Study of effectiveness of craving control with topiramate in patients with substance dependence disorders

J. Bobes[a], J. E. Carreño[b], C. E. Gutiérrrez[c], G. I. San Narciso[b], M. J. Antuña[d], T. Díaz[e], J. J. Fernández[f], A. Cerceda[b], C. E. Álvarez[b], P. Marina[g] and M. García-García[h]

[a] *Psychiatry Department. University of Oviedo.* [b] *Clínica Médico Psicológica. Gijón.*
[c] *Mental Health Center El Coto. Gijón.* [d] *Mental Health Center 1. Gijón.*
[e] *Drug Addict Treatment Unit. Oviedo.* [f] *Drug Addict Treatment Unit. Avilés.*
[g] *Mental Health Center. Pola de Siero. Asturias.* [b] *Biométrica. Barcelona. Spain*

Estudio de la efectividad del control del* craving *con topiramato en pacientes con trastornos por dependencia de sustancias

Summary

Introduction. *Effectiveness and tolerability of topiramate at 3 and 6 months was assessed in patients requesting dehabituation programs.*

Methods. *Observational, prospective, national and multicenter study of 6 months, in patients on treatment with topiramate, who fulfilled criteria for dependence of opiates according to ICD-10 participating in therapeutic programs of dehabituation, without concomitant psychiatric illnesses and any responsible relative. Main measures of effectiveness were retention rates, alcohol consumption and other illicit drugs by urine tests (opiates, cannabis, cocaine) and treatment needs by EuropASI scale. Other parameters were HAM-D, DAS-SV and SF-36.*

Results. *Patients with consumption by urine tests decreased from 94.1 % (n = 64) at baseline to 39.6 % (n = 19) after 6 months of treatment, as was seen by means of the mean score in EuropASI scale, for all substances except methadone. No consumption was accompanied by a low rate of relapse of 33.3 % at 6 months. Twenty one patients had adverse reactions (28 %). The most frequent adverse reactions were somnolence (n = 9; 12 %), paraesthesia (n = 5; 6.7 %) and depression (n = 4; 5.3 %).*

Conclusions. *In real clinical practice, topiramate showed a good response with a relevant decrease of percent of patients with abuse or consumption, and a satisfactory tolerability profile for the treatment of patients with dependence on heroine, cocaine, and other opiates, showing better outcomes than those obtained in previous trials.*

Key words: *Topiramate. Alcohol abuse. Dependence of substances. Heroine. Cocaine.*

Resumen

Introducción. *En la práctica clínica habitual se ha evaluado la eficacia y tolerabilidad de topiramato a los 3 y 6 meses, en pacientes que solicitaron programas de deshabituación.*

Métodos. *Estudio observacional prospectivo, multicéntrico, de ámbito nacional, de 6 meses de tratamiento con topiramato, en pacientes con criterios de dependencia de opiáceos según CIE-10 en programas terapéuticos de deshabituación, sin otra patología psiquiátrica concomitante y con algún familiar responsable. Medidas principales de eficacia han sido: tasas de retención, consumo de alcohol y otras drogas de abuso en orina y necesidad de tratamiento del Cuestionario EuropASI. Otros parámetros han sido las escalas HAM-D, DAS-SV y SF-36.*

Resultados. *El número de pacientes consumidores según controles de orina descendió del 94,1 % (n = 64) basal al 39,6 % (n = 19) a los 6 meses de seguimiento, descenso que se reflejó también a partir de la puntuación media en el cuestionario EuropASI para todas las sustancias excepto la metadona. Esta alta tasa de no consumo se acompañó de una baja tasa de recaídas, del 33,3 % a los 6 meses. Se registraron 21 pacientes con reacciones adversas (28 %), siendo las reacciones adversas más frecuentes la somnolencia (n = 9; 12 %), las parestesias (n = 5; 6,7 %) y la depresión (n = 4; 5,3 %).*

Conclusiones. *El topiramato mostró en condiciones asistenciales reales una buena respuesta, con una importante disminución del porcentaje de pacientes consumidores, y un satisfactorio perfil de tolerabilidad en el tratamiento de pacientes con dependencia de heroína, cocaína, y/u otros derivados opiáceos, mejorando los resultados obtenidos en ensayos clínicos previos.*

Palabras clave: *Topiramato. Abuso de alcohol. Dependencia de sustancias. Heroína. Cocaína.*

Correspondence:
Julio Bobes
Departamento de Psiquiatría
Universidad de Oviedo
Julián Clavería, 6
33006 Oviedo (Asturias) (Spain)
E-mail: bobes@correo.uniovi.es

INTRODUCTION

Craving or longing for drugs that appears during the treatment of different addictions is one of the most difficult situations to treat[1,2,3]. Craving is considered by many

clinicians and investigators as a central element in addictions, although this importance has also been questioned. Litt, Cooney and Morse[4] point out the fact that some individuals do no report craving. It is not clear if they simply do not experience it, if they experience it without recognizing it or, on the contrary, they experience it but, even recognizing it, do not report it.

In spite of this lack of agreement on its significance and definition, the craving concept is widely used to assess the degree of problems with alcohol. It has been implicitly or explicitly applied in many studies, which clearly indicates the need to study and establish some consensus on the nature and relevance of the phenomenon that craving tries to define. At present, its importance in the transition of controlled consumption to dependence is widely recognized[5], in the mechanisms that underlie relapses[6,7] and in treatment of alcoholism[8]. In any event, some theoretical models do not consider craving essential for the explanation of the relapses[1] since it has been difficult to demonstrate empirically its existence in some situations. This has made it difficult to reach total agreement on its validity as a construct and has established conceptual and methodological limitations for much time.

In the last 10 years, interest in the role of craving has reappeared in investigation of addictions. Its study has been approached from several perspectives, giving rise to different models and the craving construct occupies a central site in all of them. The most relevant reviews were performed by Singleton and Gorelick in 1998, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (1999) and the journal *Addiction* (2000). Although the DSM-IV does not include craving as such among the diagnostic criteria of dependency, it does define it (strong impulse of consuming the substance) as one of the characteristics that probably occur[9].

Greater knowledge on the cerebral mechanisms and structures related with craving[3,10] has made it possible to increase knowledge on craving and better understand its central role in addictive disorders and in relapses. Several attempts have been made to reach a consensus among the different models. These have led to new approaches in regards to therapeutic strategies to investigate. Specifically, it has been described that there is a decrease in dopamine release in mesoestriatal areas after the chronic use of psychoactive substances, due to the sensitization phenomena of the pre- and postsynaptic dopaminergic receptors. The sensitization process seems to depend on two different and independent neurobiological substrates. Thus, the effects of the different addictive substances in the ventral tegmental area level would initiate the process of sensitization while the actions of these substances on the nucleus accumbens would be necessary for its expression and maintenance. Several mechanisms that may mediate in the onset of sensitization to the drug effects have been identified in the ventral tegmental area. One would be the product of an increase in the activity of the mesoaccumbens pathway due to the development of subsensitivity phenomena of the presynaptic receptors (type D_2), that regulate by inhibition the dopaminergic activity of this pathway, causing an increase in dendritic release of dopamine. For other authors, the mechanism involved in the sensitization induction would be the activity of somatodendritically released dopamine on the D_1 receptor located in the synaptic terminals of the gabaergic striatofugal pathways, that are projected towards the mesencephalic areas and that contain the cellular bodies of the mesostriatal dopaminergic pathways. Supersensitivity of the dopaminergic D_1 receptor is involved in the expression of sensitization on the postsynaptic level. These data suggest that the action of the different psychoactive substances in the ventral tegmental area (increase of dopamine and subsensitivity of the D_2 type autoreceptors) is necessary in order to produce changes in the activity of the dopaminergic neurons of the mesoaccumbens pathway which, in turn, would lead to subsequent alterations in the dopaminergic transmission in terminal areas (supersensitivity of the D_2 receptors).

However, the effects of most of the addictive substances on dopaminergic transmission are not caused by direct actions on the intrinsic activity of the dopaminergic neurons (except for the psychostimulants). Thus, they are mediated by different neurotransmission systems that directly (by synaptic connections) or indirectly (through other neurotransmission systems that exert direct modulating effects) modulate the activity of the mesostriatal dopaminergic neurons. These systems that are involved may be the gabaergic, opioid, cholinergic, noradrenergic, glutamatergic and serotoniergic systems. On the other hand, when positive reinforcement effects are obtained in other brain areas, in which dopamine supposedly does not mediate these effects, it is necessary to examine the possible connections of these brain areas with those that innervate the mesostriatal dopaminergic system since, on occasions, they can also modulate the mesostriatal dopaminergic activity, as occurs in the case of the opiates in the lateral hypothalamus.

The increase of the GABA turnover in several brain regions of patients treated with topiramate and the effect on the glutamatergic system may be useful in the treatment of craving in substance dependent patients after the physical detoxification phase, above all in opiate dependent patients in whom the effects of the opiates on the dopaminergic system are basically performed through gabergic and glutamatergic mechanisms. This is the contrary to cocaine dependent patients, in whom the cocaine actions are direct dopaminergic (D_1 and D_2), although it also has the previously mentioned gabaergic and glutamatergic mechanisms.

The project and the CRAVING study (study of effectiveness of craving control with topiramate in patients with substance dependency disorders) carried out in Spain and whose results are presented in this article were done in this framework. The objectives of the study were to assess, in the common clinical practice, the effect of topiramate in the retention and relapse rates in dehabituation programs in heroin, cocaine and/or opiate derivative dependent patients at 3 and 6 months as well as to describe this treatment's safety and tolerability.

METHODOLOGY

Investigators and patients

The study was performed by nine psychiatric investigators from different centers in Spain.

Patients over 18 years of age with opiate dependency criteria according to the ICD-10, who came to the participating treatment centers to be admitted in their therapeutic programs and who requested dehabituation treatment between October 1, 2001 and February 1, 2002, who did not present another concomitant psychiatric disease and for whom there was a responsible family member figure to verify compliance in taking the medication by the patient were included in the study. The exclusion criteria established were the exclusion of pregnant women and breast-feeding mothers and patients with serious organic disorders (concomitant uncontrolled or unstable digestive, cardiovascular, renal, hepatic diseases or endocrine disease).

Prior to their participating in the study, all the patients were requested to give their informed consent for it.

Study design

This is an observational, post-authorization follow-up, multicenter, prospective and single cohort study with a six month follow-up period. A total of 4 assessment visits were established for the study in the 6 month follow-up: one baseline or patient inclusion and three during the follow-up after 1, 3 and 6 months, respectively.

A single treatment group with topiramate with the doses established by clinical criterion, as well as the concomitant treatments necessary were contemplated in the study design in order to be able to respond, for observation, in real health care conditions.

Measurements of effectiveness and tolerability

In addition to the patients' sociodemographic and baseline clinical data, data regarding the following parameters were collected in each follow-up visit: results of urine controls (abuse drugs), EuropASI (only on baseline vi-sit and month 6), craving and HAM-D (in all the visits except month 1) and DAS-SV (only in baseline visit and month 6) scales. In addition, concomitant drug treatments obtained were collected. These were classified by the Anatomic-Therapeutic-Chemical Classification System[11] of the World Health Organization. Adverse reactions produced during the study follow-up, recorded by spontaneous communication, were also collected and were classified by the WHO-ART[12] Adverse Reactions Classification System, also from the World Health Organization.

As this was an observational study, the investigator was free to set up any other follow-up or control visit considered appropriate. In addition, the investigator was free to prescribe, change or continue the study treatment, as well as possible concomitant treatments, according to his clinical judgement.

Retention rate, detection of abuse substances in urine, EuropASI treatment need and craving levels were considered as main efficacy parameters. The secondary parameters used were the HAM-D, disability assessment level (DAS-SV) and quality of life level (SF-36).

Statistical analysis

Tolerability analysis included the description of the nature of the spontaneously reported adverse reactions during the study, including the investigator's assessment of seriousness, action performed with the drug and patient outcome. Frequencies were calculated for this.

Effectiveness analysis was performed by intention to treat (ITT) and by the last observation carried forward (LOCF) analysis, carrying the last value available in the cases of early interruption. This analysis included:

- Description of the urine analysis results evolution: number of urine controls performed, how many were positive to opiates and other addictive substances, and percentage of positive controls of all consumers.
- Description of the evolution of this disorder's seriousness during the study, comparing the values of each visit with the baseline situation in the scales used as described in the following.
- EuropASI scale[13]: in addition to the consumption table in the last month per substance, the severity evolution for the 7 dimensions for which scores are available (baseline and month 6) was assessed.
- Craving scale: Evolution of each one of the items, in addition to the total scores of the scale's five dimensions (anxiety, autonomic, sensory, motor and cognitive examination symptoms) and total score were analyzed; score was considered as not evaluable for analysis if the response to an item was not evaluable (baseline, month 1, month 3 and month 6).
- Hamilton depression scale (HAM-D)[14,15]: evolution of the total score with a maximum score of 50 points on the scale was analyzed.
- Disability assessment scale-short version (DAS-SV): evolution of the total global disability score according to specific areas (baseline and month 6) was assessed.

Once the study data were listed and quality control performed, the results were analyzed with the SPSS statistical program, version 11.0. In the descriptive analysis, the mean, standard deviations and range for quantitative variables and the frequency and percentage of patients in each category for the qualitative variables were estimated. For comparison between successive visits in regards to baseline values, comparative analyses were performed, using Cochran's statistical test of comparison of proportions for it when dealing with dichotomic categorical variables and Wilcoxon comparison of scores when dealing

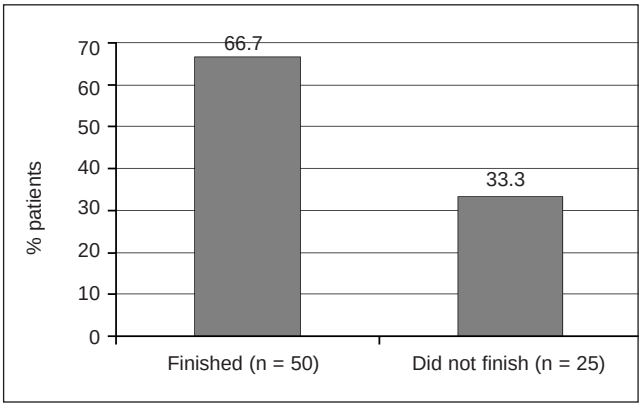

Figure 1. Retention rate.

with ordinal variables. The referenced «p» values in this publication correspond to the statistical significance of bilateral tests. Values lower than or equal to 0.05 are considered statistically significant.

RESULTS

Evaluable patients

Eighty three (83) patients were enrolled by nine participating study investigator physicians. Eight out of these 83 patients were excluded from the tolerability and effectiveness analyses because four cases did not comply with the opiate dependence criteria according to ICD-10, three patients did not report any follow-up data after the baseline visit and one patient had another concomitant psychiatric disease. After this, 75 evaluable patients remained, 25 (33.3 %) of whom had an early interruption before finishing the study's 6 month follow-up, which means a 66.7 % retention rate in the dehabituation program (fig. 1).

TABLE 1. Biosociodemographic characteristics of the patients

Characteristic	*n = 75*	
Gender (n, %)		
Man	59	78.7
Woman	16	21.3
Age (m, SD) (years) (n = 67)	30.1	5.1
Weight (m, SD) (kg) (n = 66)	71.5	11.2
Height (m, SD) (cm) (n = 66)	174.0	8.2
BMI (m, SD) (kg/m^2) (n = 66)	23.5	2.4
Work situation (n, %)		
Full time	32	42.7
Part time	12	16.0
Unemployment with unemployment benefits	9	12.0
Temporary incapacity	2	2.7
Retirement	1	1.3
Others	16	21.3

m: mean; SD: standard deviation.

Patients' characteristics

Table 1 shows the baseline biosociodemographic characteristics of the sample patients. Most patients were men (78.7 %), whose ages were mostly around 30 years (m = 30.1 years; SD = 5.1), with a mean BMI of 23.5 kg/m^2 (SD = 2.4), corresponding to a mostly normal weight sample, and most were working full-time or partial time (n = 44; 58.7 %). The most frequent concomitant diseases in the sample of 75 evaluable patients were presence of hepatitis (24.0 %) and gastrointestinal disorders (17.3 %). No serious concomitant disease was observed nor was possible deterioration of any disease reported in any case. Regarding the treatment of these diseases, 8.0 % of the evaluable patients had some drug treatment on the baseline visit.

Table 2 shows the toxicological consumption background of the patients. It can be observed that cocaine,

TABLE 2. Toxicological background of the patients' consumption

	Total patients	*No consumers*		*Consumers*		*Onset age (years)*		*Duration (years)*	
	n	*n*	*%*[1]	*n*	*%*[1]	*m*	*SD*	*m*	*SD*
Alcohol (in g)	75	21	28.0	54	72.0	15.3	2.3	7.6	7.2
Opiates (in ud)	75	11	14.7	64	85.3	19.4	3.7	9.0	6.1
Benzodiazepines (in ud)	75	28	37.3	47	62.7	22.2	4.4	3.7	5.6
Cocaine (in g)	75	11	14.7	64	85.3	19.1	3.9	5.0	5.9
Cannabis (in ud)	75	12	16.0	63	84.0	15.5	2.0	7.4	6.6
Amphetamines (in ud)	75	32	42.7	43	57.3	17.2	2.2	2.3	3.6
Hallucinogens (in ud)	75	29	38.7	46	61.3	17.7	2.7	1.3	2.8
Inhalants	75	71	94.7	4	5.3	18.0	9.4	8.4	15.8
Other substances	75	73	97.3	2	2.7	25.0	1.4	3.8	4.6
Other addictive behaviors	75	74	98.7	1	1.3	20.0	—	0.5	0.0

[1] The percentages were calculated on the total patients who specified such information. m: mean; SD: standard deviation.

TABLE 3. Evolution of patients with positive urine controls

	Baseline (n = 68)		*1st month (n = 71)*		*3rd month (n = 62)*		*6th month (n = 48)*	
	n	*%*[1]	*n*	*%*[1]	*n*	*%*[1]	*n*	*%*[1]
Total								
Patients with positive controls[2]	64	94.1	33	46.5	31	50.0	19	39.6
Marihuana								
Patients with positive controls	8	11.8	7	9.9	7	11.3	5	10.4
Opiates								
Patients with positive controls[2]	47	69.1	7	9.9	4	6.5	3	6.3
Cannabis								
Patients with positive controls	18	26.5	11	15.5	14	22.6	13	27.1
Alcohol								
Patients with positive controls	6	8.8	0	0.0	1	1.6	2	4.2
Psychostimulants								
Patients with positive controls	32	47.1	19	26.8	22	35.5	4	8.3
Barbiturics[a]								
Patients with positive controls[2]	12	17.6	2	2.8	0	0.0	0	0.0

[1] Percentage of patients out of all the patients in whom at least one control was performed in the last 30 days. [2] Statistically significant differences were found during the study (Cochran; [2] $p < 0.001$).

opiates and cannabis were the abuse substances with the most extended consumption, there being an 80% rate of consumers in the three cases.

In regards to the other previous and present clinical aspects of the substance consumption pattern of the patients studied, it stands out that cocaine consumption was generally sporadic (47.6%) or excessive (7.9%), although almost half the consumers (44.4%) already had abuse (20.6%) or dependence (23.8%) problems. One third (31.3%) received specific treatment for their abuse or dependence problem. One out of every three cannabis consuming patients had abuse (18.3%) or dependence (11.7%) problems, although only 8.3% received specific treatment for it. Regarding heroin and analogue consumption, the enormously dependent character of these substances was observed, since almost all the consumers had an opiate dependence disorder (96.9% of the 64 consumer patients). Furthermore, 74.2% of these patients received treatment for their dependence. Consumption of the other substances was mostly sporadic, except for the use of benzodiazepines without prescription, since 15.6% of them had an abuse problem.

Mean topiramate dose for all the evaluable patients was 86.6 mg/day in the baseline visit, slowly increasing in the subsequent visits until the mean dose of 190.5 mg/day on the month 6 visit. This increase was statistically significant in regards to the baseline visit from the first treatment month (Wilcoxon test; $p < 0.001$).

Effectiveness

Table 3 shows the evolution of patients with positive urine controls used in this study. The urine analysis results performed during the 30 previous days were obtained in each one of the visits performed during the study. The number of consumer patients, according to the urine control results, globally decreased from 94.1% (n = 64) on the baseline visit to 39.6% (n = 19) after the 6 months of follow-up. A total of 94.1% of the patients (n = 64) who had urine controls in the baseline visit had at least one positive. The percentage of patients who consumed opiates, psychostimulants, barbiturics and alcohol decreased significantly. Consumption of marihuana and cannabis remained more or less constant during the follow-up. The decrease observed in substance consumption evaluated by urine toxic measurement was also reflected, as seen in table 4, in the frequency of consumption obtained from the EuropASI questionnaire. In this, a reduction in substance consumption was observed in the last month for all the substances, except for the logical exception of methadone, understanding that this consumption responds to a therapeutic intervention. This high rate of non-consumption was also accompanied by a low relapse rate. As is shown in figure 2, this was 33.3% at 6 months of treatment.

Table 5 shows the results obtained in the rest of the different effectiveness variables used in this study. The results obtained on the Craving Scale showed a reduction in consumption anxiety (or Craving) in the patients included during the six months of the study. This reduction could be observed in the 5 dimensions that made up the scale (anxiety, autonomic symptoms, sensory symptoms, motor symptoms and cognitive examination). The dimension that evaluates the anxiety symptoms should be especially stressed, since at baseline, they appeared as the most serious clinical symptoms (m = 6.5; SD = 3.0) and at the end of the study, they had decreased to levels

TABLE 4. Evolution of patients with substance consumption according to EuropASI questionnaire

	Baseline			*6th month*		
	Mean	*SD*	*n*	*Mean*	*SD*	*n*
Alcohol (any dose)[1]	11.0	7.5	53	7.6	6.2	38
Alcohol (large amounts)	10.8	4.4	6	1.7	2.3	6
Heroin[1]	27.6	5.9	58	0.7	4.1	38
Methadone	17.0	12.0	5	12.0	16.4	5
Other opiates/ analgesics	14.3	12.1	7	0.0	0.0	6
BDZ/barbiturics/ sedatives/hypnotics[4]	12.8	9.7	29	3.1	8.1	16
Cocaine[1]	14.3	11.1	47	1.3	3.6	33
Amphetamines	10.0	0.0	1	—	—	4
Cannabis[2]	15.9	11.7	27	7.0	8.9	28
Hallucinogens	—	—	—	—	—	3
Inhalants	—	—	—	—	—	1
Others	—	—	—	—	—	—
More than 1 substance/ day (items 2 to 12)	20.0	8.2	4	—	—	4

[1-4] Statistically significant decreases were observed (Wilcoxon; [1] $p < 0.001$; [2] $p < 0.005$; [3] $p < 0.01$; [4] $p < 0.05$).

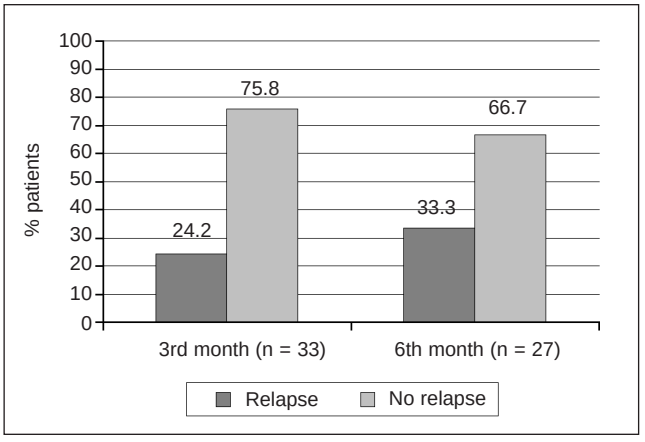

Figure 2. Relapse rate.

close to minimum seriousness (m = 1.8; SD = 2.2). As a complement, depression symptoms of degree of disability associated to substance consumption disorder were also evaluated with the HAM-D and DAV-SV scales, respectively. In both cases, a decrease in the mean scores of both scales was recorded, indicating an improvement of

TABLE 5. Evolution of the scores on the EuropASI, Craving, HAM-D and DAS-SV questionnaires

	Total patients	*Baseline*		*1st month*		*3rd month*		*6th month*	
	n	*m*	*SD*	*m*	*SD*	*m*	*SD*	*m*	*SD*
EuropASI									
Physician (range: 0-9)	50	2.4	2.4	—	—	—	—	2.0[2]	2.2
Employment/Supports (range: 0-9)	51	2.5	2.1	—	—	—	—	2.0[1]	2.0
Alcohol (range: 0-9)	51	2.1	2.4	—	—	—	—	1.5[2]	1.6
Drugs (range: 0-9)	50	7.0	1.3	—	—	—	—	4.5[1]	1.9
Legal (range: 0-9)	51	1.7	1.9	—	—	—	—	1.4[3]	1.7
Family/social (range: 0-9)	51	3.5	2.1	—	—	—	—	2.6[1]	1.8
Psychology (range: 0-9)	51	4.3	2.3	—	—	—	—	3.3[1]	2.1
Craving									
Anxiety	67	6.5	3.0	3.3[1]	2.3	2.3[1]	2.4	1.8[1]	2.2
Autonomic	58	1.6	1.4	0.4[1]	0.8	0.2[1]	0.6	0.1[1]	0.3
Sensitive	65	0.5	1.0	0.5	0.7	0.2[1]	0.4	0.2	0.4
Motor symptoms	59	2.4	2.3	1.1[1]	1.4	0.5[1]	0.7	0.3[1]	0.6
Cognitive examination	66	1.1	1.4	0.3[1]	0.7	0.2[1]	0.7	0.2[1]	0.4
Total score	58	12.3	6.0	5.8[1]	4.1	3.3[1]	3.4	2.5[1]	2.0
HAM-D									
Total score	45	11.7	7.6	—	—	5.6[1]	5.5	4.5[1]	5.3
DAS-SV									
Total global disability scale	20	23.1	17.7	—	—	—	—	10.9[1]	14.7
Personal care and survival	53	23.5	17.2	—	—	—	—	14.4[1]	18.2
Occupational functioning	53	32.1	22.0	—	—	—	—	20.1[1]	24.9
Functioning in the family	53	34.4	17.0	—	—	—	—	19.3[1]	21.7
Social behavior in general	53	33.6	17.6	—	—	—	—	20.1[1]	22.8

m: mean; SD: standard deviation ; [1-3]: statistically significant differences were found in the final total score in regards to initial one (Wilcoxon; [1] $p < 0.001$; [2] $p < 0.005$; [3] $p < 0.01$).

TABLE 6. Summary table of adverse reactions reported

Patients with adverse reactions	*n*[1]	*%*[2]
Psychiatric disorders	12	16.0
Somnolence	9	12.0
Depression	4	5.3
Anxiety	2	2.7
Anorexia	1	1.3
Gastrointestinal and peripheral system disorders	3	4.0
Unspecified gastrointestinal disorder	2	2.7
Dyspepsia	1	1.3
Vision disorder	1	1.3
Abnormal vision	1	1.3
General disorders of all the body	1	1.3
Fatigue	1	1.3
Total patients with adverse reactions	21	28.0
Total adverse reactions	37	—

[1] Number of patients with adverse reactions. Ten patients had more than one adverse reaction. [2] Percentage of patients with adverse reactions. Calculated on total number of evaluable patients (n=75).

the depressive symptoms and greater degree of function independence of the patient.

Tolerability

Table 6 shows the number and percentage of patients who presented each one of the adverse reactions reported in this study. In all, 21 patients were recorded with adverse reactions (28.0%) for the sample of 75 evaluable patients. Of these, a single case of severe intensity (1.3%) was recorded, corresponding to a patient who had anorexia. None of them were considered serious. The systems/organs most affected by the appearance of adverse reactions were those referring to psychiatric disorder (n=12; 16.0%) and central and peripheral nervous system disorders (n=9; 12.0%). Specifically, the most frequent adverse reactions were somnolence (n=9; 12.0%), paresthesia (n=5; 6.7%) and depression (n=4; 5.3%).

DISCUSSION

The results of the present observational study corroborate those obtained in previous studies that suggest that topiramate is an effective and well tolerated drug in the treatment of substance abuse or dependence disorders[17,18] and thus a therapeutic option to be considered, especially among the limited treatments presently available for this type of disorder.

Treatment with topiramate was shown to be effective in the middle term in substance addicted patients in terms of retention, relapse rates, consumption reduction (abuse drugs in urine), reduction of consumption craving and improvement in depression symptoms and disability degree, evaluated with the HAM-D and DAS-SV scales. These results coincide with those of previous studies. In this study, an 85.3% retention rate at 3 months was found. This is somewhat superior to that previously obtained in a previous clinical trial in alcoholic patients that was 70.5%[17,19,20] .

In addition, treatment with topiramate, also as in previous clinical trials, was shown to be better tolerated in this patient group. Specifically, in this study, somnolence (n=9; 12,0%) and paresthesias (n=5; 6.7%) were the most frequent adverse reactions, as in a placebo controlled clinical trial of topiramate in which the adverse reaction observed as most frequent was also paresthesia, but in a much greater proportion of patients (57.3%)17. These differences between previous clinical trials (CT) and observational studies (OS) should be interpreted considering that: *a)* adverse events, that may or may not have a casualty relation with the study drug are evaluated in clinical trials, while observational studies such as this one only record adverse reactions which, by definition, should have a causality relationship, and *b)* the spontaneous communication method of adverse reactions as that used generally leads to infrareporting, since only those adverse reactions having clinical or unexpected relevance are reported.

Finally, it must be mentioned that the naturalistic design type used, although it limits internal validity, has the advantage that it reflects effectiveness and treatment problems with topiramate in the real clinical practice. Emphasis should be placed on the usefulness of this naturalistic type design used when attempting to generalize the conclusions obtained in clinical trials and to exceed, to a certain degree, its limitations to be able to thus respond to the demands of the daily clinical practice[21,22] .

In conclusion, topiramate, under real health care conditions, showed a good clinical response, with significant decrease in the percentage of consumer patients and satisfactory tolerability profile, improving the results obtained in previous clinical trials

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