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NALTREXONE VERSUS ACAMPROSATE: ONE YEAR FOLLOW-UP OF ALCOHOL DEPENDENCE TREATMENT

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Abstract — Naltrexone and acamprosate reduce relapse in alcohol dependence. They have not yet been compared in a published trial. The aim of this study was to compare the efficacy of these compounds in conditions similar to those in routine clinical practice. Random allocation to a year of treatment with naltrexone (50 mg/day) or acamprosate (1665–1998 mg/day) was made in 157 recently detoxified alcohol-dependent men with moderate dependence (evaluated using the Addictions Severity Index and Severity of Alcohol Dependence Scale). All were patients whom a member of the family would accompany regularly to appointments. Alcohol consumption, craving and adverse events were recorded weekly for the first 3 months, and then bi-weekly, by the treating psychiatrist who was not blinded. At 3-monthly intervals, investigators who were blinded to the treatment documented patients' alcohol consumption based on patients' accounts, information given by the psychiatrists when necessary, and reports from patients' families. Serum gamma-glutamyltransferase (GGT) was also measured. Efforts were made to sustain the blindness of the investigators. The same investigator did not assess the same patient twice. The integrity of the blindness was not checked. There was no difference between treatments in mean time to first drink (naltrexone 44 days, acamprosate 39 days) but the time to first relapse (five or more drinks in a day) was 63 days (naltrexone) versus 42 days (acamprosate) ($P = 0.02$). At the end of 1 year, 41% receiving naltrexone and 17% receiving acamprosate had not relapsed ($P = 0.0009$). The cumulative number of days of abstinence was significantly greater, and the number of drinks consumed at one time and severity of craving were significantly less, in the naltrexone group compared to the acamprosate group, as was the percentage of heavy drinking days ($P = 0.038$). More patients in the acamprosate than the naltrexone group were commenced on disulfiram during the study. Naltrexone patients attended significantly more group therapy sessions, though this could not explain their better outcome. There were non-significant trends for the naltrexone group to comply better with medication, to stay in the study longer, and to show greater improvement over baseline in serum GGT.

INTRODUCTION

Alcoholism is an important and difficult problem from several public health perspectives. For a long time, pharmacological treatments have been limited mainly to the detoxification period exclusively, and to the use of aversive drugs over the rehabilitation period (incorporating the time and process during which 'normal' levels of intake are attained and maintained). In the last decade, naltrexone and acamprosate have been proposed for use in the treatment of alcohol dependence.

Naltrexone is an opioid receptor antagonist, with a verified efficacy for the reduction of euphoria, alcohol intake and relapse risk by alcohol-dependent or -misusing individuals (Volpicelli *et al.*, 1992, 1995*a*,*b*, 1997; O'Malley *et al.*, 1992; Anton *et al.*, 1999; Chick *et al.*, 2000*b*). These actions seem to be mediated by the property to block opiate receptors (Ulm *et al.*, 1995), not least in forebrain areas. This antagonism appears to inhibit the actions of endogenous opioids, released because of alcohol intake, upon the mesolimbic pathway, which would otherwise produce a rise in dopamine (DA) in the accumbens nuclei (Benjamin *et al.*, 1993; Valenzuela and Harris, 1997; Catafau *et al.*, 1999). Naltrexone efficacy has been demonstrated in short-term double-blind studies (6–12 weeks) (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992, 1995*a*, 1997; Anton *et al.*, 1999; Chick *et al.*, 2000*b*). However, from the available evidence, naltrexone efficacy has not yet been verified in long-term studies.

Long-term efficacy studies (6–12 months) have been carried out, however, on acamprosate, calcium acetyl homotaurinate, a drug marketed in Europe. This has been shown to increase the time to relapse, to reduce the number of days of consumption and to augment the abstinence period (Pelc *et al.*, 1992; Ladewig *et al.*, 1993; Paille *et al.*, 1995; Sass *et al.*, 1996; Geerlings *et al.*, 1997; Poldrugo, 1997; Besson *et al.*, 1998; Tempesta *et al.*, 2000). However, not all the studies confirm its efficacy compared to placebo (Chick *et al.*, 2000*a*). This compound modulates the GABA-ergic transmission and decreases postsynaptic potentials in the neocortex, possibly via its action on NMDA (*N*-methyl-D-aspartate) receptors. Hypotheses have been drawn up concerning its actions on calcium channels as well as on the NMDA receptors reducing conditioned alcohol-withdrawal craving (Littleton, 1995).

The aim of this study was to demonstrate the efficacy and treatment compliance of naltrexone compared to acamprosate in typical treatment conditions for these patients. An open randomized trial has been chosen for two reasons: (1) this is the experimental situation most similar to daily clinical practice; (2) if a double-blind trial had been carried out, both drugs would have to be administered in three doses per day (because of the pharmacokinetics of acamprosate and manufacturer's recommendations). However, taking into account the resistance to treatment compliance in these patients, especially in the medium and long-term, a double-blind trial in which the medication was administered three times a day would place naltrexone at a disadvantage since this drug is usually given in a single daily dose.

PATIENTS AND METHODS

Design

This was a randomized 12-month single-blind trial of naltrexone versus acamprosate. The treatment conditions were as similar as possible to daily clinical practice.

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The participants were alcohol-dependent males who had requested detoxification in the Addictive Behaviour Unit of 'Doce de Octubre Hospital'. Inclusion criteria were as follows: (1) male gender aged between 18 and 65 years; (2) meeting DSM-III-R criteria for alcohol-dependence (American Psychiatric Association, 1987); (3) having a stable family environment so that the family can help with treatment compliance and provide information during follow-up visits. Exclusion criteria were: (1) presence of another substance use disorder (with the exception of nicotine); (2) presence of another psychiatric disorder diagnosed by SCID for DSM-III-R (SCID); (3) a medical condition which could hinder treatment compliance; (4) impaired liver function [an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value more than three times normal values]; (5) previous treatment with naltrexone or acamprosate.

After completing detoxification, in the hospital or as an outpatient, the subjects were informed about the study objectives. They were informed about the two pharmacological treatments, naltrexone or acamprosate, elective treatments at the time of the study for the treatment of alcohol-dependence, but were told that the drug they would receive would be chosen at random. They would know which drug they would receive. They were told that relapse, or not taking the prescribed treatment punctually, would not lead to their being asked to leave the trial. However, they would be taken out of the trial if they did not keep in touch with the investigators for more than 15 days (i.e. two consecutive visits). They were also told that they could choose to leave the study at any time.

Procedure and assessments

After signing the informed consent, participants were assessed with the following instruments: a structured clinical interview for DSM-III-R (SCID) (Spitzer *et al.*, 1992); the Addiction Severity Index (ASI) (McLellan *et al.*, 1980), Severity of Alcohol Dependence Scale (SADS) (Rubio *et al.*, 1998); three analogue scales to measure craving (frequency, duration and intensity) (Anton *et al.*, 1999); and a weekly calendar in which participants recorded all alcohol consumed, so that the 'time-line follow-back' method could be used to document the pattern of consumption during follow-up (Miller, 1996). The following baseline biological parameters were determined: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), bilirubin, and carbohydrate-deficient transferrin (CDT).

After randomizing the patients (using a random numbers table), patients received either one tablet (50 mg) per day of naltrexone, or six tablets (or five if of lower body weight) of acamprosate (i.e. 1665–1998 mg/day) divided into three doses following the manufacturer's recommendation. Patients visited their psychiatrists every 7 days (± 3 days) over the first 3 months, after which they visited every 15 days, till the end of the study. In the event of relapse, the frequency of visits was increased in order to help curtail the relapse and to offer the patient assistance if required. At each visit, entries in the diary of alcohol consumption were checked, together with craving, and whether the patient continued the treatment. Consumption and compliance data were compared with information given by the family.

Both groups of patients were offered supportive group therapy, once weekly over the entire study period. The groups were 'open' groups. Therapy was less structured than in classical relapse prevention programmes. Basic relapse prevention was tackled (dealing with situations of risk, craving and negative emotional states). Abstinence was positively reinforced. Patients also received symptom-directed pharmacological treatment for complaints, such as anxiety, depression, insomnia, etc., when these symptoms presented during follow-up. If anxiety or depression emerged, sertraline could be prescribed (100–200 mg/day), and for insomnia patients were given hydroxyzine, an H_1 receptor antagonist of the piperazine family used as a hypnotic (50–100 mg/night). In cases of relapses which were difficult to control pharmacologically or psychotherapeutically, disulfiram was added to the treatment until the relapse was fully over (2–3 weeks).

The 'blind' investigators

Study data on outcome were collected by investigators (at 3, 6 and 12 months) who were blind to the drug taken by the patients. They used the following sources of data: (1) the patient himself, who was asked not to talk about the type of medication he was receiving; (2) the psychiatrist appointed to the case, who provided any data required from the clinical records, including biochemical results, and who was requested not to divulge the treatment prescribed; (3) the patient's family who provided information about drinking and any attempts by the patient to cease the pharmacological treatment. The degree of concordance between data from the family and the psychiatrists increased from 80% in the first few months to 95% in the final 3 months.

It was hoped that asking the family would help reduce the bias, which could occur if the information were obtained only from the psychiatrist who had prescribed the treatment. The investigators never interviewed the same patient at the three time points, since, at the end of an interview, they could have knowledge of the type of treatment the patient was receiving, which could affect future interviews with the same patient. Patients and relatives were asked not to tell the investigator the name of the treatment they were taking, its appearance, or how often per day they were taking it. Information from the psychiatrist was to complement that obtained from patients and their families and consisted mainly of data from clinical records and results of analyses. The main role of the psychiatrists in the study was to encourage patients to take the medication and to attend psychotherapy sessions.

Outcome measures

The primary outcome variables were: days of accumulated abstinence and days to first relapse (relapse is defined as the consumption of more than five drinks or 40 g ethanol per day). Additional outcome variables were number of drinks consumed per week, number of drinks consumed at a time, craving, abandonment of pharmacological treatment, drop-out from the study and 3-monthly serum GGT.

Statistical analysis

Pairwise χ^2- and *t*-tests were used to analyse differences between the two therapeutic groups, naltrexone versus acamprosate. All outcome analyses were conducted under an intention-to-treat analysis plan, with drop-outs regarded as relapsed for the abstinence and relapse analyses. Time to relapse and time to first drink were analysed by Kaplan–Meier

survival analysis. The difference in variables, such as number of drinks consumed per day, drinks consumed at one time or percentage of days abstinent, were analysed by analysis of covariance (ANCOVA), taking baseline levels as covariants, and for drop-outs using the last observation carried forward. The biological drinking markers, CDT and GGT levels, were evaluated by both repeated measures and end-point ANCOVA with baseline levels as covariants. A composite craving severity score was created, as the average of the three scale scores (intensity, duration and frequency). Group differences were analysed by repeated measures ANCOVA with baseline values on the respective scales used as covariants.

RESULTS

Recruitment and retention

The total number of patients from the different health centres considered for inclusion in the study was 356, of whom 197 were examined at the start of the study (Fig. 1). Of these, some were not selected: 30% refused to participate; in 30% the family could not commit themselves to accompany the patient to the Centre throughout the follow-up period; 27% had been treated previously with naltrexone or acamprosate; 25% presented comorbidity of another disorder; and in 15% naltrexone was contra-indicated because of impaired liver function. Of 160 subjects selected, three then refused to participate, so 157 were submitted to the pre-treatment analysis.

Randomization gave 77 (naltrexone) and 80 (acamprosate). Sociodemographic variables respectively were: age (mean ± SD = 43 ± 10; and mean = 44 ± 12 years), married (95 and 92%), employed full time (75 and 75%), secondary education (84 and 85%). There was no significant difference between the groups in any of these variables. There was no significant difference between the variables when related to severity of dependence; in both groups the severity of dependence measured with both the ASI and the SADS was moderate (Table 1).

The average period between the last drink and the start of treatment was 16 days (range 10–22).

A total of 26 patients dropped out during the study (eight naltrexone, 18 acamprosate). In the naltrexone group, two patients dropped out in the 1st month, four in the 3rd month and two in the 4th month. In the acamprosate group, two dropped out in the 1st month, five in the 2nd, five in the 3rd, four in the 4th, one in the 7th and one in the 8th month. The reasons for drop-out are shown Fig. 1.

Efficacy

At the end of the treatment year the number of abstinent patients in the naltrexone group was twice that in the acamprosate group and the accumulated abstinence was significantly greater in the former (Table 2). The survival until the first relapse was longer for naltrexone than acamprosate patients ($P = 0.02$) (Fig. 2). At the end of the study, 41% of the naltrexone group had not relapsed and 54% were abstinent since the last assessment (6 months), compared to 17 and 27%, respectively, in the group treated with acamprosate. Table 2 shows further alcohol consumption data, including the drinks consumed in a session, which was less for patients receiving naltrexone than those receiving acamprosate. In the group treated with naltrexone fewer patients used disulfiram. If a patient drank some alcohol, relapse occurred on average 12 days later in the naltrexone group (SD = 16) whereas it occurred in the group treated with acamprosate after 6 days (SD = 8).

A survival curve of time to first alcohol consumption revealed no significant differences between the two groups (the mean number of days to the first consumption was 44 for the naltrexone group and 39 for the acamprosate group; $P = 0.34$).

Regarding the composite score, severity of craving, patients receiving naltrexone had significantly lower scores over the entire study period.

Treatment compliance

In the naltrexone group there was a trend towards fewer drop-outs, fewer attempts to abandon pharmacological treatment, more weeks of completed treatment, and greater attendance at psychotherapy support sessions. The latter reached statistical significance. We considered the hypothesis that the number of days of abstinence could be related to attendance at therapy sessions, rather than to the use of naltrexone or acamprosate. To test this, we compared the mean number of days of abstinence at 3, 6 and 12 months follow-up, taking the number of psychotherapy sessions as the covariant (ANCOVA). The results showed that, in the naltrexone group the mean number of days of abstinence remained constant after the 3rd month, whereas in the acamprosate group the mean number of days of abstinence decreased over the follow-up period ($F = 8.23$, df = 2, 248, $P > 0.05$).

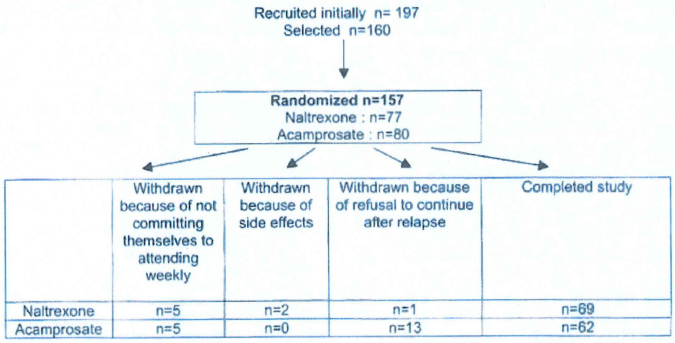

Fig. 1. Retention in the study.

Table 1. Severity of alcoholism, recent consumption pattern and biological markers of drinking at study entry

Parameter	Naltrexone group (n = 77) Mean	SD	Acamprosate group (n = 80) Mean	SD
Severity of Alcohol Dependence Scale	29	5	28	6
Addiction Severity Index	0.70	0.14	0.71	0.12
Composite craving severity score	52	19	51	22
Percentage of days drinking in past 6 months	87	20	87	21
No. of drinks per drinking day	12.3	5.0	12.2	5.1
Gamma-glutamyltransferase (IU/l)	110	98	125	101
Aspartate aminotransferase (IU/l)	81	21	84	19
Alanine aminotransferase (IU/l)	64	30	67	31
Carbohydrate-deficient transferrin (U/l)	25	17	26	20
Days between last drink and start of study medication	15	3	16	5

No significant group differences were detected ($P > 0.05$). All comparisons were t-tests with df = 155.

Sertraline was prescribed for two patients in whom a depressive episode emerged, and hydroxyzine was prescribed to 16 patients because of inability to fall asleep. The distribution between treatment groups was even, although this was not the case with prescriptions for disulfiram, which was prescribed to significantly more patients in the acamprosate group than the naltrexone group (Table 2).

The GGT determinations done at 3, 6 and 12 months were compared with baseline levels and ANCOVA showed significant temporal improvements in the whole sample ($F = 52.3$, df = 2, $P < 0.0001$). Table 3 shows the number of days of heavy drinking and the mean values of GGT. There was a non-significant trend for greater improvement in GGT in the naltrexone patients but a significant reduction in percentage of days of heavy drinking.

Side-effects were more common in the group receiving naltrexone, the most important of which were: nausea (25 vs 4%, $\chi^2 = 14.1$, $P = 0.0001$), abdominal pain (23% vs 4%, $\chi^2 = 12.9$, $P = 0.0003$), drowsiness (35 vs 2%, $\chi^2 = 27.4$, $P = 0.0000$), nasal congestion (23 vs 1%, $\chi^2 = 12$, $P = 0.0004$), headache (13 vs 6%, $\chi^2 = 2.0$, $P = 0.15$), diarrhoea (1 vs 4%, Fisher test $P = 0.3$) and epigastric discomfort (4 vs 4%, Fisher test $P = 0.64$). These side-effects gradually disappeared after the first 2 weeks of the study.

DISCUSSION

Naltrexone was associated with reducing relapse, achieving more days of accumulated abstinence, reducing the number of drinks consumed at any one time and reducing craving, compared to acamprosate. There was a trend for naltrexone to be associated with a greater retention in the treatment programme.

It is difficult to compare our results with those of other studies, since ours is the first published comparative study of these two

Table 2. Outcome after 1 year

Parameter	Naltrexone group (n = 77) n	%	Acamprosate group (n = 80) n	%	Analysis χ^2 (df = 1)
Subjects who completed study	69	90	62	78	4.14, $P = 0.14$
% subjects abstinent since last assessment (6 months)	41	54	22	27	14.5, $P = 0.0002$
No. of subjects prescribed disulfiram	17	22	42	52	15.3, $P = 0.0002$
No. of subjects who received sertraline to treat depression	1	1	1	1	0.0, $P = 0.9$ (Fisher test, $P = 0.74$)
No. of subjects receiving hydroxyzine to treat insomnia	7	9	9	11	0.20, $P = 0.6$
Patients who tried to abandon pharmacological treatment[a]	28	36	37	46	1.57, $P = 0.21$
Subjects who relapsed during the study	32	41	14	17	10.89, $P = 0.0009$
	Mean	SD	Mean	SD	t (df = 155)
No. of weeks of study completed	44	6	35	6	1.92, df = 1, 154, $P = 0.53$
No. of therapy sessions attended	43	5	32	8	6.8, df = 1, 154, $P = 0.01$
	Mean	SD	Mean	SD	F, df, P
Days to first alcohol consumption	44	36	39	28	2.19, df = 1 $P = 0.34$[b]
Days to first relapse (≥5 drinks per day)	63	38	42	32	6.96, df = 1, $P = 0.02$[b]
No. of drinks consumed at one time	4	6	9	7	7.01, df = 1, 141, $P = 0.01$
No. of days abstinence (accumulated abstinence)	243	115	180	129	5.76, df = 1, 140, $P = 0.03$
Composite craving severity score	11.3	10.1	15.3	12.1	6.2, df = 1, 139, $P = 0.01$

[a]This information was provided by the family member accompanying the patient.
[b]Kaplan–Meier survival (log-rank) statistic.

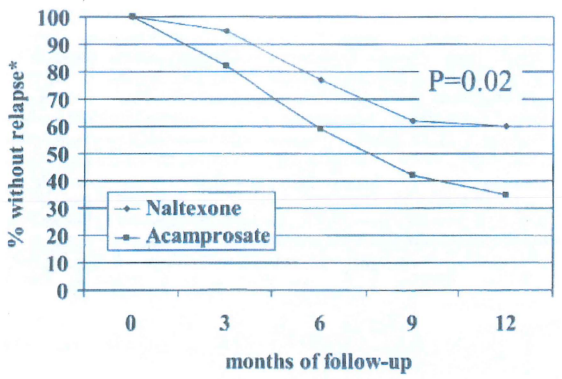

Fig. 2. Survival analysis to first relapse.
◆, naltrexone; ■, acamprosate. *Five or more drinks per day.

drugs. With regards to other research on naltrexone, in previous studies abstinence rates after 6 weeks were 23–62% (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992, 1997; Anton *et al.*, 1999; Chick *et al.*, 2000*b*). The results of our study, which was four times longer than the aforementioned ones, are within this range. The levels of abstinence with acamprosate in placebo-controlled trials with a 1-year follow-up are between 18 and 35% (Paille *et al.*, 1995; Sass *et al.*, 1996; Whitworth *et al.*, 1996; Besson *et al.*, 1998). In our study, we recorded a rate of 17%. If we extrapolate these results, it seems that long-term treatment of patients with naltrexone is more beneficial than with acamprosate.

Two hypotheses could explain the benefits of naltrexone seen in our study. First, it may be that naltrexone increases the period elapsed before the subject takes the first drink. Prolonging the abstinence period enables the learning of strategies taught in the support therapy and increases feelings of self-efficacy. Second, it may be that naltrexone has an effect on control of alcohol consumption once this has already begun, resulting in a delay in relapse. This could also increase the patients' faith in the treatment.

The first of these hypotheses was not confirmed, because the survival time to the first drink did not differentiate between treatments. In contrast, the action of naltrexone on control of alcohol consumption is shown in the survival curve to first relapse and in the number of drinks consumed at any one time. This effect has been described in other studies and has been explained by a reduction in the reinforcing effects of ethanol after drinking (O'Malley *et al.*, 1996*a*,*b*), or by an improvement in the ability to resist thoughts or cravings to continue drinking (Anton *et al.*, 1999). Whichever explanation, the higher degree of control over their drinking achieved by patients treated with naltrexone could explain their lesser use of disulfiram and their achieving more days of abstinence and a greater use of therapy. In our opinion, this effect could be explained as follows: the craving triggered by consumption is slightly less with naltrexone than with acamprosate, which enables those treated with naltrexone to stop drinking earlier. Since relapses are very common in these patients, those treated with naltrexone would be more capable of interrupting the relapse or diminishing its intensity. This would help to prevent progression in alcohol consumption and increase the probability that the patient seeks help from a therapist and, therefore, ultimately, curtail relapse. This is supported by the fewer absences from therapy in the naltrexone-treated group. Since naltrexone reduces the intensity of relapse, patients attend more therapy sessions. Although this latter effect has not been found by other authors (Anton *et al.*, 1999), this could be due to the shorter duration of their studies. Finally, the increased number of attempts to abandon treatment with acamprosate may relate to the number of doses required daily, and this could contribute to the smaller percentage of days of abstinence achieved by these patients.

Anticraving effects of naltrexone were more important than those of acamprosate, although this difference could be due to their different mechanisms of action and the fact that most patients drank alcohol during the study period. Given that acamprosate probably exerts its anticraving action by reducing the intensity of the symptoms of the conditioned withdrawal syndrome and naltrexone probably reduces the reinforcing effects of the alcohol, this difference would favour the use of naltrexone in patients who are likely to consume some alcohol. This would explain why the patients treated with naltrexone reported less craving than the acamprosate group over the study period (Rubio *et al.*, 1999). It is also possible that naltrexone would be more effective at reducing craving in patients with moderate dependence, in whom craving mechanisms related to positive reinforcement could be over-represented. Since our sample was of patients with moderate dependence, this could explain the results obtained.

With regards to the tolerability of both drugs, although the group treated with naltrexone experienced more side-effects, these only lasted for the first 2 weeks of the study and there was no significant difference in the rate of drop-out due to this.

Limitations of this study

This was an open study, and there is the possibility that the investigators did not remain blinded. We tried to prevent the investigators from gaining direct information about the type of

Table 3. Percentage of days of heavy drinking and serum gamma-glutamyltransferase (GGT) from baseline to 1 year

	Baseline period (90 days)		1–3 months follow-up (90 days)		4–6 months follow-up (90 days)		6–12 months follow-up (180 days)	
Group	% of days heavy drinking	GGT $n = 157$	% of days heavy drinking	GGT $n = 139$	% of days heavy drinking	GGT $n = 133$	% of days heavy drinking	GGT $n = 131$
Naltrexone	96	110 ± 98	23	76 ± 42	44	85 ± 46	33	87 ± 62
Acamprosate	96	125 ± 101	48	90 ± 75	52	99 ± 72	53	107 ± 90

% of days heavy drinking differed between the groups ($F = 5.04$; df = 1, 140; $P = 0.038$).
GGT (mean ± SD): not significant.

pharmacological treatment taken by the patients, although it is possible that they could have guessed the treatment from the patients' side-effects. However, this can also occur in double-blind trials, except in studies with total integrity of the double-blindedness (Moncrieff and Drummond, 1997). Objective outcome criteria are not subject to bias: in our study, GGT (which is a helpful, but not perfect, marker of drinking) appeared to corroborate a better reported outcome in the naltrexone group, but the advantage failed to reach statistical significance.

Some of the advantages of naltrexone seen in this study could be explained by the fact that the participants were patients with moderate alcohol dependence. Impaired liver function as an exclusion criterion will have ruled out some of the most severe cases. Possibly, the latter would have responded better to acamprosate than to naltrexone.

At the start of the study, the psychiatrists did not know which pharmacological treatment would be most effective and, therefore, had a similar attitude towards encouraging compliance with both treatments. However, as the study progressed and subjects treated with naltrexone appeared to have a better outcome, the psychiatrist may have made more effort to encourage compliance with naltrexone treatment, which could, at least hypothetically, have then introduced a bias.

Our assessment of the degree of compliance to the pharmacological treatment was conducted by questionnaires corroborated by information from the family. It would have been more accurate to use a urinary marker such as riboflavin.

A difficulty in extrapolating the results of this study to other treatment settings could be that, in our study, there was a high level of family support available to patients. If this had not been available, the retention levels, and compliance with medication, might have been lower for both treatments, and there would possibly have been no measurable difference between them. In our opinion, further studies comparing the efficacy of these two drugs are required in varying therapeutic contexts in patients with different severity profiles.

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REFERENCES

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised. American Psychiatric Association, Washington, DC.

Anton, R. F., Moak, D. H., Waid, L. R., Latham, P. K., Malcolm, R. J. and Dias, J. K. (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. *American Journal of Psychiatry* **156**, 1758–1764.

Benjamin, D., Grant, E. R. and Phorecky, L. (1993) Naltrexone reverses ethanol-induced dopamine release in the nucleus accumbens in awake, freely moving rats. *Brain Research* **621**, 137–140.

Besson, J., Aeby, F., Kasas, A., Lehert, P. and Potgieter, A. (1998) Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. *Alcoholism: Clinical and Experimental Research* **22**, 573–579.

Catafau, A. M., Etcheberrigaray, A., Pérez de los Cobos, J., Estorch, M., Guardia, J. and Flotats, A. (1999) Regional cerebral blood flow changes in chronic alcoholic patients induced by naltrexone challenge during detoxification. *Journal of Nuclear Medicine* **40**, 19–24.

Chick, J., Howlett, H., Morgan, M. Y., Ritson, B. and UKMAS investigators (2000*a*) United Kingdom Multicentre Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. *Alcohol and Alcoholism* **35**, 176–187.

Chick, J., Anton, R., Checinski, K., Croop, R., Drummond, C., Farmer, R., Labriola, D., Marshall, J., Moncrieff, J., Morgan, M., Peters, T. and Ritson, B. (2000*b*) A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol and Alcoholism* **35**, 587–593.

Geerlings, P. J., Ansoms, C. and van den Brink, W. (1997) Acamprosate and prevention of relapse in alcoholics. *European Journal of Addiction Research* **3**, 129–137.

Ladewig, D., Knecht, Th., Lehert, P. H. and Fend, A. (1993) Acamprosat — ein stabilisierungsfktor in der langzeitentwohnung von alkoholabhangigen. *Therapeutische Umschau* **50**, 182–187.

Littleton, J. (1995) Acamprosate in alcohol dependence: how does it work? *Addiction* **90**, 1179–1188.

McLellan, A. T., Luborsky, L., Woody, G. E. and O'Brien, C. P. (1980) An improved diagnostic evaluation instrument for substance abuse patients: the Addiction Severity Index. *Journal of Nervous and Mental Disease* **168**, 26–33.

Miller, W. R. (1996) *Form 90: A Structured Assessment Interview for Drinking and Related Behaviors Test Manual: NIAAA Project Match Monograph Series*, vol. 5, Mattson, M. E. and Marshall, L. A. eds, pp. 14–22. National Institute on Alcoholism and Alcohol Abuse, Rockville, MD.

Moncrieff, J. and Drummond, D. C. (1997) New drug treatments for alcohol problems: a critical appraisal. *Addiction* **92**, 939–947.

O'Malley, S. S., Jaffe, A. J., Chang, G., Schottenfeld, R S., Meyer, R. E. and Rounsaville, B. (1992) Naltrexone and coping skills therapy for alcohol dependence. *Archives of General Psychiatry* **49**, 881–887.

O'Malley, S. S., Jaffe, A. J., Rode, S. and Rounsaville, B. (1996*a*) Experience of a 'slip' among alcoholics treated with naltrexone or placebo. *American Journal of Psychiatry* **153**, 281–283.

O'Malley, S. S., Jaffe, A. J., Chang, G., Rode, S., Schottenfeld, R. S., Meyer, R. E. and Rounsaville, B. (1996*b*) Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. *Archives of General Psychiatry* **53**, 217–224.

Paille, F. M., Guelfi, J. D., Perkins, A. C., Royer, R. J., Steru, L. and Parot, P. (1995) Randomised multicentre trial of acamprosate in a maintenance programme of abstinence after alcohol detoxification. *Alcohol and Alcoholism* **30**, 239–247.

Pelc, Y., Le Bon, O., Verbanck, P., Lehert, P. H. and Opsomer, L. (1992) Calcium acetyl homotaurinate for maintaining abstinence in weaned alcoholic patients; a placebo controlled double-blind multicentre study. In *Novel Pharmacological Interventions for Alcoholism*, Naranjo, C. and Sellers, E. M. (eds), pp. 348–352. Springer-Verlag, New York.

Poldrugo, F. (1997) Acamprosate treatment in a long-term community based alcohol rehabilitation programme. *Addiction* **92**, 1537–1547.

Rubio, G., Urosa, B. and Santo-Domingo, J. (1998) Validación de la escala de la intensidad de la dependencia alcohólica (EIDA). *Psiquiatría Biológica* **10** (Suppl. 1), 44–47.

Rubio, G., Ponce, G., Jiménez-Arriero, M. A. and Santo-Domingo, J. (1999) La pérdida de control en la dependencia alcohólica: conceptualización. *Adicciones* **11**, 143–158.

Sass, H., Soyka, M., Mann, K. and Zieglgansberger, W. (1996) Relapse prevention by acamprosate: results from a placebo controlled study on alcohol dependence. *Archives of General Psychiatry* **53**, 673–680.

Spitzer, R. L., Williams, J. B. W., Gibbon, M. and First, M. B. (1992) The Structures Clinical Interview for DSM-III-R (SCID), I: History, rationale, and description. *Archives of General Psychiatry* **49**, 624–629.

Tempesta, E., Janiri, L., Bignamini, A., Chabac, S. and Potgieter, A. (2000) Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. *Alcohol and Alcoholism* **35**, 202–209.

Ulm, R. R., Volpicelli, J. R. and Volpicelli, L. A. (1995) Opiates and alcohol self-administration in animals. *Journal of Clinical Psychiatry* **56** (Suppl. 7), 5–14.

Valenzuela, F. and Harris, A. (1997) Alcohol: neurobiology. In *Substance Abuse. A Comprehensive Textbook*, 3rd edn, Lowinson, J. H., Ruiz, P., Millman, R. B., Langrod, J. G. eds, pp. 119–142. Williams and Wilkins, Baltimore.

Volpicelli, J. R., Alterman, A. I., Hayashida, M. and O'Brien, C. P. (1992) Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* **49**, 876–880.

Volpicelli, J. P., Clay, K. L., Watson, N. T. and O'Brien, C. P. (1995*a*) Naltrexone in the treatment of alcoholism: predicting response to naltrexone. *Journal of Clinical Psychiatry* **56**, 39–44.

Volpicelli, J. R., Watson, N. T., King, A. C., Sherman, C. E. and O'Brien, C. P. (1995*b*) Effect of naltrexone on alcohol 'high' in alcoholics. *American Journal of Psychiatry* **152**, 613–615.

Volpicelli, J. R., Rhines, K. C., Rhines, J. S., Volpicelli, L. A., Alterman, A. I. and O'Brien, C. P. (1997) Naltrexone and alcohol dependence. Role of subject compliance. *Archives of General Psychiatry* **54**, 737–742.

Whitworth, A. B., Fisher, F., Lesch, O., Nimmerrichter, A., Oberauer, H., Platz, T., Potgieter, A., Walter, H. and Fleischhacker, W. W. (1996) Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. *Lancet* **347**, 1438–1442.