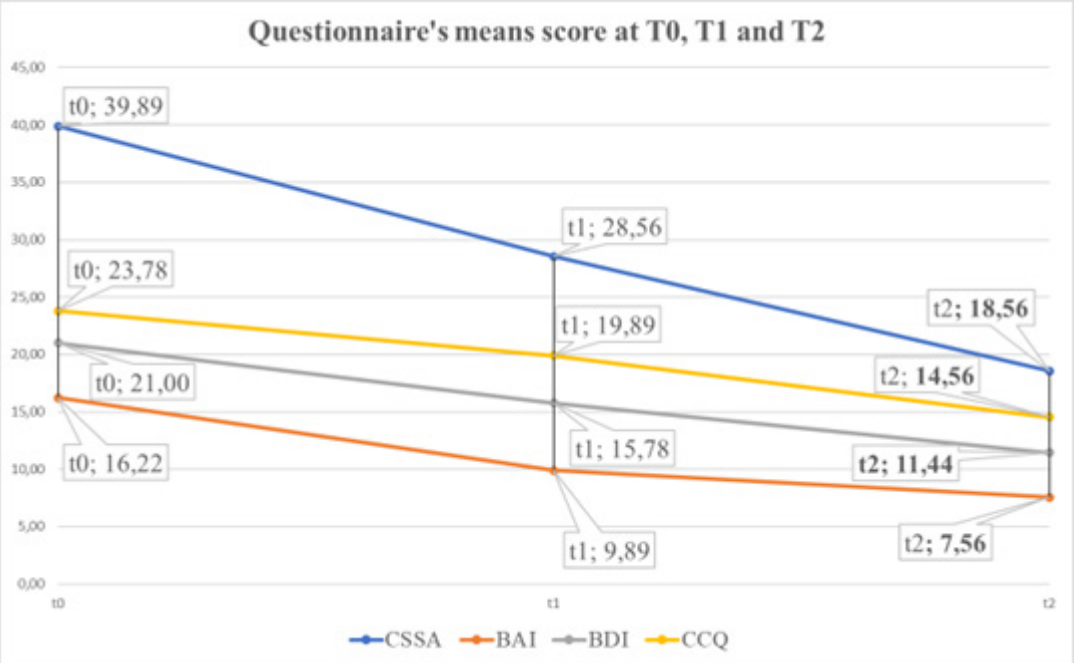
	T0 N 38 (5 F)	T1 N 16 (3 F)	T2 N 9 (2 F)
Mean Age ± d.s.	39± 10	40 ± 11	45 ± 9
Homelessness	3 (8%)	2 (13%)	0
Single	16 (42%)	10 (63%)	4 (44%)
Married	11 (29%)	3 (19%)	3 (33,3%)
Sep. or div.	11 (29%)	2 (13%)	2 (22,2%)
Offspring	17 (45%)	2 (13%)	2 (22%)
Employed	22 (58%)	8 (50%)	6 (67%)
Psychiatric diagnosis	11 (29%)	6 (38%)	3 (33%)
Alcohol	6 (15%)	4 (25%)	1 (11%)

Out of the 38 enrolled patients, 29 (76%) did not complete the study. Their discontinuation was observed over the 8-week treatment period as follows: 23 patients (61%) withdrew from the study before reaching the 4-week mark (T1). The reasons for discontinuation were varied: six (16%) were placed into a Therapeutic Community while seventeen (45%) suspended access to the service for addiction-related reasons. Additionally, six patients (16%) dropped out after T1 but before the completion of the full 8 weeks for evaluation at T2: one patient was admitted to a therapeutic community, another cited financial difficulties in acquiring Tractana, and one reported experiencing drowsiness as a light side effect, resolved with the discontinuation of the drug. Three patients (8%) discontinued access to the service for addiction-related reasons.

The high rate of treatment discontinuation is characteristic of populations attending addiction services, particularly among patients with a cocaine use disorder. These findings underscore the challenges associated with retaining patients throughout the study duration and highlight the complexities involved in managing addiction treatment programs.

Overall, the analysis conducted indicates a significant decrease in the scores recorded across all four administered scales at the eight-week follow-up (T2).

Figure .



As can be seen from the graph, the CCQ score showed a statistically significant decrease from T0 (23.78 ± 13.75) to T2 (14.56 ± 6.69). The CSSA score decreased from T0 (39.89 ± 15.67) to T2 (18.56 ± 15.21). The BDI score started at T0 (21.00 ± 9.925)

Journal of Psychiatry Research (ISSN 2995-6439)

and decreased to 11.44 ± 11.27 at T2. The BAI score showed a decrease from T0 (16.22 ± 10.592) to T1 (9.89 ± 6.66), which was further confirmed at T2 (7.56 ± 9.11). Next, the results of the individual scales will be illustrated.

Cocaine Craving Questionnaire-Brief

The CCQ-Brief consists of 10 statements regarding the participant's feelings and thoughts about cocaine use while completing the questionnaire [16]. Each item is scored on a scale ranging from 1 for "Strongly Disagree" to 7 for "Strongly Agree." A total score is obtained by averaging all items. This tool provides an instant snapshot of the participant's overall cocaine craving experience.

The total CCQ score showed a statistically significant decrease from T0 (23.78 ± 13.75) to T2 (14.56 ± 6.69) ($F = 3.580$, $p = 0.052$, $df = 2/16$; post-hoc T0 vs T2: $p = 0.023$). In addition to analysing the overall scale results at the three time points, individual items were also considered to study which dimensions contributed to the total change.

The statistical analyses conducted to identify the variation of each individual item revealed a statistically significant change from T0 (3.22 ± 2.49) to the reassessment at T2 (1.11 ± 0.33) for statement N3 of the questionnaire, which relates to "I intend to use cocaine as soon as possible" ($F = 4.734$, $p = 0.024$, $df = 2/16$; post-hoc T0 vs T1: $p = 0.223$; T0 vs T2: $p = 0.026$).

Cocaine Selective Severity Assessment

The CSSA is a simple scale that reliably and validly measures the signs and symptoms of cocaine withdrawal [17]. The scale assesses symptoms over the past 24 hours, evaluating 18 specific symptoms (hypophagia, hyperphagia, craving for carbohydrates, intensity of craving for cocaine, frequency of craving for cocaine, bradycardia, qualitative sleep disturbance, quantitative sleep disturbance, anxiety, energy level, activity level, tension, attention, paranoid ideation, anhedonia, depression, suicidality, irritability), each rated on a scale from 0 to 7. CSSA scores tend to be higher in patients with more severe cocaine dependence and to decrease with abstinence. Higher severity scores tend to be associated with less favourable prognosis for treatment outcome.

Analysing the variation in the total CSSA score from T0 to T2, a significant reduction was observed among the total of 9 patients between T0 (CSSA 39.89±15.67) and T2 (CSSA 18.56 ± 15.21) ($F=5.146$, $p=0.019$, $df=2/16$, post-hoc T0 vs T2 $p=0.011$).

In the analysis of this scale, particular attention was given to the evaluation of the VAS (Visual Analogue Scale) in the parameters of intensity (VAS int) and frequency (VAS freq) of Craving.

The intensity of craving episodes (VAS int) and the frequency of craving episodes (VAS freq) both showed a statistically significant decrease from T0 to T2. Specifically, the value of VAS freq decreased from VAS freq T0: 3.44 ± 2.698 to Vas freq T2: 1.33 ± 1.658, while the value of VAS int at T0 corresponded to 4.33 ± 2.784 and at T2 it was 2,11 ± 2.315.

Analyzing the variation over time of the individual items comprising the CSSA, it was observed that the values related to experienced anxiety and activity both significantly decreased from T0 to T2, while the anhedonia item showed a significant decrease between baseline and the reassessment at four weeks. All other items showed non-significant decreases (table 2).

Table 2. Significant findings for the CCQ. M =mean; SD=standard deviation; F= F-value, d/f= Degrees of Freedom; p= p-value of within-subjects effect test.

	T0 (M± DS)	T1(M± DS)	T2 (M± DS)	F, d/f	p-value	Post-hoc T0 vs T1	Post-hoc T1 vs T2
VASfreq	3.44 ± 2.698	2.11±2.315	1.33 ± 1.658	3.409, 2/16	p=0.058	p=0.195	p=0.036
VASint	4.33 ± 2.784	2.67±2.236	2,11 ± 2.315	4.255, 2/16	p=0.033	p=0.115	p=0.033
Anxiety	3.78 ± 2.386	2.00 ±1.581	1.44 ± 1.333	6.306, 2/16	p=0.010	p=0.060	p=0.009
Activity	2.78±2.635	1.78±2.167	0.56±1.333	3.792, 2/16	p=0.045	p=0.246	p=0.038
Anhedonia	3.56±2.351	1.44±2.297	1.11±1.833	7.817, 2/16	p=0.004	p=0.036	p=0.013

Beck Depression Inventory

The BDI is a scale that investigates the presence of depressive symptoms and assesses their severity. The Beck Depression Inventory consists of 21 questions, each of which can be answered in four ways; each response is associated with a number from 0 to 3, depending on the degree of applicability to the described reality. Based on the scores obtained, the symptomatology can be classified as follows: 0-13: minimal depression; 14-19: mild depression; 20-28: moderate depression; and 29-63: severe depression [18].

Journal of Psychiatry Research (ISSN 2995-6439)

The initial mean values of BDI (T0: 21.00 ± 9.925) experienced a significant decrease after eight weeks of continuous therapy intake, reaching a mean value of BDI at T2: 11.44 ± 11.27 (F=3.691, p=0.048, df=2/16, post-hoc T0 vs T2 p=0.025).
In the analysis of individual items, it was found that self-criticism, agitation, loss of interest and sleep disturbances all experienced a statistically significant decrease in score from baseline to the reassessment conducted after eight weeks of continuous therapy intake (table 3).

Table 3. Significant findings for the BDI. M= mean; SD=standard deviation; F= F-value; d/f = Degrees of Freedom; p= p-value of within-subjects effect test; BDI8 =self-criticism; BDI11 = agitation; BDI12= loss of interest; BDI16 = sleep disturbances.

	T0 (M± DS)	T1(M± DS)	T2 (M± DS)	F, d/f	p-value	Post-hoc T0 vs T1	Post-hoc T1 vs T2
BDI8	1.22±1.093	1.00±0.707	0.33 ±0.500	3.782, 2/16	p=0.045	p=0.594	p=0.035
BDI11	1.33±1.225	0.67±0.866	0.33 ±0.707	4.308, 2/16	p=0.032	p=0.141	p=0.040
BDI12	1.33±1.118	0.89±1.054	0.44 ±0.726	4.000, 2/16	p=0.039	p=0.169	p=0.035
BDI16	1.22±0.972	0.56±0.527	0.67±0.500	4.960, 2/16	p=0.021	p=0.050	p=0.051

Beck Anxiety Inventory

The BAI is a self-administered tool consisting of 21 items that assess the presence and severity of anxiety symptoms. Each item is rated on a 4-point scale (0 = not at all, 3 = severely). Total scores are interpreted as follows: < 9 indicates no anxiety, 10-18 mild/moderate anxiety, 19-29 moderate/severe anxiety, and 30-63 severe anxiety [19].
The analyses conducted in this case revealed a significant decrease in the experienced anxiety symptoms from T0 (16.22 ± 10.592) to T1 (9.89 ± 6.66) to T2 (7.56 ± 9.11) (F=8.723, p=0.003, df=2/16, post-hoc T0 vs T2 p=0.003; T0 vs T1 p=0.037).
In the analysis of individual items of this scale, it was found that the inability to relax and palpitations both experienced a significant decrease from T0 to T2, while items representing mood instability and significantly decreased already at the first reassessment at four weeks (table 4).

Table 4. Significant findings for the BAI. M= mean; SD=standard deviation; F= F-value; d/f = Degrees of Freedom; p= p-value of within-subjects effect test; BAI4 =inability to relax; BAI7 = palpitations; BAI8 = mood instability; BAI10 = agitation.

	T0 (M± DS)	T1(M± DS)	T2 (M± DS)	F, d/f	p-value	Post-hoc T0 vs T1	Post-hoc T1 vs T2
BAI4	1.78±1.093	1.11±0.601	0.89±0.928	4.119, 2/16	p=0.036	p=0.081	p=0.021
BAI7	1.22±0.833	0.78±0.833	0.44±0.527	4.774, 2/16	p=0.024	p=0.104	p=0.008
BAI8	1.67± 0.707	0.67±0.500	0.78±0.833	11.019, 2/16	p=0.001	p=0.003	p=0.002
BAI10	1.67±1.118	0.78±0.667	0.33±0.707	10.419, 2/16	p=0.001	p=0.021	p=0.002

DISCUSSION

The above report indicates that the population of patients affected by Cocaine Use Disorder (CUD) exhibits poor compliance due to the difficulty in maintaining even a simple therapy like passionflower for limited periods such as the two months considered. Out of 38 patients enrolled, 16 (42%) completed one month of therapy, and only 9 (24%) managed to maintain the treatment as prescribed for two months. This dropout rate of 29 patients (74%) was not due to the presence of side effects from the medication, which occurred in only one case (3%) where the patient complained of daytime sleepiness. For 7 patients (18%), the study was interrupted due to admission to a therapeutic community; the majority, or 20 patients (53%), did not attend scheduled follow-ups without a specific reason (service abandonment); only one patient (3%) discontinued the study due to the cost of the therapy, which was their responsibility.
The study was conducted using a “real-world” methodology, meaning no modifications were made to the usual prescribing practices of the doctors working at the addiction treatment center located in Monza, Italy. This was a longitudinal naturalistic study in which no changes were made to the usual clinical practice. Instead, the focus was solely on observing the phenomenon through the administration of the described scales.

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Patients who adhered to the prescription for the two months showed a significant decrease in the scales administered for assessing craving (CCQ-brief and CSSA) and for evaluating anxiety and depression (BAI and BDI). This improvement was significant mainly between the start of therapy (T0) and the two-month evaluation (T2). The high dropout rate may have influenced the outcome of the comparison between T0 and T1, so through a multifactorial statistical analysis, the comparison between T0 and T2 was found to be significant.

Breaking down the various scales into individual items, it was observed that statement N3 of the CCQ-brief questionnaire, "I intend to use cocaine as soon as possible," exhibited a significant reduction only at T2. This delayed effect can be attributed to the fact that this item addresses a crucial aspect of substance craving, which requires more time to show noticeable changes. The CCQ-brief is designed to reflect overall cocaine craving rather than investigating its individual components. Multi-item measures like the CCQ-brief are often better suited for monitoring craving throughout treatment, as they tend to be more sensitive to changes in drug desire compared to single-item measures [20]. The literature highlights that patients in recovery from cocaine addiction frequently identify increased craving as a major trigger for relapse [21; 22]. Therefore, addressing this specific item is highly promising.

The CSSA scale, different from the CCQ-Brief, is a multi-voiced questionnaire that evaluates the experienced cocaine withdrawal by exploring the emotional, cognitive, physiological, and behavioural components involved. In the analysis of the CSSA scale, cocaine craving emerged as a substantial component, with both the intensity and frequency of cocaine desire showing strong correlations with the overall scale. A significant decrease was observed in Visual Analogue Scale (VAS) values for both the intensity (VAS int) and frequency (VAS freq) of craving. However, both parameters required an extended duration of treatment with "Tractana" to demonstrate effectiveness, with improvements noted at eight weeks. Among the other items analysed, experienced anxiety and activity levels significantly decreased from T0 to T2, while anhedonia was the only item that exhibited a significant reduction as early as four weeks.

Craving has multidimensional facets that extend beyond the mere category of desire. In particular, levels of depression and anxiety have shown strong positive correlations with cocaine craving [23; 24]. For this reason, the assessment of changes in experienced depression (BDI) and anxiety (BAI) was included in our study.

Analysing the overall values of the Beck Anxiety Inventory (BAI), it can be observed that the mean BAI score shifts from a value indicative of mild/moderate anxiety (BAI meanT0 = 16.22) to a value consistent with the absence of anxiety symptoms (BAI meanT2 < 9). In this case, mood instability and agitation significantly reduced after the first month, while inability to relax and palpitations required more time to improve, showing progress after two months. These findings support existing literature, which highlights the anxiolytic activity of P. incarnata [13;25].

Regarding the Beck Depression Inventory (BDI), a reduction in both the overall score and significant individual items was observed from T0 to T2. The reduction led to a shift in category; while the initial mean BDI score was 21, indicative of moderate depression, by the end of the follow-up, the mean score had decreased to 11.44, consistent with minimal depression. The items that showed significant improvement included self-criticism, agitation, loss of interest, and sleep disturbance.

These findings indicate a substantial positive impact of the intervention on depressive symptoms. The notable improvements in specific areas such as self-criticism and sleep disturbance suggest a comprehensive amelioration of both cognitive and physiological aspects of depression.

Therefore, we could hypothesise that the reduction in craving for patients treated with passionflower is due to the GABAergic anxiolytic effect of the molecule, which acts on sleep, agitation, irritability, tension, inability to relax, and palpitations. These symptoms are characteristic of anxiety and are part of the discomfort experienced by individuals who feel the absence of the substance they depend on. This discomfort, subjectively felt both physically through lack of rest and palpitations, and psychologically through tension, agitation, and irritability, increases the desire to use the substance that alleviates them, in this case, cocaine craving. The combined reduction of these symptoms and the relative desire for the substance allows for the disappearance of intentions to use it and the resumption of other interests, reducing anhedonia and instability.

CONCLUSION

The results of this study underscore the potential efficacy of Passiflora (P.) Incarnata L. herba in reducing cocaine craving and associated anxiety and depressive symptoms in individuals with Cocaine Use Disorder (CUD). Despite the high dropout rate, the data from patients who completed the study indicate significant improvements in craving, anxiety, and depression scores after two months of treatment. One of the key findings is the significant reduction in craving intensity and frequency, as measured by the CCQ-Brief and CSSA scales. This reduction is particularly noteworthy given the complex nature of craving and its strong correlation with relapse risk. The significant decrease in the intent to use cocaine (CCQ statement N3) and the overall improvement in craving parameters suggest that Passiflora incarnata could be a valuable addition to CUD treatment protocols.

Journal of Psychiatry Research (ISSN 2995-6439)

Furthermore, the improvements in anxiety and depression scores, as measured by the BAI and BDI, provide additional support for the anxiolytic and antidepressant properties of P. incarnata. These findings are consistent with the existing literature on the plant's effects on the GABAergic system, which is implicated in both anxiety and depressive disorders. The challenges faced in this study, particularly the high dropout rate, highlight the difficulties in maintaining patient engagement in addiction treatment programs. These challenges are not unique to this study and reflect broader issues in the treatment of substance use disorders. Future studies could benefit from strategies to improve patient retention, such as more frequent follow-ups, support interventions, and addressing barriers to medication access.

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