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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Support

Pharmaceutical Industry Jansen-Cilag

ABSTRACT

Objectives: Evaluate anti-craving action and tolerability of topiramate in cocaine user treatment.

Methods: Male users of inhaled cocaine (N=28) which met criteria from DSM IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) for cocaine dependence were selected for outpatient 12 week, open label trial with topiramate, individual dosage varied (25to300mg/day). Main clinical variables were: abstinence rate, craving intensity, frequency and duration, adherence, dropouts, side effects and impulsivity measure through Barratt Impulsivity Scale (BIS11). Patients received assertive strategic counseling for abstinence assistance and medication monitoring evaluation every two weeks. Comparative analysis was made with Intention to Treat, missing values were replaced (LOCF – Last Observation Carried Forward), significance level was 5%.

Results: Adherence to treatment was 57% (at least three evaluations), 32% dropped out (one evaluation). There were no severe side effects. Negative test average was 25.4%$\pm$31.2.Significant statistical reduction regarding duration was (p=0,012), and craving intensity (p=0,018). Craving frequency was not significant (p=0,783). No significant statistical variations in BIS11 or in the total score were found in the final evaluation when compared to baseline (p>0,05).

Conclusion: Topiramate is a possible approach for craving reduction in cocaine users. However, more randomized placebo-controlled trials with topiramate for cocaine dependants should be made.

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

INTRODUCTION

Cocaine use causes an initial increase in dopamine and serotonin neurotransmission responsible for pleasure and reinforcing drug effects. Neurotransmitters dysregulation during withdrawal play an important part in craving. [1]

Given the magnitude and complexity of dependence, various pharmacological agents have been investigated with the intention of lessen craving abstinence intensity and acquirement. Recognition of dopamine neurotransmission in cocaine cerebral reward system encouraged clinical trials with dopaminergic agonists and antagonists; however results were disappointing.[1,2,3]

Several pharmacological interventions (PI) have been studied for this condition, including dopaminergic agents, antidepressives, antagonists 5HT3, serotonergic agents, antiepileptics, amphetamines, gabaergic agents and miscellaneous drugs as naltrexone, nootropics agents, vaccines and dissulfiram. There is no evidence about these medications effectiveness for pharmacological cocaine dependence treatment.[1,2,3]

In spite of few controlled studies, topiramate (TPM), medication initially used for some epilepsy types has been found effective for chemical dependence treatment. [4]

Rubio (2002), Zullino (2002), Johnson (2003), Kampman (2004) and Bobes (2004), obtained favorable results with TPM in alcohol, opiate, benzodiazepine detoxification and cocaine dependents.[5,6,7,8,9]

TPM exercises its action in virtue of the gabaergic and glutamatergic system involvement in the cerebral reward system modulation. TPM exercises anti-craving action through an increase in the gabaergic neurotransmission and inhibition of the activity of AMPA/kainate receptors.[4]

This clinical trial aims to describe TPM anti-craving effect and tolerability as an aid in the cocaine dependence treatment. The following clinical variables were considered: abstinence rate, craving intensity, frequency and duration, adherence, dropouts, side effects, impulsivity measure through BIS11.

METHODS

This open uncontrolled clinical trial involved inhaled cocaine dependents. Candidates were assisted with TPM in outpatient treatment for 12 weeks.

Study conducted at Uniad-Unifesp, from January - December 2004. Approved by University Ethics Committee (protocol number 0699/03).

- Inclusion criteria: male patients, 18-55 age, fulfilling DSM-IV diagnostic criteria for cocaine dependence, intranasal cocaine use, patients abstinence period of 7 days, permanent residents in São Paulo, volunteers in this clinical research, be able to read and sign consent forms.

- Exclusion criteria: hypersensitivity to TPM, exposure to other pharmacological agents 12 months prior to the initial evaluation, kidney stones, since 1.5% of patients treated with TPM may develop this clinical condition, kidney failure history, serious mental disorders, patients using psychotropic drugs, patients using carbonic anhydrase inhibitors due to risk of developing kidney stones concomitant with TPM, uncontrolled hypertension, hepatic disease evidence, life threatening situation in investigator's opinion, women due to possibility of oral contraceptive (OCs) levels reduction related to TPM use and consequent pregnancy risk during the treatment since, some initial TPM studies suggest that this medication could decrease estrogenic component of OCs when used concomitantly.[10]

- **Procedures:** clinical anamnesis, physical examination and application of instruments. Follow-up assessment was performed every two weeks by two psychiatrists, Urine Test application and side effect assessment. Patients received assertive strategic counseling for abstinence assistance. An independent psychologist applied other scales in the 1st, 6th and 12th week of treatment.

-Instruments:

- Urine Benzoylecgonine Test: rapid test: visual, competitive immunoassay that can be used for the benzoylecgonine qualitative detection (cocaine biotransformation product in the urine), cutoff 300ng/ml. Test sensitivity is 99% and specificity 98%. Test does not identify intoxication level, nor reflects frequency or amount of drug used. It merely indicates the presence or absence of drug .The test generally detects cocaine use for 24 to 60 hours after last use. The widely accepted period for benzoylecgonine to be cleared from the urine is three to five days. [11]

- Minnesota Cocaine Craving Scale (MCCS): composed of 5 items which correspond to intensity, frequency, duration of craving, changes in relation to previous week and craving response to medication. We used the first three items of the scale, since these items can be used independently, as it was done in others studies. Its internal consistency in studies showed an alpha Cronbach coefficient (0.826).[12]

- ASI: semi structured clinical interview which works as an intentional standard for addiction severity assessment. It consists of seven areas: medical, employment/support, drug and alcohol use, legal, family/social, and psychiatric. After each interview, a severity score was calculated based on the physician's judgment and

patient self-evaluation. Scores indicate whether problems exist in any of the areas assessed. ASI was submitted to validation and proved to have high rate of confidence and effectiveness.[13]

- BIS11: self-ratting questionnaire, 30 Likert-type composed questions, which provides a total score and three sub-scores: attention, nonplanning and motor. Scores vary from 30 to 120 with no established cutoff point. The BIS11 score is a consistent measure of impulsiveness and has proven potential clinical use for measuring impulsiveness among selected patient.[14]

Attempting to minimize side effects, doses were scaled from small doses. This seems to have clinically reduced side effects. Rate of abstinence considered was the number of negative tests divided by the total number of tests during the study. Adherence to treatment defined was attendance to at least three consultations. Research subjects who did not appear for the second consultation were considered dropouts.

Comparative analysis was made with Intention to Treat and the missing values were replaced by LOCF. Paired T test was used to compare craving intensity baseline results to final evaluation results through MCCS and BIS11. Craving frequency and duration baseline results were compared to final result evaluation using Wicoxon related sample test. Confidence interval 95% was calculated to frequent adverse effects. Statistical significance level 0,05 (α= 5%).

RESULTS

The sample was composed of 28 male subjects; mean age of 30.39 ± 6.74 years, average for dependence symptoms was 6.08 ± 1.22. The average number of abstinence syndrome symptoms was 3,24±1.09 (Table1).

Twelve subjects (43%) tested negative in urine screenings. Average negative result rate throughout tests was 25.4%±31.2.

Reduction in craving intensity was observed: 7,32(2,26) in baseline and 6,14(2,98) in final evaluation,(p_1: paired T=0,012), n=7(25%) presented significant reduction and n=21(75%) did not present significant alteration.

The same occurred with craving duration: n=7(25%) presented a significant reduction while n=21(75%) did not present significant alteration (p_2: Wilcoxon test=0,018).

Statistical significant reduction was not found in craving frequency (p_2=0,783): 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 .

Drop out rate in this clinical trial corresponded to 32%(n=9) and the adherence was 57%(n=16). Average consultations number was 3.14±1.80.

Average TPM dose was 127.27±93.19mg/day. Greatest percentage of tolerability dosage was 100mg/day, which corresponds to 68.2% of research subjects.

Main adverse effect with incidence above 10% was included: somnolence (68%[n=13], IC=46.0-84.6), paresthesia (63%[n=12], IC=41.0-80.9), difficulty concentrating (47%[n=09], IC=27.3-68.3), xerostomy (21%[n=4], IC=8.5-43.3), anorexia (16%[n=3], IC=5.5-37.6), polyuria/polydipsia (16%[n=3], IC=5.5-37.6). Nineteen subjects were analyzed since n=9 patients failed to appear for the second medical evaluation. Adverse events incidence was mild.

Statistical significant variation was found neither regarding use of BIS11 nor in the final results compared to baseline: BIS11 Total mean (dp) were: 76,75 (9,24) at baseline and 75,86 (10,46) in the final (p=0,474).

DISCUSSION

A statistically significant finding in this clinical trial was a decrease in the craving intensity and duration. The main clinical implication of this result is that TPM seems to reduce craving and it could improve the people outcome with cocaine dependence since craving is related to many relapses.

Limitations in this trail to mention were: decrease in craving was significant, but this was an open trail without placebo or control group. So, there is a possibility that craving reduced occurred just due to the fact that, after 12 weeks craving is expected to decrease. Another limitation was the small number of subjects and males only. As a result, the sample does not represent all current cocaine users in treatment centers.

Only 25.4% obtained abstinence acquisition. Nevertheless, it is important to emphasize that a negative quality in urine screening is a conservative outcome measure to evaluate the rate of abstinence.

However, the most mentioned side effects 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 prevented the troublesome side effects of TPM. Overall; adverse event profile was similar to that reported for other indications. [10]

Chemical dependents clinical trails used to have high dropout rates, which very often compromise data extrapolation. The drop out (32%[n=9]) was similar to other clinical trials with the same profile and reasonable for a study that was not coupled to psychosocial intervention. [15]

About impulsivity measure, no statistically relevant variations were found on the BIS11. Longer observation time, may demonstrate some alterations in this sense.

It seems important that future clinical trials could include multiple psychoactive substances users, larger samples, longer follow-up and women as commonly encountered in outpatient clinics. This would increase the power of evidence and capacity of generalization.

CONCLUSION

TPM seems to be a promising PI for the craving reduction but more randomized, placebo controlled clinical trials with cocaine users should be carried out in order to confirm these findings.

FINANCING AND ACKNOWLEDGMENTS

This study had the support of Jansen-Cilag Pharmaceutical Industry in supplying the medication used. Thanks to UNIAD for providing adequate approval for conducting this study as well as the colleagues who contributed to the accomplishment of this clinical trial.

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

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