

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

Objective: To evaluate anticraving action and tolerability of topiramate in cocaine user treatment. **Method:** Male users of inhaled cocaine which met criteria for cocaine dependence (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) were selected for outpatient 12-week, open label trial with topiramate; individual dosage ranged between 25-300 mg/day. Main clinical variables were abstinence rate, craving intensity, frequency and duration, adherence, dropouts, side effects and impulsivity measure through Barratt Impulsivity Scale. 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 (last observation carried forward), and 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% (31.2). Significant reduction in craving intensity and duration was observed in 25% of the sample. No statistical significant reduction in craving frequency was observed in 7.1%. Increase in frequency was observed in 10.7% and 82.1% did not present any variation. No significant statistical variations in Barratt Impulsivity Scale or in the total score were found in the final evaluation when compared to baseline. **Conclusion:** More randomized placebo-controlled trials with topiramate for cocaine dependants should be performed to evaluate preliminary evidence.

Descriptors: Cocaine-related disorders; Behavior, addictive; Topiramate; Clinical trial [Publication type]; Clinical protocols

Resumo

Objetivo: Avaliar a ação anticraving e tolerabilidade do topiramato em usuários de cocaína. **Método:** Homens usuários de cocaína inalada que preenchem critérios para dependência de cocaína (Manual Diagnóstico e Estatístico de Desordens Mentais, quarta edição) foram selecionados para 12 semanas de tratamento ambulatorial, em ensaio clínico aberto com topiramato; dosagens escalonadas entre 25-300 mg/dia. As principais variáveis clínicas foram taxa de abstinência, intensidade, frequência e duração do craving, aderência, perdas, efeitos colaterais e impulsividade medida por meio da Escala de Impulsividade Barratt. Os pacientes receberam estratégias assertivas de aconselhamento para manutenção da abstinência e monitoramento da medicação avaliada a cada duas semanas. Análises comparativas foram feitas com intenção de tratar, valores perdidos foram substituídos (última observação carregada ao final) e o nível de significância de 5%. **Resultados:** A aderência ao tratamento foi de 57% (pelo menos três avaliações), 32% de perdas (uma avaliação). Não houve efeitos colaterais graves. A média de testes negativos foi 25,4% (31,2). Significante redução na intensidade e duração do craving foi observada em 25% da amostra. Nenhuma redução significativa na frequência do craving foi observada em 7,1%. Aumento na frequência foi observado em 10,7% e 82,1% não apresentaram nenhuma variação. Nenhuma variação estatisticamente significativa na Escala de Impulsividade Barratt ou na pontuação total foi encontrada no final da avaliação quando comparado à inicial. **Conclusão:** Mais ensaios clínicos placebo-controlados com o topiramato para dependentes de cocaína deveriam ser conduzidos a fim de avaliar a evidência preliminar.

Descritores: Transtornos relacionados ao uso de cocaína; Comportamento, adicto; Topiramato; Ensaio clínico [Tipo de publicação]; Protocolos clínicos

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Introduction

Cocaine use causes an initial increase in dopamine and serotonin neurotransmission, responsible for pleasure and reinforcing drug effects. Neurotransmitter dysregulation during withdrawal plays an important role in craving.¹

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

Several pharmacological interventions (PI) have been studied for this condition, including dopaminergic agents, antidepressants, 5HT₃ antagonists, serotonergic agents, antiepileptics, amphetamines, GABAergic agents and miscellaneous drugs as naltrexone, nootropic agents, vaccines and disulfiram. There is no evidence about the effectiveness of these medications in pharmacological cocaine-dependence treatment.¹⁻³

In spite of few controlled studies, topiramate (TPM), a drug 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.⁵⁻⁹

TPM exercises its action by virtue of the GABAergic and glutamatergic system involvement in the cerebral reward system modulation. TPM exercises anticraving action through an increase in the GABAergic neurotransmission and inhibition of AMPA/kainate receptor activity.⁴

Considering the lack of substantial effective PI for cocaine dependence, this study, which is the first Latin American clinical trial with TPM in cocaine dependents, aims to add scientific evidence to the subject. Preliminary data indicates that controlled clinical trials in this area should be of further interest.

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

Method

Since this was a pilot open clinical trial involving inhaled cocaine dependents, a small sample was elected. Candidates were assisted with TPM in outpatient treatment for 12 weeks. The study was conducted at Uniad-Unifesp, from January through December 2004. It was approved by the University Ethics Committee (protocol number 0699/03). Inclusion and exclusion criteria were applied to all patients who sought treatment.

1. Inclusion criteria

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

2. 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 the investigator's opinion, women due to possibility of reduction in oral contraceptive (OC) levels related to TPM use and consequent pregnancy risk during the treatment, since some initial TPM studies suggest that this drug could decrease estrogenic component of OC when used concomitantly.¹⁰

3. Procedures

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

4. Instruments

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

2) Minnesota Cocaine Craving Scale (MCCS): Composed of five 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 (none 0 to 10 maximum visual score analogue scale), since these items can be used independently, as it was done in other studies. A translation of the scale was used. Its internal consistency in this study showed an alpha Cronbach coefficient similar to that of other international studies (0.814).¹²

3) 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

4) BIS11: Self-rating questionnaire, comprised of 30 Likert-type questions, which provides a total score and three subscores: attention, nonplanning and motor. Scores vary from 30 to 120 with no established cutoff point. The BIS11 was validated in Brazil for an adolescent sample and its score is a consistent measure of impulsiveness and has proven potential clinical use for measuring impulsiveness among selected patients.¹⁴

Attempting to minimize side effects, doses were scaled from small doses. The starting dose was 25 mg (25, 50 and 100 mg pills) increasing every 3 or 4 days to a maximum of 300 mg/day, according to assessment and clinical criteria of each psychiatrist to each individual. 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 was defined as attendance to at least three consultations, which corresponded to half of the study (six weeks); aiming to obtain

a more reliable time to observe clinical results. Research subjects who did not appear for the second consultation were considered dropouts. Comparative analysis was performed with intention to treat and the missing values were replaced by LOCF. Paired *t* test (parametric) was used to compare craving intensity (quantitative variable) baseline results to final evaluation through MCCS and BIS11. The Wilcoxon test (nonparametric), which takes the categorized magnitude of increase and decrease variables into consideration, was used to evaluate both dependant groups (baseline and final) in relation to craving duration and frequency. Confidence interval 95% was calculated to frequent adverse effects. Statistical significance level 0.05 ($\alpha = 5\%$).

Results

The sample was composed of 28 male subjects, mean age of 30.39 years (6.74), and average for dependence symptoms was 6.08 (1.22). The average number of symptoms of abstinence syndrome was 3.24 (1.09) (Table 1).

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 ($p_1 = \text{paired}, t = 0.012$), 25% had significant reduction and 75% did not have significant alteration.

The same occurred with craving duration: 25% had reduction, while 75% did not have changes ($p_2 = \text{Wilcoxon test} = 0.018$).

Reduction was not found in craving frequency ($p_2 = 0,783$): 7.1% had reduction in frequency; 10.7% related an increase in frequency and 82.1% did not.

Dropout rate in this clinical trial corresponded to 32% and adherence was 57%. Average consultation number was 3.14 (1.80).

Average TPM dose was 127.27 (93.19) mg/day. The highest percentage of tolerability dosage was 100 mg/day, which corresponds to 68.2% of research subjects.

Main adverse effect with incidence above 10% was included: somnolence (68%, IC = 46.0-84.6), paresthesia (63%, IC = 41.0-80.9), concentration deficit (47%, IC = 27.3-68.3), xerostomia (21%, IC = 8.5-43.3), anorexia (16%, IC = 5.5-37.6), and polyuria/

polydipsia (16%, IC = 5.5-37.6). Nineteen subjects were analyzed, since nine patients failed to appear for the second medical evaluation. Incidence of adverse events was mild.

Statistical significant variation was found neither regarding use of BIS11 nor in the final results compared to baseline: BIS11 total mean (SD) was 76.75 (9.24) at baseline and 75.86 (10.46) in the final result ($p = 0.474$).

Discussion

A statistically significant finding in this clinical trial was a decrease in craving intensity and duration. The main clinical implication of this result is that TPM seems to reduce craving, which is one of the main factors related to relapses in drug dependence.

So far, no medication has been approved for the specific indication of "anticraving," and indeed, even the concept of craving is controversial. In clinical trials, however, reductions in craving usually predict reduced drug use or maintenance of abstinence. Craving has been measured in a variety of ways, from a 100 mm Likert scale to a more complex questionnaire. Some have argued that "craving" is not a useful concept, and certainly, no one would claim that drug use never occurs without a conscious craving or that craving always leads to drug use. Some compulsive drug use has an automatic quality without a conscious buildup of desire. Yet most former addicts recognize a state of intense desire for drugs that is triggered by environmental cues or appear spontaneously. Despite the controversy, craving has been measured in many clinical trials.¹

One limitation in this trail was that decrease in craving was significant, but this was an open trail without placebo or control group. Therefore, there is a possibility that reduced craving only occurred due to the fact that, after 12 weeks, craving is expected to decrease. Another limitation was the small number of subjects and an all-male sample. 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 abstinence rate.

However, the most mentioned side effects were present in more than half of the sample. Side effects were mild and there were none that would limit drug use or losses. In these cases, a slow dose titration prevented the troublesome TPM side effects. Overall, adverse event profile was similar to that reported for other indications.¹⁰

Clinical trials in chemical dependents used to have high dropout rates, which very often compromised data extrapolation. The 32% dropout rate was similar to other clinical trials with the same profile and reasonable for a study that was not coupled to psychosocial intervention.¹⁵

With regard to 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 include multiple psychoactive substance users, larger samples, longer follow-up and women, as commonly found in outpatient clinics. This would increase power of evidence and capacity of generalization.

Conclusion

No pharmacological treatment has yet proven to be broadly effective for cocaine dependence. This study, as other recent

Table 1 – Sample characterization (n = 28). São Paulo, 2004

Age, years (average \pm SD)	30.39 \pm 6.74	
Dependence syndrome, n of symptoms (average \pm SD)	6.08 \pm 1.22	
Abstinence syndrome, n of symptoms (average \pm SD)	3.24 \pm 1.09	
ASI (average \pm SD)		
Physical complications	1.32 \pm 2.71	
Complications related to use of drugs	8.71 \pm 0.94	
Family 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	
Civil status, n (%)		
Married	15	(54%)
Single	9	(32%)
Separated/Divorced	4	(14%)
Employment status, n (%)		
Employed	20	(71%)
Unemployed	7	(25%)
Retired/Disabled	1	(4%)

Note: the number of symptoms for cocaine dependence was defined as the average number of clinical criteria necessary for cocaine dependence diagnosis (three or more diagnostic criteria according to DSM-IV).

Withdrawal symptom average: defined as the average number of clinical criteria necessary to consider diagnosis of withdrawal symptoms (two or more diagnostic criteria according to DSM-IV).

clinical trials, highlights TPM as a potential medication for reduction of craving and use in cocaine dependants. However, a larger randomized placebo-controlled trial with TPM in a less selective cocaine-dependant sample should be performed to evaluate preliminary evidence.

Future studies should consider the inclusion of psychiatric comorbidity and the association of psychosocial treatment.

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