

**Craving Decrease with Topiramate in Outpatient Treatment for Cocaine Dependence:  
an open label trial.**

**Diminuição da Fissura com Topiramato no Tratamento Ambulatorial para  
Dependência de Cocaína: um Ensaio Clínico Aberto.**

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## ABSTRACT

**Objectives:** To evaluate the anti-craving action and tolerability of oral topiramate in inhaled cocaine users' treatment.

**Methods:** A sample of 28 male users of inhaled cocaine which met criteria from DSM IV for cocaine dependence were selected for outpatient 12 week treatment with topiramate, individual dosage varied increasingly (25 to 300 mg/day) in an open label trial. The main clinical variables were: (1) Rate of abstinence, (2) Intensity, frequency and duration of craving, (3) Adherence, (4) Dropouts, (5) Side effects, (6) Impulsivity measure through Barratt Impulsivity Scale (BIS 11). Each patient received both assertive strategic counseling for abstinence assistance and medication monitoring evaluation every two weeks. Comparative analysis between evaluations was made to the subjects with Intention to Treat (ITT); the missing values were replaced by the last observed value of that variable (LOCF – Last Observation Carried Forward) and the significance level was 5%.

**Results:** Adherence to the treatment was of 57% (received three evaluations), 32% dropped out (only one evaluation) to an attendance average of 3,14 ( $\pm$  1,80). The mean dose was 127,27 mg/day ( $\pm$  93,19). There were no severe side effects noted. Negative test average was 25.4%  $\pm$  31.2. From the N= 28 evaluated patients a significant statistical reduction was observed in n= 7 (25%) regarding the intensity of craving of 1,18 (dp=2,33) when compared to baseline evaluation (p= 0,012), regarding the duration of craving a significant statistical reduction was also observed n= 7(25%) (p=0,018). Craving frequency variation was not significant (p= 0,783). There were no significant statistical variations for the use of BIS11 nor in the total score in the final evaluation when compared to baseline impulsivity assessment (p> 0,05).

**Conclusion:** Topiramate seems to be a possible therapeutic approach for craving reduction in cocaine users. However, more randomized placebo-controlled trials with topiramate for cocaine dependants should be made to investigate this finding.

**Key words:** Craving, Cocaine - Related Disorders, Topiramate, Clinical trial

## RESUMO

**Objetivos:** Avaliar a ação antifissura e tolerabilidade do topiramato oral no tratamento de usuários de cocaína aspirada.

**Métodos:** Ensaio clínico aberto, com 28 usuários de cocaína aspirada, todos masculinos, que preencheram critérios do DSM IV para dependência da droga; tratados ambulatorialmente, durante 12 semanas com topiramato em doses escalonadas e individualizadas (25 a 300 mg/dia). Os principais desfechos clínicos foram: (1) Taxa de abstinência, (2) Intensidade, frequência e duração da fissura, (3) Aderência, (4) Perdas, (5) Efeitos colaterais, (6) impulsividade mensurada pela Escala de Impulsividade de Barratt (BIS 11). Os pacientes foram avaliados individualmente a cada duas semanas para monitoramento da medicação e auxílio em estratégias assertivas para a manutenção da abstinência. As análises comparativas entre as avaliações foram realizadas na amostra com intenção de tratamento (ITT) e os dados ausentes substituídos pela informação da última avaliação (método LOCF – Last Observation Carried Forward) e o nível de significância foi de 5%.

**Resultados:** Encontramos 57% de adesão (frequência em pelo menos três consultas), 32% de perdas (pacientes com apenas uma única avaliação), com média de presença em consultas de 3,14 ( $\pm 1,80$ ). A dosagem média tolerada foi de 127,27 mg/dia ( $\pm 93,19$ ). Não houve efeitos colaterais graves. A média da taxa de testes negativos foi 25.4%  $\pm$  31.2. Dos N= 28 pacientes avaliados, observou-se que n= 7 (25,0%) apresentaram redução estatisticamente significativa da intensidade da fissura em média de 1,18 (dp = 2,33) na avaliação final quando comparada à inicial (p = 0,012). O mesmo ocorreu quanto à duração da fissura; n= 7 (25,0%) apresentaram redução estatisticamente significativa.(p= 0,018).

Não foi encontrada variação estatisticamente significativa na frequência da fissura ( $p = 0,783$ ). Não foram encontradas variações estatisticamente significantes nos domínios da escala BIS e na pontuação total na avaliação final quando comparada à inicial ( $p > 0,05$ ).

**Conclusão:** O topiramato parece ser uma opção terapêutica na redução da fissura em usuários de cocaína. No entanto, mais ensaios clínicos randomizados, placebo controlados com o topiramato devem ser realizados para este perfil de pacientes a fim comprovar este achado.

**Descritores:** Fissura, Transtornos Relacionados à Cocaína, Topiramato, Ensaio Clínico.

## INTRODUCTION

Cocaine dependence syndrome is a present and important public health problem affecting various countries and social classes worldwide. This phenomenon is associated with poor clinical responses and many relapses.

Cocaine dependence treatment used to receive an exclusively non-pharmacological approach in the early 70's when researchers showed that cocaine brought on neurophysiologic changes <sup>1</sup>.

Cocaine use causes an initial increase in dopamine and serotonin neurotransmission which is largely responsible for pleasure and reinforcing effects of the drug. Dysregulation of these neurotransmitters during withdrawal plays an important part in craving. <sup>2,3,4</sup>

Given the magnitude and complexity of dependence, various pharmacological agents have been intensely investigated for the treatment of this disorder with the intention of lessen craving and abstinence intensity and acquirement.

Anticraving medications are not well known and are underused by clinicians although positive results have been obtained in clinical trials. Addiction is a heterogeneous condition, with variable reactivity to the drug of abuse and to the medication treatment available. <sup>2</sup>

The recognition of dopamine neurotransmission in the cocaine cerebral reward system encouraged clinical trials with dopaminergic agonists and antagonists; however the results were disappointing. The fact is that, after more than two decades of intense research, it has been impossible to identify any agent to promote consistent effective treatment for cocaine dependence. <sup>2,3,4,5</sup>

Several pharmacological interventions (PI) have been studied for this condition over the last years, including dopaminergic agents (i.e., methylphenidate), antidepressives (i.e., desipramine), antagonists 5HT3 (i.e., ondasetron), serotonergic agents (i.e., fluoxetine), antiepileptics (i.e., carbamazepine and valproic acid), amphetamines (i.e., dextroamphetamine), gabaergic agents ( i.e., Baclofen (agonist GABA-B), Tiagabine (inhibits transporter GABA type I- GAT I) and other miscellaneous drugs such as naltrexone, nootropics agents, vaccines and disulfiram. Nevertheless, there is no evidence that any of these medications is effective for the pharmacological treatment of cocaine dependence.<sup>2,3,4,5</sup>

PI over the glutamatergic neurotransmission are potential candidates for investigations; since glutamate is involved in many cerebral regions of reward and there has been evidence of cocaine induced glutamatergic imbalance.<sup>6</sup> Recent data suggest that cystine-glutamate transportation would be the target for drugs, which could possibly prevent cocaine relapse.<sup>7</sup>

GABA is the main inhibitory neurotransmitter in the brain. Pre-clinical studies showed that GABA system modulates the dopaminergic system and the rewarding effects of cocaine. Further more chronic use of cocaine may affect the GABA's functionality system. Cocaine dependant individuals may have an increase in the receptors GABA-A. These changes in GABA response may be associated to the decrease of GABA levels in the brain of those addicted to cocaine. GABA-A GABA-B are possible targets for the medical treatment of cocaine dependant individuals<sup>4</sup>.

Over the last years, topiramate (TPM), medication initially used in the treatment of some epilepsy types such as partial seizures and Lennox-Gastaut syndrome was found effective in chemical dependence treatment, in spite of the few controlled studies.<sup>8</sup>

Antiepileptics have an advantage when compared to other chemical dependence pharmacological treatments due to the absence of potential abuse, anti-kindling action and clinical indication in psychiatric co-morbidities management especially affective disorders.<sup>9</sup>

TPM seems to be a promising PI in the treatment of cocaine dependence in virtue of the involvement of gabaergic and glutamatergic systems in the cerebral reward system modulation. TPM exercises its anti-craving action in promoting an increase in the gabaergic neurotransmission and inhibition of the activity of AMPA/kainate receptors.<sup>10</sup>

Rubio et al., (2002) reported during an open trial with 24 alcohol dependent subjects reduction in alcohol craving and use with TPM.<sup>11</sup>

Zullino et al. (2002) reported that TPM has been found to be efficacious in opiate and possibly benzodiazepine detoxification and also has theoretical potential as a preventive therapy.<sup>12</sup> TPM would inhibit AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxalepropionic acid) receptors, which play an important part in the activation of the abstinence syndrome through glutamate liberation in locus coeruleus.

Johnson et al. (2003) in a controlled, randomized, double-blind clinical trial found that TPM (up to 300 mg/day) was effective in the treatment of alcohol dependants for the reduction of frequency, quantity of consumption and craving.<sup>13</sup>

Kampman et al. (2004) evaluated cocaine dependents treatment with TPM for 13 weeks in a pilot, double blind, placebo controlled clinical trial and found that, as of the third week into the scaled treatment, patients who received TPM continued to be more abstinent than those from the placebo arm.<sup>14</sup>

Recently, Bobes et al. (2004) in a multicenter prospective observational study of six months evaluated heroin, alcohol and cocaine dependents in rehabilitation programs. TPM was well tolerated, effective as to preventing the use of drugs and had a better outcome

when compared to previous clinical studies based on the same medication. In this study, there was a reduction from 94.1% (n= 64) of positive urine exams in the beginning of the treatment to 39.6% (n= 19) at the end of six months; only 28% of non-serious side effects and 33.3% of relapse.<sup>15</sup>

This open, uncontrolled, outpatient clinical trial aims to describe the anti-craving effect and tolerability of TPM as an aid in the treatment of cocaine dependence. The following clinical variables will be considered: (1) Rate of abstinence, (2) Intensity, frequency and duration of craving, (3) Adherence, (4) Dropouts, (5) Side effects, (6) impulsivity measure through Barratt Impulsivity Scale (BIS 11).

## **METHODS**

### **- SETTING**

This study was carried out at the Research Unit of Alcohol and Drugs at the Psychiatric Department of the Universidade Federal de São Paulo, which is dedicated to the treatment of patients with disorders related to the use of psychoactive substances. This study started in January 2004 and finished in December of the same year. It was approved by the University Committee of Ethics according to the Helsinki 1975 declaration under the 0699/03 Protocol number. The subjects signed the informed consent having kept the good rules of clinical practice (CPMP/CIH/135/95).

Research subjects were recruited through written, oral and televised media announcements, as was the spontaneous search at the Outpatients Clinic of Cocaine of

UNIAD and then were invited to participate in a group meeting along with their families, for the presentation of a video about the clinical research and to clarify doubts regarding the study. Each volunteer was interviewed to evaluate inclusion criteria for the study by one of the psychiatrists individually.

## - STUDY DESIGN

This was an uncontrolled clinical trial involving inhaled cocaine-dependent patients according to the DSM IV criteria. Candidates were assisted for 12 weeks by the Outpatient clinical treatment with the use of TPM.

Clinical trial **inclusion criteria** were: (1) male patients, (2) age group 18 to 55, (3) fulfilling the diagnostic criteria of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) for cocaine dependence,<sup>16</sup> (4) use of intranasal cocaine. Patients, therefore, had to be active in the use of the drug with a period of abstinence no longer than 7 days, (5) permanent residents in the city of São Paulo, (6) patients who wished to be volunteers in this clinical research, (7) those who were able to read and sign the consent forms also enlightened after the nature of the study had been explained completely before the fulfillment of any procedure related to the same.

The **exclusion criteria** comprised: (1) knowledge of hypersensitivity to TPM, (2) exposure to any other pharmacological or experimental agent during the 12 months prior to the initial evaluation, (3) kidney stones, since 1.5% of patients treated with TPM had developed this clinical condition with an index 10 times greater than those with placebo, (4) history or evidence of significant clinical kidney failure (including serum creatinine >133

mmol/L in men corresponding to >1.51 mg/d, (5) serious mental disorders (i.e., psychoses), which required psychiatric hospitalization or the prescription of other psychotropic drugs (e.g., antipsychotics), (6) patients using other psychotropic drugs, (7) patients using carbonic anhydrase inhibitors (acetazolamide or diclorfenamide), due to the risk of developing kidney stones, concomitant with TPM (9) uncontrolled hypertension (defined as diastolic arterial pressure >100 mm/Hg and/or systolic arterial pressure >180 mm/Hg with or without medication, (10) history or evidence of clinically significant hepatic disease (including ALT or AST > twice the superior range of normality)<sup>17,18</sup> (11) condition or situation which in the investigator's opinion would be life threatening, which could confound the results or interfere substantially in the participation of the individual being studied, (12) women, due to the possibility of oral contraceptive levels reduction and spotting related to TPM use and consequent risk of pregnancy during the treatment since, some initial pharmacokinetic and pharmacodynamic TPM studies suggested that this medication could decrease the estrogenic component of oral contraceptives (OCs) when used concomitantly.<sup>17</sup> In these cases the suggestion would be the use of preparations with 50 micrograms of estrogens for birth control.<sup>19</sup> However, new studies with TPM and other antiepileptic drugs have already started to evaluate this question showing a direct relationship between TPM and OCs.<sup>20</sup> Doose et al. (2003) in an uncontrolled randomized study evaluated five groups of women during two menstrual cycles of 28 days and found that TPM in daily doses of 50 to 200 mg/day do not interact with Ocs containing norethindrone and ethinyl estradiol<sup>21</sup>. These studies tend to increase the available evidence about the medication, but it continues to reinforce the importance of caution, orientation and vigilance (13) abuse of other drugs (except nicotine and cannabis).

## - PROCEDURES

The following procedures were performed in the initial evaluation: clinical anamnesis, physical examination and the application of the Addiction Severity Index (ASI), the Minnesota Cocaine Craving Scale and Barratt Impulsivity Scale (BIS 11). Besides these, laboratory tests were requested, such as a complete hemogram, fast glycemia, total and fractional cholesterol, triglycerides, liver transferases (ALT, AST and GGT), urea, creatinine and electrocardiogram. Follow-up assessment was performed every two weeks by two psychiatrists and it included a Urine Benzoyllecgonine Test (totaling six tests throughout the study) application and side effect assessment.

In an attempt to minimize side effects doses were scaled starting with a small dose and slowly increasing the dosage, this seems to have clinically reduced side effect events.

During clinical consultation, the team of psychiatrists used a basic set of relapse and social ability prevention techniques aiming to provide the patients with strategies to adapt more easily and maintain abstinence.

Every visit medication utilized was counted. An independent psychologist applied the others scales in the 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> week of treatment.

The rate of abstinence was considered by the number of negative tests divided by the total number of tests done during the study.<sup>6</sup> Adherence to the treatment was defined by the frequency in at least three consultations. The subjects of the research who did not appear on the first return, which corresponded to a second consultation, were considered dropouts.

## - INSTRUMENTS

- Urine Benzoylecgonine Test (UBT): this is a rapid test; visual, competitive immunoassay that can be used for the qualitative detection of benzoylecgonine (product by biotransformation of cocaine in the urine) which has a 300 ng/ml cutoff. Test sensitivity is 99% and the specificity 98%. The test does not identify the level of intoxication, nor reflects the frequency or amount of drug used. The standard biological indicator of drug use is usually a qualitative urine drug test, which has some limitation because it merely indicates the presence or absence of a drug or its metabolite which can generally detect use of cocaine for 24 to 60 hours after last use or exposure.<sup>12</sup> But the widely accepted time period for benzoylecgonine to be cleared from the urine is three to five days.
- Minnesota Cocaine Craving Scale: The scale is composed of 5 items which correspond to intensity, frequency, duration of craving, changes in relation to the previous week and the response of craving to medication. We used the first three items of the scale, which point out craving values from zero (none) to ten (maximum) since, these items can be used independently, as it has already been done in others studies<sup>23,24</sup>. This scale has been used in its Portuguese translation in a 4 week double-blind controlled study to evaluate the use of pergolide in Brazil by Focchi et al. (2001).<sup>25</sup> Its internal consistency in other studies showed an alpha Cronbach coefficient of 0.826.<sup>23</sup> Patients were requested to fill out the scale under supervision of an independent evaluator.
- Addiction Severity Index (ASI): is a semi structured clinical interview which works as an intentional standard for the assessment of addiction severity. It consists of seven areas of

daily life activities: medical, employment/support, drug and alcohol use, legal, family/social, and psychiatric. After each interview, a score of severity was calculated based on the physician's judgment and the self-evaluation of the patient. These scores indicate whether there are problems in any of the areas assessed by the interview. The ASI has been submitted to rigorous validation and it was concluded that it possesses a high rate of confidence and effectiveness.<sup>26</sup>

-Barratt Impulsivity Scale (BIS 11): Though the concept of impulsiveness is controversial, presently many attempts are being made to measure this dimension. In this context, only psychometric measures are widely considered valid and are routinely in use. In 1985, Barratt developed the first scale that specifically measured impulsiveness. This scale is in its eleventh version and has been validated in Italy, France, Germany and several other countries.<sup>27,28</sup> Barratt scale has been applied in Brazil on pathological gamblers and it was adapted and construct validated to Brazilian Portuguese for use in adolescents.

The BIS 11 is a self-rating questionnaire, composed of 30 Likert-type questions, which provides a total score and three sub-scores: attention, nonplanning and motor. Scores vary from 30 to 120 and there is no established cutoff point. The score of the BIS 11 is a consistent measure of impulsiveness and has proven potential clinical use for measuring impulsiveness among selected patient.<sup>29</sup>

## - STATISTICAL ANALYSIS

The qualitative variables were represented by the absolute and relative frequencies (%) and the quantitative variables were represented through mean and standard deviation (SD).

Comparative analysis between the evaluations was made to the sample with Intention to Treat (ITT) and the missing values were replaced by the last observed value of that variable (LOCF – Last Observation Carried Forward).

A paired T test was used to compare craving intensity baseline results to the results in the final evaluation through the Minnesota Cocaine Craving Scale and impulsivity through Barratt Impulsivity Scale (BIS 11).

Frequency and duration of craving baseline results of the sample were compared to the final result evaluation using Wilcoxon related sample test. Confidence interval 95% was calculated to the sample most frequent adverse effects. Statistical significance level of 0,05 ( $\alpha = 5\%$ ).<sup>30</sup>

The information collected was stored in data banks using the statistic program SPSS 9.0. The data was typed twice for typing error verification.

## **RESULTS**

### **- SAMPLE SELECTION**

In the initial sample twenty eight (N=28) subjects were included.

The sample was composed of male subjects with mean age of  $30.39 \pm 6.74$  years. Most of these patients were married (54% [N = 15]) and employed (71% N = 20).

According to the diagnostic criteria of DSM-IV, three or more symptoms are necessary for the diagnosis of cocaine dependence. In our sample the average for dependence symptoms was  $6.08 \pm 1.22$ . Besides the dysphoric humor the presence of two or more symptoms was necessary for the fulfillment of cocaine abstinence syndrome diagnostic criteria. Percentage of these symptoms was distributed in the following way: dyssonias (79% [N = 22]), psychomotor alterations (79% [N = 22]), fatigue (54% [N = 15]), nightmares (21% [N = 06]) and hyperfagia (21% [N = 06]). The average number of abstinence syndrome symptoms was  $3,24 \pm 1.09$  (Table 1).

## RATE OF ABSTINENCE

Twelve subjects (43%) tested negative in all urine screenings. The average rate of negative results throughout the tests was  $25.4\% \pm 31.2$ .

## - CRAVING

Statistical significant reduction in craving intensity was found in the final evaluation when compared to baseline assessment ( $p = 0,012$ ). From the N= 28 individuals involved in this study n= 7 (25%) presented a significant reduction, the remaining n= 21(75%) did not present significant alteration.

Statistical significant reduction was also found in craving duration ( $p = 0,018$ ). From the N= 28 individuals involved in this study, n= 7 (25%) presented a significant reduction while n= 21(75%) did not present significant alteration in craving duration.

Statistical significant reduction was not found in craving frequency ( $p = 0,783$ ). From the  $N= 28$  individuals involved in this study  $n= 2$  (7,1%) presented reduction in frequency  $n= 3$  (10,7%) related an increase in frequency and  $n= 23$  (82,1%) did not present alteration in craving frequency. (Table 2).

#### - ADHERENCE

The drop out rate in this clinical trial corresponded to 32% ( $n= 9$ ) and the adherence was 57% ( $n= 16$ ). The average number of consultations was  $3.14 \pm 1.80$ .

#### - DOSAGE

The average dosage of TPM used was  $127.27 \pm 93.19$  mg/day. The dosage with the greatest percentage of tolerability was 100 mg/day, which corresponds to 68.2% of the research subjects.

#### - ADVERSE EFFECTS

Adverse event assessment was made at each visit. The main adverse effect was somnolence those with incidence above 10% were included, (68% [ $n=13$ ]), followed by paresthesia (63% [ $n=12$ ]), difficulty concentrating (47% [ $n=09$ ]), xerostomy (21% [ $n=4$ ]), anorexia (16% [ $n=3$ ]) and polyuria/polydipsia (16% [ $n=3$ ]). Nineteen subjects were

analyzed since n=9 patients had failed to appear for the second medical evaluation (Table 3). Incidence of adverse events was moderated.

#### - BARRATT IMPULSIVITY SCALE (BIS 11)

Statistical significant variation was found neither regarding the use of BIS 11 scale nor in the final results when compared to baseline ( $p > 0,05$ ) (Table 4).

## **DISCUSSION**

A statistically significant finding in this clinical trial was a decrease in the intensity and duration of craving. The controversial constitution craving which most accept is a multidimensional construct that attempts to capture the propensity or compulsion to act on ideas, impulses, or innate drives to use an abused substance.<sup>13,24</sup> Therefore, the main clinical implication of this result is that TPM seems to be a promising pharmacological intervention for the reduction of craving since reducing craving should improve the outcome of people with cocaine dependence who seek treatment.

Among the limitations in this study to mention are: intensity and duration reduction of craving was significant though of uncertain and small clinical impact once this was an open study without placebo or control group. Consideration to the possibility in which craving reduced due to the simple fact that, after 12 weeks craving is expected to decrease. Another limitation of this study was the small number of subjects, male only, entered into

the trial. As a result, the sample does not represent all current cocaine users in all treatment centers.

Only 25.4% of this sample obtained satisfactory results as to the acquisition of abstinence. Nevertheless, it is important to emphasize that we had taken one of the clinical outcomes, as a sufficiently conservative measure, to evaluate the rate of abstinence; which is a negative quality in screening the urine.

There is no standard or “gold standard” measure to analyze the behavioral response to medicine in the pharmacotherapy of cocaine. Studies in general make use of measures that include the patient’s self report related to drug use and the presence of benzoylecgonine in urine. Self report accuracy is uncertain. Benzoylecgonine test while more secure than self report has limitations regarding frequency and quantity of drug used.

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There is no effective mechanism in cocaine pharmacotherapy, which would serve as reference for the development of new medicines. It is expected that future developments in pharmacogenetics may result in a better selection of medicines based on the genotype of individuals<sup>4</sup>

However the most mentioned side effects (somnolence, paraesthesia and difficulty to concentrate); were present in more than half of the samples, these were mild and there were no severe side effects that would limit the medication use or losses due to its side effects. In these cases, a slow dose titration successfully prevented the troublesome side effects noted in other trials of topiramate.<sup>14</sup> Overall; topiramate adverse event profile was similar to that reported for other indications.<sup>13</sup> Thus, with a slow dose titration, topiramate appears to be safe and tolerated by cocaine dependent patients.

Most of the clinical trials with chemical dependents have high dropout rates, which very often compromise the extrapolation of data and evidence of the efficiency of the treatments used.<sup>4</sup> We consider that the percentage of drop out (32% [n= 9]) was similar to other clinical trials with the same profile of the population and reasonable for a study that was not coupled to psychosocial intervention.<sup>31</sup>

In spite of the fact that many authors suggested an association of psychological intervention to medical treatment with the purpose of improving the adherence there seems to be other innumerable factors associated to the maintenance of these patients in clinical trials. The awareness of these phenomena certainly contributes to the understanding of the population's behavior, formerly traditional seen as being uniquely current of a psychological basis.<sup>32</sup> On the other hand, this tends to reinforce the difficulties of achieving clinical trials with chemical dependents.<sup>33,34</sup>

About the impulsivity measure, no statistically relevant variations were found on the domains of the BIS 11 scale. It is believed that a longer observation time, not just 12 weeks, may demonstrate some alterations in this sense.

Cocaine dependents show a great variation of characteristics including the severity of drug use, simultaneous abuse of other drugs, psychiatric comorbidities and different psychosocial characteristics. Some of these characteristics especially the severity of dependence and the psychiatric comorbidities may affect the response to the medicine and lead to misinterpretations in clinical essays, these must be taken into consideration in future clinical essays.<sup>4,33</sup>

It seems important that clinical trials such as this could include, for instance, the user of multiple psychoactive substances, a greater number of research subjects, longer time

of follow-up and women as commonly encountered in outpatients clinics.<sup>34</sup> This would increase the power of evidence and capacity of generalization for the general public.

## **CONCLUSION**

The subjects treated with TPM evolved a decrease of intensity and frequency of craving. As we are dealing with an open clinical trial, at last and finally, it is still impossible to affirm with absolute conviction whether the result is owed to the effect of the medication or simply the natural evolution of time and disease. Therefore, more randomized, placebo controlled clinical trials with cocaine users should be carried out in order to confirm these findings.

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## **REFERENCES**

1. Leite MC & Andrade AG. Cocaína e Crack: dos Fundamentos ao Tratamento. IN: Capítulo 19, Tratamento Farmacológico, pp. 303-310. Editora ARTMED, Porto Alegre, 1999.
2. O'Brien CP. Anticraving Medications for Relapse Prevention: A Possible New Class of Psychoactive Medications. *Am J Psychiatry* 2005; 162:1423–1431.
3. Vocci FJ, Elkashef A. Pharmacotherapy and other treatments for cocaine abuse and Dependence. *Addictive disorders Current Opinion in Psychiatry* 2005, 18:000–000.
4. Sofuoglu & Kosten. Emerging pharmacological strategies in the fight against cocaine addiction. *Expert Opin. Emerging Drugs* (2006) 11(1).
5. Lima MS, Soares BGO, Reisser AA, Farrell M. Pharmacological treatment of cocaine dependence: a systematic review. *Addiction* 2002; 97 (8): 931-949.
6. Dackis C, O'Brien C. Glutamatergic Agents for Cocaine Dependence. *NY Acad Sci* 2003; 1003: 328-345.
7. Lu L, Hope BT, Shaham Y. The cystine-glutamate transporter in the accumbens: a novel role in cocaine relapse. *Trends Neurosci* 2004; 27(2): 74-6.
8. Herranz JL. Topiramate, a new antiepileptic drug. *Rev Neurol* 1997; 25 (144): 1221-1225.

9. Zullino DF, Khazaal Y, Hattenschwiler J, Borgeat F, Besson J. Anticonvulsant drugs in the treatment of substance withdrawal. *Drugs Today* 2004; 40 (7): 603-619.
10. Sofuoglu M, Kosten TR. Novel approaches to the treatment of cocaine addiction. *CNS Drugs* 2005; 19 (1): 13-25.
11. Rubio G, Ponce G, Jimenez-Arriero MA, Palomo T, Ferre F. Effectiveness of topiramate in control of alcohol craving. *Eur. Neuropsychopharmacol* 2002; 12, S63.
12. Zullino DF, Cottier AC, Besson J. Topiramate in opiate withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26 (6): 1221-1223.
13. Johnson BA, Ait-Daoud N, Bowden CL, DiClemente C, Roache JD, Lawson K, Javors MA, Ma JZ. Oral topiramate for treatment of alcohol dependence: a randomized controlled trial. *Lancet* 2003; 361: 1677-1685.
14. Kampman KM, Pettinati H, Lynch KG, Dackis C, Sparkman T, Weigley C, O'Brien CP. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Dependence* 2004; 75 (3): 233-240.
15. Bobes J, Carreno JE, Gutierrez CE, San Narciso GI, Antuna MJ, Diaz T, Fernandez JJ, Cerceda A, Alvarez CE, Marina P, Garcia-Garcia M. Study of effectiveness of craving

control with topiramate in patients with substance dependence disorders. *Actas Esp Psiquiatr* 2004; 32(5):299-306.

16. Diagnostic and statistical manual of mental disorders. Fourth Edition – DSM IV. Am Psychiatric Association. Washington DC, 1994.

17. Topamax (topiramate product monograph).2002.

18. Shneiderman JH. Topiramate: pharmacokinetics and pharmacodynamics. *Canadian journal of neurological sciences* 1988; 25(3): 3-5.

19. Rosenfeld WE, Doose DR, Walker AS, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia* 1997; 38(3): 317-23.

20. Nallani SC, Glauser TA, Hariparsad N, Setchell K, Buckley DJ, Buckley AR, Desai PB. Dose-dependent induction of cytochrome P450 (CYP) 3A4 and activation of pregnane X receptor by topiramate. *Epilepsia* 2003; 44(12): 1521-1528.

21. Doose DR, Sheng WS, Mukund P, Stefan S, David J, Meir B. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and non obese female subjects. *Epilepsia* 2003; 44(4): 540-549.

22. Kevin L Delucchi, Reese T Jones, Steven L Batki. Measurement properties of quantitative urine benzoylecgonine in clinical trials research. *Addiction* 1997 92 (3), 297–302.
23. Halikas JA, Kuhn KL, Crosby R, Carlson G, Crea F. The measurement of craving in cocaine patients using the Minnesota Cocaine Craving Scale. *Compr Psychiatry*. 1991 Jan-Feb;32(1):22-7
24. Weiss RD, Griffin ML, Mazurick C, Berkman B, Gastfriend DR, Frank A, Barber JP, Blaine J, Salloum I, Moras K. The relationship between cocaine craving, psychosocial treatment, and subsequent cocaine use. *Am J Psychiatry*. 2003 Jul;160(7):1320-5.
25. Focchi GRA, Leite MC, Scivoletto S. Utilização do antagonista dopaminérgico pergolida no tratamento da “fissura” por cocaína. *Rev Brás Psiquiatr* 2001 23 (4): 188 – 194.
26. McLellan AT, Luborsky L, Cacciola J et al. New data from the addiction severity index: reliability and validity in three centers. *J New Ment Dis* 1985;173:412-23.
27. Bayle FJ, Bourdel MC, Caci H, Gorwood P, Chignon JM, Ades J, Loo H. Factor analysis of french translation of the Barratt scale (BIS-10). *Can J Psychiatry*. 2000 Mar;45(2):156-65.

28. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol.* 1995 Nov;51(6):768-74.
29. Von Diemen L, Szobot CM, Kessler F. Adaptation and construct validation of the Barratt Impulsivity Scale BIS 11 to Brazilian Portuguese for use in adolescents. *Rev. Bras. Psiquiatr.*, 2006, p.0-0. ISSN 1516-4446.
30. Siegel S. *Estatística não-paramétrica.* 1<sup>nd</sup>. São Paulo: McGraw Hill do Brasil; 1975.
31. Elkashef A, Holmes TH, Bloch DA, Shoptaw S, Kampman K, Reid MS, Somoza E, Ciraulo D, Rotrosen J, Leiderman D, Montgomery A, Vocci F. Retrospective analyses of pooled data from CREST I and CREST II trials for treatment of cocaine dependence. *Addiction* 2005 Mar;100 Suppl 1:91-101.
32. Spinella M. Neurobehavioral correlates of: evidence of prefrontal involvement. *Int J Neurosci.* 2004 Jan;114(1):95-104.
33. Sayre SL, Evans M, Hokanson PS, Schmitz JM, Stotts AL, Averill P, Grabowski. "Who gets in?" Recruitment and screening processes of outpatient substance abuse trials. *Addict Behav* 2004; 29 (2): 389-398.
34. Everitt BS & Wessely S. *Clinical trials in psychiatry.* Oxford University Press, 2004.



TABLE 1 – CHARACTERISATION OF THE SAMPLE (N = 28). SÃO PAULO, 2004.

<b>Age, years (average <math>\pm</math> SD)</b>	30.39 $\pm$ 6.74	
<b>Dependence syndrome, n of symptoms (average <math>\pm</math> SD)</b>	6.08 $\pm$ 1.22	
<b>Abstinence syndrome, n of symptoms (average <math>\pm</math> SD)</b>	3.24 $\pm$ 1.09	
<b>ASI (average <math>\pm</math> SD):</b>		
Physical complications	1.32 $\pm$ 2.71	
Complications related to the use of drugs	8.71 $\pm$ 0.94	
Familial complications	6.0 $\pm$ 3.41	
Legal complications	0.68 $\pm$ 2.23	
Professional complications	4.11 $\pm$ 3.51	
Psychiatric complications	4.61 $\pm$ 3.60	
<b>Civil status, N (%):</b>		
Married	15	(54%)
Single	09	(32%)
Separated/Divorced	04	(14%)
<b>Employment status, N (%):</b>		
Employed	20	(71%)
Unemployed	07	(25%)
Retired/Disabled	01	(04%)

**TABLE 2 – EVALUATION OF CRAVING ACCORDING TO THE MINNESOTA COCAINE CRAVING SCALE (N = 28). SÃO PAULO, 2004.**

Minnesota Cocaine Craving Scale	Evaluation		Comparison
	Baseline	Final	
Craving Intensity mean (dp)	7,32 (2,26)	6,14 (2,98)	$p_1 = 0,012 *$
Craving Duration – n (%)			$p_2 = 0,018 *$
0 to 5 min.	8 (28,6)	14 (50,0)	
6 to 10 min.	6 (21,4)	5 (17,9)	
11 to 20 min.	2 ( 7,1)	2 ( 7,1)	
21 to 30 min.	5 (17,9)	3 (10,7)	
31 to 45 min.	1 ( 3,6)	1 ( 3,6)	
46 to 60 min.	0 ( 0,0)	0 ( 0,0)	
1 to 2 hours	2 ( 7,1)	1 ( 3,6)	
2 hours or more	4 (14,3)	2 ( 7,1)	
Craving Frequency – n (%)			$p_2 = 0,783$
1 time per day	14 (50,0)	12 (42,9)	
2 time per day	4 (14,3)	5 (17,9)	
3 a 5 time per day	5 (17,9)	7 (25,0)	
6 a 10 time per day	1 ( 3,6)	1 ( 3,6)	
11 a 20 time per day	3 (10,7)	2 ( 7,1)	
More than 20 time per day	1 ( 3,6)	1 ( 3,6)	

$p_1$ : paired T;  $p_2$ : Wilcoxon test

**TABLE 3 – ADVERSE EFFECTS ABOVE 10% . SÃO PAULO, 2004.**

	N	%	IC <sub>95%</sub>
Somnolence	13	68.4%	46.0%; 84.6%
Paresthesia	12	63.2%	41.0%; 80.9%
Concentration difficulty	09	47.4%	27.3%; 68.3%
Xerostomy	04	21.1%	8.5%; 43.3%
Anorexia	03	15.8%	5.5%; 37.6%
Polyuria/Polydipsia	03	15.8%	5.5%; 37.6%

**TABLE 4 – BARRATT IMPULSIVINESS SCALE (BIS 11) - SÃO PAULO 2004.**

BIS 11	Evaluation		Comparison
	Baseline	Final	
BIS Attention mean (dp)	21,64 (3,72)	21,50 (3,96)	p = 0,760
BIS Motor mean (dp)	26,96 (5,48)	25,93 (6,21)	p = 0,074
BIS Non Plan mean (dp)	28,14 (5,54)	28,43 (4,39)	p = 0,602
BIS Total mean(dp)	76,75 (9,24)	75,86 (10,46)	p = 0,474