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Topiramate in the treatment of alcohol dependence: a meta-analysis

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Introduction. Several controlled clinical trials have studied the efficacy of topiramate in the treatment of alcoholism. In this paper, we have performed a meta-analysis of those trials in which topiramate was compared with placebo and then we reviewed its efficacy in trials in which it was compared with other drugs.

Method. A quantitative synthesis of data was performed using inverse variance weighting in a random effects model.

Results. Based on three placebo-controlled trials, topiramate is more efficacious than placebo in reducing the percentage of heavy drinking days (23.2%, 95% confidence interval [CI]: 15.7 to 34.4), increasing the number of days of abstinence (mean difference: 2.9 days, 95% CI: 2.5 to 3.3), and lowering the logarithm of γ-GT levels (mean difference: 0.075 95% CI: 0.048 to 0.118). Two trials suggested that topiramate is also more efficacious than naltrexone, and one open-label study reported better results for disulfiram than for topiramate.

Conclusion. Topiramate can be used in alcohol dependence. Adverse effects such as paresthesia or insomnia should be taken into account when prescribing topiramate. Its optimal dosage requires further research.

Key words:
Alcohol dependence. Topiramate. Meta-analysis. Naltrexone. Disulfiram

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Topiramato en el tratamiento de la dependencia etílica: un metaanálisis

Introducción. Algunos ensayos clínicos controlados han estudiado la eficacia del topiramato para el tratamiento del alcoholismo. En este artículo, primero realizamos un metaanálisis de los ensayos donde el topiramato era comparado con el placebo, y después revisamos la eficacia en los ensayos donde era comparado con otros fármacos.

Método. Una síntesis cuantitativa de los datos se llevó a cabo ponderando por el inverso de la varianza en un modelo de efectos aleatorios.

Resultados. En base a tres ensayos clínicos controlados, el topiramato es más eficaz que el placebo en: reducción del porcentaje de los días de consumo elevado (23,2%, intervalo de confianza [IC] del 95%: 15,7 a 34,4), incremento del número de días de abstinencia (diferencia media: 2,9 días, IC del 95%: 2,5 a 3,3) y descenso del logaritmo de los niveles de γ-GT (diferencia media: 0,075, IC del 95%: 0,048 a 0,118). Dos ensayos sugirieron que el topiramato es también más eficaz que la naltrexona y un estudio abierto refirió mejores resultados para el disulfirán que para el topiramato.

Conclusiones. el topiramato puede ser utilizado para el tratamiento en la dependencia etílica; los efectos adversos tales como las parestesias o el insomnio deben ser tenidos en cuenta cuando se prescribe topiramato. La dosis óptima precisa investigación adicional.

Palabras clave:
Dependencia alcohólica. Topiramato. Metaanálisis. Naltrexona. Disulfirán.

INTRODUCTION

Topiramate is an anticonvulsant known both for its use in the treatment of epilepsy and in the prevention of headaches. Recently, its utility is being tested in other conditions such as bulimia nervosa, binging disorders,[1] smoking addiction,[2] and alcohol dependence.[3]

The neuropharmacological actions of topiramate include facilitation of the neurotransmitter gamma-aminobutyric (GABA) inhibitory action in its non-benzodiazepine receptor and the reduction of the glutamate excitatory action in the alpha-amino-3 hydroxy-5 metylisoxazole-4 propionic (AMPA) receptor and the

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kainate receptors.[4,5] In this way, it seems to reduce the mesolimbic cortical activity of dopamine. This would be the principal mechanism to decrease alcohol consumption reward effects.[6,7]

Since 2003, several controlled clinical trials have studied the value of topiramate in the treatment of alcoholism. In this article, we have reviewed these trials and measured the efficacy of topiramate in the clinical trials with placebo.

METHODS

Search strategy

We made a search in the MEDLINE/PubMed database for controlled clinical trials on the efficacy of topiramate in the treatment of alcohol dependence. The last search was done on March 30, 2009. The abstracts were reviewed to identify the controlled clinical trials on the subjects. The references of these articles were also studied to identify studies not located in the original search.

ARTICLE SELECTION

The studies were included if they were placebo-controlled and had focused on the evaluation of topiramate with single drug therapy in the treatment of alcohol dependence. The studies controlled with other drugs were included in the systematic review, but not in the quantification. Studies aimed at patients with dual pathology and studies that re-analyzed previous data were excluded.

Data extraction

Data on the number of patients in the topiramate group patients and on the control groups, follow-up time, topiramate dose, days of high alcohol intake, changes in plasma levels of γ-GT, score on the Obsessive Compulsive Drinking Scale [OCDS]), number of drinks per day and number of abstinence days, and the principal adverse effects occurring during the trials were extracted.

Quantitative analysis

Effect measurements in the meta-analysis were: 1) percentage of days of elevated intake at the end of the follow-up in the placebo group minus percentage of days of elevated intake at the end of the follow-up in the topiramate group, 2) number of abstinence days in the topiramate group minus number of abstinence days in the placebo group, 3) variations in the levels of γ-GT. The changes in the number of drinks per day were only collected in two studies which is why this data was not analyzed.

The results of the trials selected were combined and weighted by the inverse of the variance in a random effects model (DerSimonian-Laird model). All of the statistical analyses were made with the Stata 10/SE program (Stata Corporation, College, Station, Tx, USA).

RESULTS

Six articles defined as controlled clinical trials were located.[3,8-12] One was excluded because it was a laboratory study in which the patients were voluntarily exposed to alcohol while taking topiramate.[12] Another study was an open-label study comparing topiramate with disulfiran[10] and one article was an open-label study compared with naltrexone.[11] One of the works compared topiramate with naltrexone and placebo.[9] Finally, two studies compared topiramate with placebo.[3,8] Data were obtained from the studies that compared topiramate with placebo or other drugs. However, the quantitative analysis was only performed with the three placebo-controlled studies (two made by Johnson at al.,[3,8] and another by Baltieri at al.[9] Excluding the comparison made with naltrexone in the latter, these studies were double blind. The principal characteristics of these studies are shown in table 1. Considering the six articles together, topiramate was administered to 418 patients, disulfiran to 50 patients, naltrexone to 100, and placebo to 322. The topiramate dose ranged from 150-300 mg/day, and its follow-up ranged from 12 to 38 weeks.

Table 2 collects the results of the review in these six studies.

Effect of topiramate on the days of elevated intake

In the group with topiramate, the days of elevated intake decreased 23.2% more than in the placebo group (95% confidence interval [CI]: 15.7-34.4; $p < 0.001$) and there was no evidence of heterogeneity ($Q = 0.75$, 2 degrees of freedom $p = 0.69$). The results of one of the studies[9] also suggested that naltrexone had intermediate efficacy between topiramate and the placebo in regards to day of elevated intake (table 2).

Effect of topiramate in the abstinence days

Patients with topiramate had 2.9 more days of abstinence than the placebo group patients (95% CI: 2.5-3.3; $p < 0.001$), with no evidence of heterogeneity ($Q = 3.45$, 2 degrees of freedom, $p = 0.18$).

Table 1 Principal characteristics of the controlled clinical trials used in this meta-analysis.

First author and year of publication	No. of patients under treatment with topiramate	No. of patients under treatment in the control group	Alcohol consumption: drinks necessary to enter into the study	Weeks of follow-up	Topiramate/ dose in control group
Johnson, 2003 [8]	78	80 (placebo)	21 standard drinks/week (women) 35 standard drinks / week (men)	12	up to 300 mg/day
Johnson, 2007 [3]	183	188 (placebo)	28 standard drinks/week (women) 35 standard drinks/week (men)	14	up to 300 mg/day
De Sousa, 2008 [10]	50	50 (disulfiram)	NA	38	150 mg topiramate/ day / 250 mg disulfiram/day
Baltieri, 2008 [9]	52	49 (naltrexone), 54 (placebo)	NA	12	300 mg topiramate/day / 50 mg naltrexone /day
Florez, 2008 [11]	51	51 (naltrexone)	210 grams / week (men) 140 grams / week (women)	26	hasta 300 mg topiramato/día / 50 mg naltrexona/ día

NA: Not Available

Table 2 Principal measurements included in this meta-analysis

First authors and year of publicación	Decrease in days of elevated consumption in percentage	Changes in the γ-GT log (topiramate / / control)	Obsessive-Compulsive Disorders	Drinks/day	Days of abstinence
Johnson, 2003 [8]	-27.61 (-42.20 to -13.02)	-0.07 (-0.11 to -0.02)	Obsessions with drink: -1.98 (-3.28 to -0.69) Automatism of consumption: -2.61 (-4.14 to - 1.08) Interference with alcoholic drinking -1.73 (-2.64 to -0.82)	-2.88 (-4.50 to -1.27)	26.21 (12.43 at .98)
Johnson, 2007 [3]	-16.19 (-21.60 to -1.79)	-0.05 (-0.07 to -0.03)	NA	-1.77 (-1.19 to -2.36)	13.39 (18.65 at 8.14)
De Sousa, 2008 [10]	ND	ND	NA	NA	-33 (-62 at -3)
Baltieri, 2008 [9]	-11.3 (-20.1 to -2.5)* naltrexone; -21.2 (-32.3 to -10.1)**	-0.11 (-0.13 to -0.09)**	0.0 (9.8) naltrexone; 0.5(+-9) placebo	NA	10.2 (5.4 at 19.0) (naltrexone); 18.2 (9.5 at 26.9)
Florez, 2008 [11]	ND	ND	-2.29 (+-5.6)	NA	NA

*The text only provides data on elevated consumption/week; the first author provided information on the elevated/day consumption. The confidence intervals are calculated with these data.
**Calculated based on the data published.

One trial[10] suggested that disulfiram was more effective in regards to achieving days of abstinence than topiramate, while the efficacy of naltrexone could be between that of the placebo and topiramate.[9]

Table 3 Principal side effects of the controlled clinical trials included in this meta-analysis

First authors and year of publication	Paresthesias	Headache	Anorexia	Insomnia	Concentration problems
Johnson, 2003 [8]	57.3 / 18.7	NA	NA	NA	18.7 / 5.3
Johnson, 2007 [3]	50.8 / 10.6	24.0 / 31.9	19.7 / 6.9	19.1 / 16.0	14.8 / 3.2
De Sousa, 2008 [10]	ND	NA	NA	24 / 22	NA
Baltieri, 2008 [9]	11.5 / 2.0 / 3.7	NA	7.7 / 0.0 / 3.7	9.6 / 10.2 / 5.6	NA
Florez, 2008 [11]	ND	NA	NA	NA	NA

NA: Not available

Effect of topiramate in the γ- GT levels

Two of the trials[3,8] facilitated the γ-*GT* levels on the logarithmic scale, while the other[9] did so on the arithmetic scale. We have reconverted the arithmetic scale into logarithmic, using the delta method to make the meta-analysis.

The logarithmic levels of γ-GT were lower in the topiramate group (mean difference: 0.075; 95% CI: 0.048-0.118; $p < 0.001$). However, there was evidence of heterogeneity ($Q = 14.7$, 2 degrees of freedom, $p = 0.001$). The small number of clinical trials available prevented subsequent research on the origin of this heterogeneity.

Side effects

Table 3 collects the principal side effects detected in the clinical trials used in this meta-analysis. Paresthesia was found more frequently with topiramate than with placebo. However, mention should be made regarding the significant heterogeneity between the Baltieri at al. trial (11.5% for the topiramate group and 3.7% for the placebo group)[9] and the two performed by Johnson et al., in which the paresthesias were reported in one out of every two patients with topiramate while they were found in 1 out of 9 to 1 out of 6 patients with placebo.[3,8]

Other adverse effects detected with greater frequency in the topiramate groups were anorexia and concentration problems. However, these and other side effects were collected irregularly in the trials analyzed.

DISCUSSION

Topiramate is more effective than placebo in the objective measurements of consumption, and in the γ-GT levels and in the self-reported measurements of usage and percentage of high consumption days and abstinence days, when the results of the three randomized and placebo-controls clinical trials were combined.

Although two clinical trials comparing topiramate with con naltrexone have been published, neither collected information on the differences regarding the γ-GT levels. Naltrexone, however, does not seem to favor improvement in the self-reporting of consumption, which is intermediate between those obtained with topiramate and with placebo. These data were collected in only one study.[9]

On the other hand, disulfiran has been shown to be more effective than topiramate in one study. In the same trial, the topiramate doses was 150 mg/day,[10] which is half that used in the other trials reviewed in this article. In any event, the value of disulfiran versus topiramate needs additional research at different doses.

The optimum dose of topiramate for the treatment of alcohol dependence has not been established (four of the five trials, including the three placebo-controlled ones, used 300 mg/day). As the side effects of topiramate increase with dose, the study on its efficacy at different doses is necessary.

The principal limitations of this study are that only three controlled clinical trials up to date are available. Furthermore, in some trials, the patient inclusion criteria were not defined, others excluded patients with dual pathology or with other drug treatments. This leads us to question the generalization of the results. On the other hand, the alcohol consumption indicators were not standardized (e.g.: units of consumption per day/unit, of consumption per week when reporting on elevated consumption, or use of arithmetic or logarithmic scales in the measurements of the γ-GT levels). Thus, the original data had to be transformed, which may have had a secondary effect on the statistical distribution of the data and consequently on their significance. Data were also not provided on efficacy in different types of alcoholism. For example, some authors have suggested that low treatment compliance and greater severity of the dis-

ease are characteristic of those consuming distilled versus fermented drinks,[13] raising the need for their more intensive treatments. Furthermore, as the utility of topiramate in other impulse control disorders (smoking, binging disorder, bulimia) is known, it has become clear that the efficacy of topiramate in these dual pathologies should be evaluated.

In conclusion, topiramate reduces the days of elevated intake, increases the days of abstinence and improves γ-GT levels in patients with alcohol dependence. Additional research is needed to establish the optimum doses and its utility in different alcoholism subtypes.

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