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Topiramate as add-on therapy in non-respondent alcohol dependant patients: a 12 month follow-up study

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Introduction. Topiramate is a neuromodulator drug with different action mechanisms that could be implicated in alcohol dependence. It has been studied in open and double-blind studies.

Method. In a group of patients (n = 64) undergoing standard treatment for alcohol dependence (according to ICD-10 criteria) with poor outcomes, a 12 month observational, prospective and multicenter study was conducted to assess the usefulness and tolerability of topiramate as add-on therapy. Outcome measures were retention rate, alcohol consumption (days of drinking per month and number of Standard Drink Units [SDU] per day, and results of Alcohol Dependence Intensity Scale [ADIS]), craving and priming visual scales and serum transaminase levels.

Results. In these patients, adding topiramate leads to a significant decrease ($p < 0.001$) in all the variables studied, including those derived from the craving and priming visual scales, the ADIS as well as the number of drinks/day and SDU/day consumed, the MCV and GGT values. Mean topiramate dose was almost 200 mg/day. Only three patients dropped out due to adverse reactions.

Conclusions. Topiramate showed positive results for alcohol dependence in real clinical practice, with a significant decrease in craving-priming and dependence intensity scales, number of drinking days per month reported and transaminase levels. Topiramate seems to be a useful and well-tolerated pharmacological aid for patients with bad evolution in their alcohol dependence treatment.

Key words:
Topiramate. Alcohol dependence. Treatment. Craving. ADIS.

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Topiramato como coadyuvante en el tratamiento del trastorno por dependencia de alcohol en pacientes no respondedores: un estudio de 12 meses

Introducción. El topiramato es un fármaco neuromodulador que posee diferentes mecanismos de acción que podrían estar implicados en la dependencia alcohólica. Se ha estudiado su utilidad tanto en estudios abiertos como en un ensayo doble ciego.

Método. Se estudió en un grupo de pacientes ya en tratamiento por dependencia alcohólica (criterios CIE-10) con mala evolución (n = 64) la utilidad y tolerabilidad del topiramato como coadyuvante en el programa de deshabituación mediante un estudio multicéntrico, abierto y prospectivo de 12 meses de duración. Para medir los resultados clínicos se utilizaron una escala visual de *craving* (EVC), una escala visual de *priming* (EVP), la Escala de Intensidad de dependencia alcohólica (EIDA), el número de días que bebían al mes y la cantidad bebida por el día en unidades de bebida estándar (UBE), así como parámetros analíticos como las transaminasas.

Resultados. El topiramato redujo de forma significativa ($p < 0{,}001$) todas las variables estudiadas, tanto las derivadas de las Escalas visuales Craving y Priming y la EIDA como el número bebidas/día y las UBE/día consumidas, así como los valores del volumen corpuscular medio y la gamma-glutamiltransferasa. La dosis media final fue algo inferior a 200 mg/día. Sólo tres pacientes abandonaron por intolerancia.

Conclusiones. El topiramato mostró en condiciones asistenciales reales una buena respuesta clínica, medida tanto con la disminución de puntuación en escalas de dependencia y de *craving-priming* como con las bebidas referidas y las transaminasas, y parece ser un fármaco útil y bien tolerado para tratar a pacientes que presentan dependencia alcohólica y no responden adecuadamente a terapias estándar.

Palabras clave:
Topiramato. Dependencia alcohólica. Tratamiento. *Craving*. EIDA.

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INTRODUCTION

Alcohol abuse is a serious health problem that causes 1.5% of the deaths in the world. Biopsychosocial treatment, in spite of having useful psychotherapeutic and drug alternatives, is not always effective in all the patients[1]. The stimulating effects of alcohol sensitize the limbic areas that participate in reinforcement and pleasure. Many neurotransmitters participate in these mechanisms, among them gamma-aminobutyric acid (GABA) and glutamate. These undergo neuroadaptation due to continued alcohol abuse. An abstinence syndrome occurs when the subject stops drinking alcohol, with hyperactivity, anxiety, dysphoria, sleep alteration, etc. This may last for weeks or months and often causes relapses[2].

On the other hand, although therei is a lack of agreement on its meaning and definition, the concept of *craving* is widely used to assess the grade of alcohol problems[3,4]. Even though there has been much less debate and it is even less defined, the concept of *priming* or lost of control after beginning to drink is something that all the clinicians have dealt with in their alcoholic patients and whose drug treatment has been difficult. Greater knowledge of the brain mechanism and structures related with *craving* has made it possible to better understand its central role in addictive disorder and in the relapses[5,6]. Thus, for example, the increase of GABA exchange and antagonistic effect on the glutamatergic system may be useful in the treatment of *craving* in alcohol dependent patients, whose effects on the dopaminergic system are basically through gabergic and glutamatergic mechanisms[7-9].

During recent years, medications that may improve the already classical treatments have been identified. Antiepileptics have been tested to inhibit neuronal excitation, since in theory they could substitute alcohol and reduce the abstinence symptoms. However, experience with them is limited, although both carbamazepine as well as valproic acid and gabapentin have reduced alcohol consumption in the few studies conducted. In this sense, the first clinical trial published in this regards suggests that topiramate (TPM) may be effective in patients with alcohol dependence, improving the results of standardized treatments. Indeed, this double blind, randomized 12 week study shows a significant reduction in alcohol consumption in regards to number of drinks/day, number of days in which the subject drinks, amount drunk, alterations of transaminases and *craving* to drink[10]. In any event, it is clear that more controlled studies are needed to confirm its effectiveness.

The problem of most of the studies on alcoholism is that they have been designed including patients with recent abstinence and in order to measure its maintenance. The already mentioned study of Johnson et al.[10] differs because it does not require the maintenance of abstinence to continue in the study. This is important since it adapts more to the clinical reality of most of the patients, at least in the initial treatment phases. Naturalistic studies such as that of Rubio et al.[11] and Bobes et al.[12] also contribute to the knowledge on the course of the patients in common conditions. Naturalistic studies and clinical trials and the use of topiramate in another type of addiction, such as benzodiazepines[13], opiates[14] or cocaine[15], should be remembered.

The present study was established within this framework to consolidate knowledge on the utility of antiepileptic drugs in alcoholics. It aimed to evaluate the possible effects of topiramate on the retention rates, consumption and *craving,* in dehabituation programs in alcohol to tend in patients who have been treated not effectively up to the present, at 3, 6 and 12 months by an observational, follow-up study, that is, in the common clinical practice, and to describe the safety and tolerability of such treatment.

METHODS

Subjects

A total of 64 patients were patients enrolled in the study: 54 men and 10 women. Mean age was 38.6 years (SD: 9 years). Civil status was distributed homogenously: 24 single, 23 married and 17 separated/widow(er)s. By education level, only 55% had at least completed high school, and in regards to work status, 56.3% were working when they initiated the study. Mean years of alcohol abuse was 16.8 (SD: 8.5). A total of 38% fulfilled associated personality disorder criteria, 18% that of affective disorder, 2% of psychotic disorder and 2% more neurotic disorder. In regards to concomitant medications, the most frequent were antidepressants (34%), following by anxiolytics (25%), neuroleptics (23%), opiate agonists/antagonists (22%), and drugs with antiabuse effect (11%).

During their dependence, mean days that they drank per month was 25.6 (SD: 7.6), number of SDU/day was 19 (SD: 13,3), these parameters in the last month being 23.6 (SD: 8.7) and 16 (SD:10.8), respectively.

Procedures

This is an observational, non-randomized, single cohort, open label and perspective study on alcohol dependent subjects (according to ICD-10 criteria) treated in different outpatient facilities of the mental health network of Asturias (SESPA) where dependency problems in that regional community were treated. These patients had already been previously diagnosed and were receiving dehabituation treatment during at least the previous three months. TPM used at a dose and posology established according to clinical criteria was added to this treatment. All elderly patients who failed to achieve clinical improvement of their dependency with conventional drugs, with limited or no response to treatment according to the psychiatrist's criteria and that of

the patient (from whom consent to participate in the study was requested), were included. All the patients were administered concomitant drugs. The participants in this study underwent a complete blood and general biochemical study.

A single treatment group with topiramate having fixed doses established by clinical criteria as well as the concomitant treatments required in order to respond to the interest of the observation under real care conditions was contemplated in the study design. As this is an observational study, the investigator was free to set up any other follow-up or control visit considered to be necessary. Furthermore, the investigator could prescribe, change or continue the study treatment and the possible concomitant treatments according to his/her clinical judgment.

Different evaluation measurements of therapeutic response were used to measure the clinical results. The following were done at the baseline interview as well as 1, 3, 6 and 12 months of adding topiramate associated to the usual treatment: a Visual Analogue Craving Scale (VACS), Visual Analogue Priming Scale (VAPS) and an Alcohol Dependency Intensity Scale (ADIS), with their subscales: physical symptoms, psychological symptoms, behavior to decrease the symptoms, consumption and control of symptoms after relapse[16]. This scale is very useful to study problems derived from alcohol as it is a validated and comfortable tool to administer. Furthermore, the number of days that the subject drank in a month and the amount drank per day in SDU were recorded. Laboratory analyses of the parameters of indirect measurement of change in alcohol consumption and the Mean Corpuscular Value (MCV) and Gamma Glutamyl Transferase (GGT) were conducted at least at 6 and 12 months of the study.

The following variables were recorded and analyzed in the baseline interview: age, gender, civil status, educational level, current work status, years of abuse, medical and psychiatric background, previous alterations in complete blood tests and biochemistry study, and concomitant medications (psychiatric or not). There was also a first control of the variables of the clinical results: VACS, VAPS, ADIS, days of drinking/month, SDU/day, MCV and GGT. The study duration was one year. It began in September 2004 and was completed in August 2005. TPM safety was also analyzed, collecting the adverse effects declared.

As primary treatment outcome parameters, retention rate, scores on the craving and priming visual analog scale (VAS) and ADIS, days of drinking and SDU, MCV and GGT levels were considered. Analysis of the outcome was done by «intention to treat» and carrying forward the last available value in the cases of early interruption. This analysis included the description of the disorder course during the study, comparing the values of each visit with the baseline condition on the scales used (CVAS, PVAS, ADIS) as well as consumption (days of drinking/month, SDU/day) and biological markers (MCV and GGT).

The analysis of tolerability included a description of the nature of spontaneous communication adverse reactions during the study, including the assessment of seriousness by the investigator, action done with the drug and results in the patient.

Statistical analysis

The difference of the scores on the tests between the initial visit and intermediate and final visits was calculated for all the variables of the clinical outcome and its 95% confidence intervals (95% CI) were calculated. Furthermore, the differences of the means were analyzed with the Student's *t* test if the distribution was normal. Qualitative variables were analyzed with χ^2 and its 95% CI.

Excel 2003 was used as the database program and SPSS 10.0 as the statistical one.

RESULTS

A total of 57 out of the initial 64 patients remained in the first month and 48 in the third one. Forty (40) continued at the sixth month and 22 at one year (10 were discharged between the 6th and 12th month). No statistically significant difference was found in the values of the variables obtained in the baseline interview between the group of patients retained and not retained at six months. Thus we consider that these are representative of the initial group.

All the changes analyzed from the first to the 12th month were statistically significant ($p<0.001$), both in absolute as well as relative terms. This is summarized in table 1.

Table 1 Changes in the efficacy variables during the treatment

	Crav. vs	Prim. vs	ADIS	No. days D/month	SDU/D month	MCV*	GGT	TPM dose
Baseline	6.33 (2.12)	6.52 (2.00)	39.60 (16.41)	23.63 (8.72)	15.97 (10.78)	98.92 (6.50)	212.15 (382.27)	87.10 (65.09)
1 month	4.43 (2.27)	4.14 (2.28)	35.82* (22.34)	10.00 (11.27)	5.14 (5.83)	–	–	159.72 (63.77)
3 month	3.35 (2.03)	2.80 (1.92)	21.33 (16.34)	7.60 (10.08)	3.69 (4.85)	91.86 (20.15)	123.22 (254.45)	187.79 (102.55)
6 month	2.83 (1.67)	2.23 (1.72)	15.71 (13.25)	6.10 (7.43)	2.55 (2.79)	90.48 (20.13)	102.43 (196.80)	202.03 (107.75)
12 month	2.58 (1.56)	2.25 (1.36)	13.40 (8.19)	4.83 (8.52)	1.92 (1.78)	95.82 (1.08)	61.18 (33.99)	195.83 (95.80)

Quantitative variables: mean and standard deviation. All the changes $p < 0.001$ regarding baseline except *.

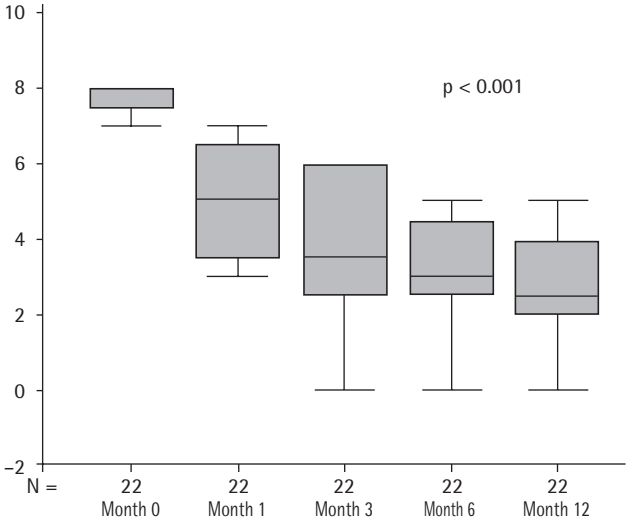

Figure 1 *Change in Visual Craving Scale.*

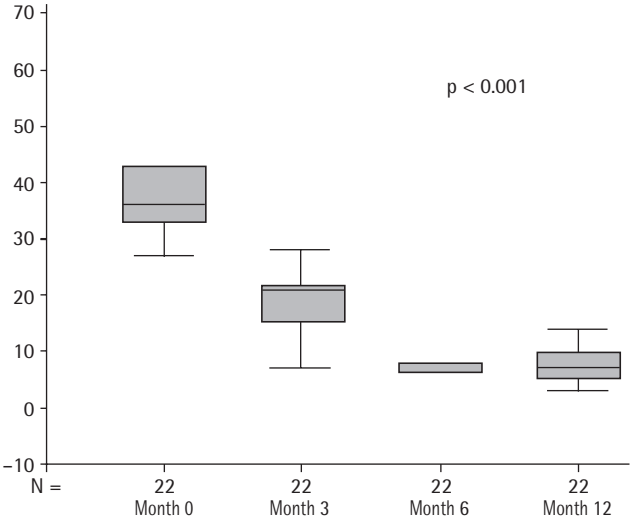

Figure 3 *Change in Alcohol Dependence Intensity Scale (ADIS) (global).*

Thus, all the subscales of the ADIS, except the global ADIS of the baseline visit at month 1 (p=0.1), showed significant reductions in both physical as well as psychological symptoms, in the changes to reduce symptoms, in consumption, in loss of control and in the symptoms after relapse (figs. 1, 2, 3 and 4). Furthermore, significant decreases were observed in mean MCV and GGT of more than 7 points in the first (98.9 to 91.8) and more than 88 in the second (212.1 to 123.2 IU/l) from the third month of treatment. These remained constant during the rest of the study. The results obtained in the Craving and Priming Scale showed an already significant reduction in craving to consume and loss of control in the patients included during the 12 months of the study (p<0.001) from the first month of treatment with topiramate. A significant reduction was also detected in the number of days that the patient drank per month and in the measure of SDU/day (figs. 5 and 6).

In regards to taking concomitant medications, it was possible to reduce all those related with dependency at the end of the study, with a 10% decrease in opiate antagonist/agonist dose, 8% in antipsychotics, 5% in anxiolytics and 1% in antiabuse, except for anti-depressants, in which intake increased 12%.

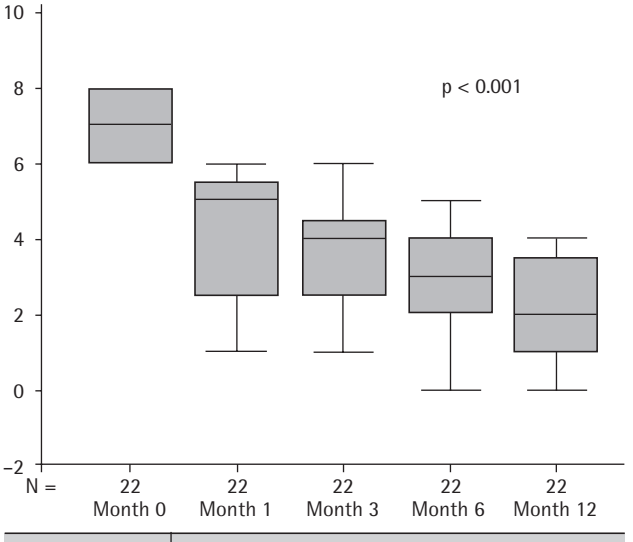

Figure 2 *Change in Visual Priming Scale.*

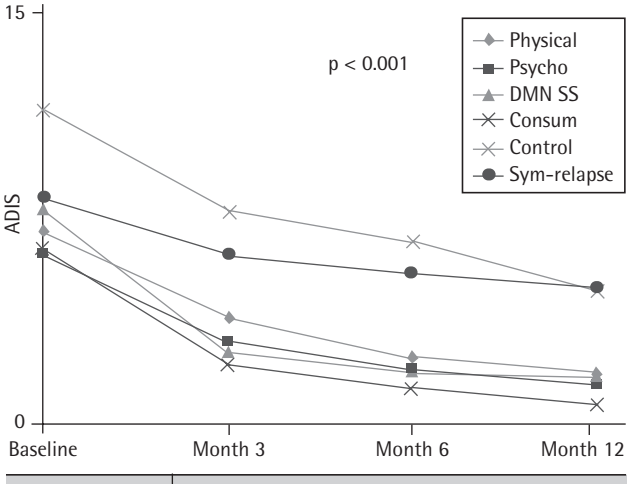

Figure 4 *Changes in ADIS subscales. Physical: physical symptoms; Psycho: psychological symptoms; DMN SS: behaviors to decrease symptoms; Consum: consumption; Control: control; Sym-relapse: symptoms after relapses.*

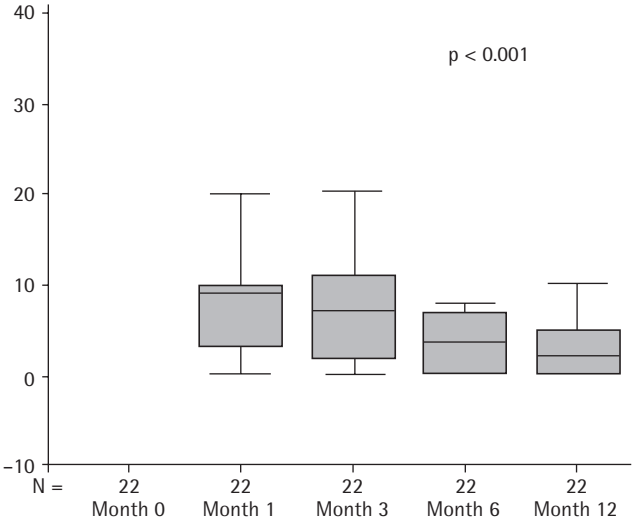

Figure 5 *In the last month: no. of days subject drinks per month.*

At the end of the study, the mean TPM dose was 196 mg/day (SD: 96 mg/day), with a range of 50 to 400 mg/day. Nineteen (30%) out of all the patients (n=64) did not complete the study due to lack of follow-up, 12 (18.7%) and 3 (4.7%) due to intolerance, the causes being: nausea and weight loss and paresthesias/somnolence, respectively. The side effects collected during the study are summarized in table 2.

DISCUSSION

The results obtained in this observational study corroborate the idea suggested in previous studies that topiramate may be a useful and well-tolerated treatment for alcohol dependence when associated to the usual treatments. These beneficial effects have been observed in all the scales studied and from the first month of follow-up in both the Craving and Priming Visual Scale and in the different ADIS subscales as well as in the quantification of the number of days that the patient drank per month, and in the measurement of the SDU/day. Other variables to be considered are the objective analytic measurements. This is an indirect and relatively reliable way of verifying that the subjective data described by the patient are true. In our series, a significant decrease in MCV and GGT was observed from the first control laboratory analysis sample after baseline (at month three). This corroborates the results obtained in the different scales. Regarding the taking of other drugs, it was possible to reduce the rest of the medications, except for the anti-depressants. This seems logical given the clinical improvement of the dependency itself and the better drug management of it when topiramate is introduced.

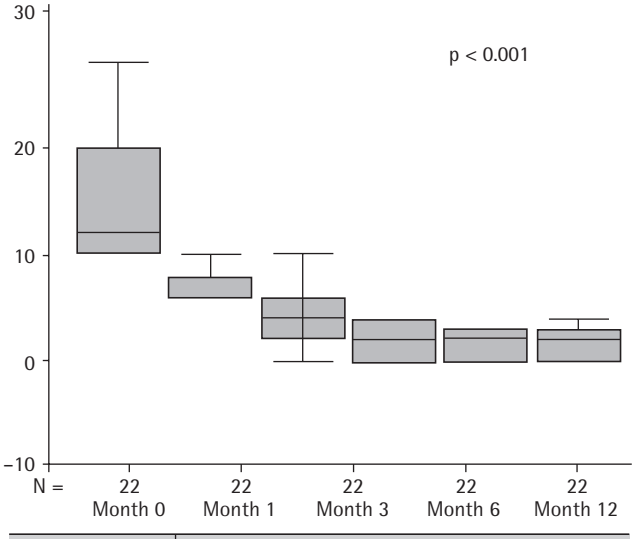

Figure 6 *In the last month: no. of Standard Drink Units (SDU) per day.*

Table 2 **Total of side effects reported during 12 months of study**

Side effects	Total	Percentage
Weight loss	10	15.6
Somnolence	4	6.2
Paresthesias	3	4.7
Nausea/vomiting	2	3.1
Memory difficulty	2	3.1
Sweating	1	1.6
Disturbance in sense of smell	1	1.6

The results obtained in the work agree with those found in other studies. The first reference, although anecdotic, on the utility of topiramate in alcohol dependence, may have been made by Komanduri[17] in 2003, based on two patients with a *craving* reduction response. In a double blind clinical trial with 150 patients over 12 weeks, Johnson et al.[10] observed how topiramate significantly reduced the number of days that the patients reported drinking, alcohol *craving* and GGT levels. In a series of 14 patients followed-up for 12 weeks in Spain, Rubio et al.[11] also showed how topiramate decreased alcohol consumption, *craving,* and another objective measure in blood, such as carbohydrate deficient transferrin. Also in our country, Bobes et al.[12] found a good response to topiramate in real care conditions with an important decrease of the percentage of patients who consumed different illegal drugs and alcohol and of the severity of the addiction and *craving* and a satisfactory tolerability profile, even improving the results obtained in previous studies. In all of these studies, statistically significant

differences were observed for the parameters studied. This stresses the possible utility of this drug for alcohol dependence.

It should be pointed out that although three subjects dropped out due to adverse events, none of them were considered as serious or unknown by the investigators and the rest of the side effects were mild and/or transitory. Thus, treatment with topiramate, also as in the previous studies, was well tolerated in this group of patients. However, it must be considered that in observational studies such as the present one, only the adverse reactions which, by definition, should have a causality relationship are recorded. Furthermore, the method of spontaneous reporting of adverse reactions such as that used are also generally under-reported, since only clinical relevance or unexpected adverse reactions are reported.

In general terms, retention in treatment is more than acceptable if we compare it with that which is normal in this type of patient, especially when there are severe dependents having previous torpid course in conventional treatments. At 6 months, only one third of those enrolled in the study were lost. Even at 12 months, this is an acceptable retention rate, since some were even discharged and other had to interrupt the study as it was ineffective or due to intolerance or for reasons outside of the treatment, which is logical given the length of the follow-up.

It is important to state that the naturalistic type design used, although it limits the internal validity, has the advantage that it reflects the utility and problems of treatment with topiramate in the real clinical practice. The complementarity of the design used should be stressed when trying to generalize the conclusions obtained in clinical trials and overcome to a certain point their limitations to be able to thus respond to the needs of the daily clinical practice[18].

In the case of the present investigation, two previously unmade contributions are offered. First of all, there is a follow-up of the treatment at 12 months, much greater than that done up to now, and it has a temporality that is more in accordance with the duration of the treatments of the addiction as well as the maintenance of the benefits of the introduction of topiramate for some many months. The second contribution is the profile of the patients, since they are alcoholics with a torpid course with conventional treatments, which frequently occurs, in whom adding topiramate has clearly lead to improvement. Thus, we consider that the fact that this is an open study is an important advance in drug therapies with alcohol dependent subjects from the initial moments, both for abstinence purposes as well as intermediate objectives: reduction of drinking, of *craving* for a drink and of the derived complications.

CONCLUSIONS

Under real health care conditions, topiramate has been shown to be a useful and well-tolerated drug to treat patients with alcohol dependence who do not respond adequately to standard therapies, since adding it is related with decrease in drinking, craving for a drink and intensity of the dependence. Furthermore, greater retention in treatment then usual in these patients was observed. Although this is an open study, with all the methodological limitations implied by an observational study, our results corroborate that observed by the still few previously published studies, improving them in regards to study duration and profile of previous bad course of the patients.

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