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Efficacy of naltrexone in the treatment of alcohol dependence disorder in women

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Alcoholism is a major public health problem. Although its prevalence is higher in men, the clinical and social repercussions of alcoholism in women are also of great concern, as they have differential characteristics in different vulnerability, and thus therapeutic implications. In recent years, we have seen an increase of the percentages of women with problems related to alcohol consumption in Spain. Several pharmacological treatments as the antagonist of the opioid receptors naltrexone have demonstrated efficacy in the treatment of dehabituation of alcoholism in males, however, there are no studies in the female population. This report is the first randomized study about the efficacy of naltrexone in the treatment of dehabituation in women with alcohol dependence disorder.

Methods. In a 12 week, single-blind, randomized trial, we studied 100 women with alcohol dependence disorder (DSM-IV), evaluating the efficacy of adding naltrexone as adjunctive treatment to the dehabituation treatment.

Results. The naltrexone group showed a lower rate of alcohol relapse during the follow-up period (76% vs. 46%; $\chi^2 = 8.239$; p = 0.004), and significantly lower dropout rates (16% vs. 38%; $\chi^2 = 5.074$; p = 0.024). We also found a lower number of days of intoxication (2.88 vs. 14.64; t = 2.732; p = 0.011).

Conclusions. Naltrexone shows efficacy as adjunctive treatment to maintain abstinence in women with alcohol dependence disorder. Further studies are needed to confirm the efficacy of this treatment and to find specific predictors of good outcome in women.

Key words:
Alcoholism in women. Naltrexone. Alcoholic dehabituation. Adjunctive treatment.

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Eficacia de naltrexona en el tratamiento de mujeres con trastorno por dependencia del alcohol

El alcoholismo constituye un importante problema de salud pública. Aunque su prevalencia es mayor en varones, son también de extraordinaria relevancia las repercusiones clínicas y sociales del alcoholismo femenino por poseer características diferenciales en la distinta vulnerabilidad y consiguientemente implicaciones terapéuticas. En los últimos años se está constatando en España un aumento en la proporción de mujeres con trastornos asociados al consumo de alcohol. Diversos tratamientos farmacológicos, como el realizado con el antagonista de los receptores opioides naltrexona, han demostrado eficacia en el tratamiento de deshabituación del alcoholismo en varones, pero no existen estudios en población femenina. Este trabajo es el primer estudio aleatorizado sobre la eficacia de naltrexona para el tratamiento de deshabituación en mujeres con trastorno por dependencia del alcohol.

Métodos. Estudio aleatorizado en 100 mujeres con trastorno por dependencia del alcohol (DSM-IV), simple ciego a 12 semanas, en el cual se evalúa la eficacia de añadir naltrexona al tratamiento de deshabituación.

Resultados. En el grupo que recibe tratamiento coadyuvante con naltrexona es mayor la tasa de pacientes que no presentan recaídas durante el período de seguimiento (76 frente a 46%; $\chi^2 = 8.239$; p = 0,004) y menor la tasa de abandonos (16 frente a 38%; $\chi^2 = 5.074$; p = 0,024). Es también menor el número de días de embriaguez (2,88 frente a 14,64; t = 2.732; p = 0,011).

Conclusiones. La naltrexona resulta eficaz como tratamiento coadyuvante para mantener la abstinencia en mujeres con trastorno por dependencia del alcohol. Son necesarios nuevos estudios para confirmar la eficacia de este y otros tratamientos y encontrar potenciales predictores de respuesta específicos en población femenina.

Palabras clave:
Alcoholismo en mujeres. Naltrexona. Deshabituación alcohólica. Tratamiento coadyuvante.

INTRODUCTION

Alcoholism constitutes an important public health problem with individual and psychosocial biological repercussion[1]. In the past, the pharmacological treatments of alcoholism were principally confined to the detoxification, having the antidipsotropic or aversive agents as a therapeutic option for dehabituation[2]. During the last fifteen years, there has been an important advance in the knowledge of the neurobiological bases underlying alcohol dependence. This knowledge has made it possible for new pharmacological strategies to arise for the treatment of alcohol dependence. Among these new alternatives, those known as «anticraving» drugs, mainly naltrexone and acamprosate, stand out[1,3-12]. The main action mechanism of these drugs is focused on the cerebral reward system and consists in blocking the biological mechanisms that underlie the positive or negative reinforcement that they generate and maintain anxiety for consumption[2].

Naltrexone is an opioid receptor antagonist, with proven efficacy for the reduction of alcohol intake[3,13-15], of the euphoria associated to it[16] and in the tendency to relapse[17-21] in patients with dependence or alcohol abuse diagnoses. In spite of some debatable findings that initially questioned its utility[22], the efficacy of naltrexone has been demonstrated in different paradigms: double blind studies versus placebo at 12 weeks in combination with different psychotherapy forms and even in single blind studies versus acamprosate[3,15-23]. However, no studies have been performed on its efficacy in women. This is a usual circumstance in the study of efficacy of different therapeutic measures in this area, since women being treated are a minority in the alcoholism attention mechanisms. Even though logistic and organization considerations advise performing certain studies on alcoholism in men, the importance of female alcoholism should not be overlooked[24-27]. In our setting, between 50% and 80% of women drink alcohol and alcohol consumption in 5.9% of women is above the risk levels[28,29]. In recent years, there has been an important increase of alcohol consumption in women, with a progressive tendency to equal the man-woman ratio. Two decades ago, this ratio was 10/1, it presently being estimated at 3/1 (according to regions and countries). In the 1997 home survey, it was seen for the first time in our country, with an emerging phenomenon character, that young women between 15 and 18 years of age had greater alcohol consumptions in recent years than men of their same age group (73.6% versus 72.5%)[30,31].

The woman has genetic factors that condition greater biometabolic sensitivity to alcohol (greater absorption rate; less amount of water; greater fatty tissue percentage; less activity of gastric alcohol-dehydrogenase enzyme and decrease of «first pass» metabolism)[32-35]. There are also sociocultural factors that would explain the increase in problems related with alcohol in women. Included among them would be the approach of the woman to traditionally masculine behavior patterns and the release of taboos in relationship with alcohol consumption. Finally, the most frequently involved psychological factors in the appearance of problematic consumption of alcohol or alcohol dependence conditions in the woman are conflicts in sexual role, low self-esteem and adult life stress and depression.

Given that their proportion in the samples is generally in the minority, and that, in general, their number if insufficient to study them as an independent group, it is frequently decided to exclude them from the studies[2,20,36,37]. Thus, together with the lower frequency of arrival to the treatment units, there are other factors that explain the limited research on therapeutic efficacy in this population group. One of them is that the reasons for exclusion in different research paradigms may be more common in the female gender (possibility of pregnancy, frequent comorbidity with depressive condition)[38]. As a whole, the aspects mentioned would make it necessary to prolong the studies for long periods to gather representative samples. However, the same considerations suggesting that they should not be included in the general samples together with the men determine that it is not adequate to extrapolate the results obtained in them to the women. In this way, there is the conviction that specific studies would be necessary on the problems related with alcohol and the possible therapeutic approaches in the female population.

Our objective in the present work is to study the improvement associated to the implementation of naltrexone in the treatment of dehabituation of women with alcohol dependence disorder.

METHODOLOGY

Design

This is a randomized, single blind, 12 week long study in which the efficacy of adding naltrexone or not to the usual treatment used for alcohol dehabituation and relapse prevention is compared. The treatment conditions were as similar as possible to the usual clinical practice.

The participants were women with alcohol dependence disorder (DSM-IV) who had undergone deintoxication in the Addictive Behavior Unit of the Doce de Octubre Hospital of Madrid. Inclusion criteria were the following: *a)* female gender, y *b)* stable family environment that would support treatment compliance and provide information on the course. The exclusion criteria were the following: *a)* presence of another substance use disorder, except nicotine; *b)* presence of another psychiatric disorder that would comply with DSM-III-R criteria; *c)* presence of medical disorders that would contraindicate the treatment; *d)* presence of hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase values greater than three times the normal ones); *e)* previous treatment with naltrexone or acamprosate, y *f)* pregnancy or non-use of effective contraceptive measures during the study.

After completing hospital or out-patient detoxification, the patients were informed on the study's nature and objectives. They were informed of the efficacy and safety data of naltrexone in the treatment of alcoholic males and of the absence of data in women. They were also informed on the efficacy and safety of the usual treatments, both psychopharmacological as well as psychotherapeutical, which were available to them. They were told that the possibility that naltrexone would be added or not to their treatment would be determined randomly and that they would know if they were taking this substance. They were informed that the existence of relapses or non-compliance of the drug would not lead to their being excluded from the study, but that interruption of contact with the therapists for a period greater than 15 days (two consecutive visits) would cause them to be excluded. It was indicated that they could leave the study at any time they wanted to.

The present study was approved by the Bioethics Committee of the Hospital Doce de Octubre.

Patient evaluation measures

After signing the informed consent, the participants were evaluated with the following instruments:

- Structured clinical interview for DSM -III-R (SCID)[31].
- Addiction Severity Index (ASI)[32].
- Severity of Alcohol Dependence Scale (SADS)[33].
- A weekly calendar in which the patients recorded alcohol consumed.

Measurement of the following serum parameters in the baseline evaluation: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), bilirubin, carbohydrate deficient transferrin (CDT).

After randomizing the patients using a random numbers table, a daily tablet of naltrexone, 50 mg, was added. The patients visited their psychiatrist every 7 days the first month and then every 15 days. In case of relapse, the visit frequency was increased to shorten the relapse and offer the necessary support. In each visit, the alcohol consumption diary was reviewed and additional information gathered from the family.

Both groups were offered supportive group therapy during the entire period. Given that the patient enrolment rhythm was too slow to form closed groups in which all the patients entered at the same time, they were included in «open» groups of therapy less structured than the classical relapse prevention programs. However, the characteristic aspects of these programs were approached (dealing with risk situations and negative emotional states, assertiveness, skills training, etc.).

All the treatment was explicitly aimed at achieving total abstinence. Patients also received symptomatic drug treatment of the anxious and depression symptoms, etc., if they appeared. Under this supposition, sertraline was used in a dose of 100-200 mg/d. All the patients were told of the recommendation to use antidipsotropic agents, if alcohol consumption occurred during the treatment.

The «blind» investigators

The patient's evolution data were collected at 4, 8 and 12 weeks by investigators who were blind to treatment taken by the patients. They used the following data sources: *a)* the patient herself, who was advised that she should not reveal the treatment she was using; *b)* the psychiatrist in charge of her treatment, also informed that he should not reveal the treatment used; *c)* the family, since it was expected that the relatives were less biased regarding the evaluation of the results based on the treatment used, and *d)* the consumption records and laboratory results.

Course data

The course endpoints studied were: accumulated days of abstinence, accumulated consumption days, accumulated days of intoxication or consumption in the pattern prior to treatment initiation, treatment drop-out, maintained abstinence of at least one month prior to the end of the study and general positive or negative course. A positive course implied continuity in the treatment and alcohol consumption less than three consecutive days and less than three units per occasion.

Statistical analysis

The chi squared test with Yates continuity correction and t-tests for comparison of the course measurements between both groups were used.

RESULTS

Table 1 shows the characteristics of the patients of both treatment groups. There were no significant differences for any of them.

The difference in the course between the naltrexone treated group and non-treated group can be seen in table 2. Drop-out rate was significantly less among women treated with naltrexone. In this group, the percentage of women who achieved at least 1 month of continued abstinence at the end of 3 months and those who had followed a good evolution, as they had remained abstinent all the period or had only consumed sporadically and small quantities, was greater. Although there were no differences in the number of consumption days (table 3), there was a significant difference in the number of intoxication days. In regards to the

Table 1 Characteristics of the treatment groups

	Naltrexone (n = 50)	No naltrexone (n = 50)
Age at treatment onset	37.37 (DS: 9.67)	36.28 (DS: 10.62)
Age of first contact with alcohol	15.91 (DS: 6.17)	16.13 (DS: 6.23)
Age when usual consumption begins	23.58 (DS: 10.48)	22.93 (DS: 11.44)
Age when abuse criteria is fulfilled	29.46 (DS: 12.32)	29.12 (DS: 14.01)
Age when depencence criteria is fulfilled	35.68 (DS: 11.02)	34.27 (DS: 13.32)
Daily consumption	81.63 %	77.1 %
Single consumption	87.5 %	84.1 %
	51.6 %	52.9 %
Behavior problems	30.6 %	33.89 %
Psychiatric family background	33.7 %	31.9 %
Alcoholic family background	64.8 %	62.4 %

fact that the percentage of women who had consumed alcohol seemed similar, it must be considered that there were more drop-outs among those who had not received naltrexone, so that there could be more consumption among those who dropped-out.

DISCUSSION

In our study, naltrexone clearly improves the course of women under alcohol dehabituation treatment, decreasing the drop-out rate and consumption severity, and, on the other hand, increasing the likelihood that they maintain continued abstinence. As has been reported in men, naltrexone seems to improve the prognosis of women who consume alcohol at some time during the treatment, probably stopping the reinforcement mechanisms and loss of control. Our data thus support the use of naltrexone also in the female population.

Table 2 Clinical course according to administration or not of naltrexone

	Naltrexone (n = 50)	No naltrexone (n = 50)	
Drop-out	19	8	$\chi^2 = 5.074$; p = 0.024
Abstinence at period end	21	38	$\chi^2 = 10.583$; p = 0.001
Patients with good course	23	38	$\chi^2 = 8.239$; p = 0.004
Concomitant use of SSRI	25	23	$\chi^2 = 0.04$; p = 0.841
Concomitant use of antidipsotropic agents	16	11	$\chi^2 = 0.812$; p = 0.368

Table 3 Clinical course of patient who have alcohol consumption

	No naltrexone	Naltrexone	
Patients who report consumption	11	17	$\chi^2 = 1.24$; p = 0.265
Number of consumption days in which they consume	30.18 (DS: 27.71) n = 11	21.58 (DS:26.87) n = 17	t = 0.817; p = 0.422
Number of intoxication days in which they consume	14.64 (DS: 16.72) n = 11	2.88 (DS: 5.12) n = 17	t = 2.732; p = 0.011

Naltrexone has shown a variable efficacy in the studies performed in the male population and the identification of predictive variables of response to this treatment has been a constant concern. In 12 month double blind studies in male patients, good course rates have been obtained (abstinence or consumption without relapse criteria between 62.2 % and 77%)[1,34], although the results have varied significantly based on treatment compliance. In a single blind study during 1 year, compared with acamprosate, also in males, the rate of patients who had good course was 41 %, significantly greater than the 17 % of those who received acamprosate[20]. In our population of women with alcohol dependence disorder, 76% of those treated with naltrexone maintained abstinence or had had small consumptions without relapse criteria at 3 months, so that these values are similar to those found in men. As this is a single blind study, there may be clear biases, so that the same conclusions cannot be drawn as in a double blind trial versus placebo. In regards to the follow-up form proposed in the methodology, it is logical that subjects with alcohol consumptions had worse results, so that the greater frequency of follow-up secondary to consumption would not favor this group's results. On the other hand, the analysis of the treatment branches with or without naltrexone does not show differences in the application of sertraline or antidipsotropic agent. This suggests that the latter factors also did not affect the results. In spite of these limitations, some dictated by the naturalistic design of the study, we consider that this study supplies reasonable evidence, since the results are similar to that found in alcoholic men, in absence of data in the female population. Furthermore, this is a study performed under similar

conditions to the real clinical practice, with weaker inclusion criteria that permit treatment observation in a wider range of circumstances.

Given the heterogeneity of alcoholism and both biological and psychosocial factors that influence its genesis, maintenance and tendency to relapse, it has been proposed that certain patient groups could especially benefit from treatment with opioid antagonists38. However, up to now, valid predictors have not been identified. These characteristics may be very different in the women, given that the pharmacokinetics and pharmacodynamic factors of alcohol, and also the psychological conditioners and consumption patterns are clearly different from the male ones.

Thus, the study of potential response predictors in women should be performed independently. The difficulties to achieve large samples in short time periods advise the performance of multicenter studies, combining the efforts of several devices. However, we consider that the importance of performing more studies on alcoholism in women will more than justify these efforts.

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