A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF NALTREXONE IN THE TREATMENT OF ALCOHOL DEPENDENCE OR ABUSE

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Abstract — The opioid antagonist, naltrexone, is reported, in single centre studies, to improve the clinical outcome of individuals with alcohol dependence participating in outpatient psychosocial programmes. This is the first multicentre controlled study to evaluate the efficacy and safety of naltrexone as adjunctive treatment for alcohol dependence or abuse. Patients who met criteria for alcohol dependence ($n = 169$) or alcohol abuse ($n = 6$) were randomly assigned to receive double-blind oral naltrexone 50 mg daily ($n = 90$) or placebo ($n = 85$) for 12 weeks as an adjunct to psychosocial treatment. The primary efficacy variable was time to first episode of heavy drinking; secondary efficacy assessments included time to first drink, alcohol consumption, craving, and changes in the serum biological markers gamma-glutamyl transferase (GGT), and aspartate and alanine aminotransferases. Compliance was assessed by tablet counts and, in the naltrexone-treated group, by measurement of urinary concentrations of 6-β-naltrexol. Forty-nine (58%) patients randomized to placebo and 53 (59%) randomized to naltrexone did not complete the study. In intention-to-treat analyses, there was no difference between groups on measures of drinking. The median reduction from baseline of serum GGT ($P < 0.05$) and the reductions in alcohol craving (Obsessive and Compulsive Drinking Scale: OCDS) were greater in the naltrexone group ($P < 0.05$), from approximately half-way through the study. Of 70 patients (35 placebo; 35 naltrexone) who met an *a priori* definition of compliance (80% tablet consumption, attendance at all follow-up appointments), those allocated to naltrexone reported consuming half the amount of alcohol ($P < 0.05$), had greater median reduction in serum GGT activity ($P < 0.05$), and greater reduction in alcohol craving (OCDS total score: $P < 0.05$; Obsessive subscale score: $P < 0.05$), compared to patients in the placebo group. Use of naltrexone raised no safety concerns. Naltrexone is effective in treating alcohol dependence/abuse in conjunction with psychosocial therapy, in patients who comply with treatment.

INTRODUCTION

Psychosocial treatment programmes for alcoholism have only limited success and pharmacotherapy may help to prevent early relapse. Preclinical and clinical findings support the hypothesis that alcohol stimulates endorphin activity and reduces deficiencies in endogenous opioid transmission [reviewed by Froehlich and Li (1993) and Volpicelli *et al*. (1995*a*)].

The orally administered opioid antagonist, naltrexone, was shown in randomized, double-blind, placebo-controlled clinical trials to reduce the relapse rate of individuals with alcohol dependence participating in outpatient psychosocial programmes (O'Malley *et al*., 1992; Volpicelli *et al*., 1992) with moderate effect sizes of 0.42 and 0.60 respectively (Volpicelli *et al*., 1995*c*). Further studies have replicated this (Volpicelli *et al*., 1997; Anton *et al*., 1999). Another opioid antagonist, nalmefene, appears to have a similar action in the treatment of alcohol dependence (Mason *et al*., 1994, 1999).

This paper reports the first multicentre study, and the largest study to date, of naltrexone's efficacy and safety in alcohol dependence and abuse and differs from previous studies in offering generally less intensive psychosocial support, which varied between centres, thus perhaps better reflecting routine clinical practice.

PATIENTS AND METHODS

The study was conducted over a 13-month period at six sites in the UK, which were five alcohol treatment units and one academic department of hepatology with a special interest in alcohol-related illness.

Patient selection

Men and women, aged 18–65 years, who met DSM-III-R (American Psychiatric Association, 1987) criteria for alcohol dependence or alcohol abuse were eligible for the study. Patients had to be abstinent from alcohol for 5–30 days before entry into the study and enrolled in, or about to enter, an outpatient alcohol rehabilitation treatment programme or routine out-patient follow-up. Patients were excluded if they had psychiatric conditions requiring medication, polysubstance abuse, serum aspartate (AST) or alanine aminotransferase (ALT) activities greater than three times the upper reference range, a total serum bilirubin concentration greater than twice the upper reference range, or significant physical illnesses such as, for example, ischaemic heart disease, chronic obstructive airways disease or insulin-dependent diabetes mellitus. Patients using opioids in any form, other opioid antagonists, disulfiram, acamprosate, lithium salts, antidepressants, antipsychotics or benzodiazepines except as a bedtime hypnotic, were also excluded. All patients provided written informed consent. The study was conducted in accordance with world-wide standards for Good Clinical Practice (GCPs) and conformed to acceptable ethical standards as outlined by local requirements and the Declaration of Helsinki.

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Randomization and treatment

Patients with alcohol dependence or abuse were randomized to receive either naltrexone 50 mg or a placebo preparation, identical in appearance, once daily for up to 12 weeks in addition to psychosocial treatment. Randomization was stratified according to diagnosis based on DSM-III-R criteria (alcohol dependence or alcohol abuse) with equal assignment of placebo and naltrexone in each stratum. Each study centre entered the trial patients into its usual psychosocial treatment programme; the type and amount of treatment provided was not subject to protocol constraints. Patients were free to attend alternative facilities, such as Alcoholics Anonymous or other support groups. At the point of giving consent, patients were informed that naltrexone had been shown in previous studies in alcoholism treatment centres to reduce craving for alcohol and alcohol consumption. After screening and enrolment visits, patients returned for study visits every 2 weeks during the 12-week treatment period.

Assessments

The primary goal of each patient's treatment was to support abstinence from alcohol and to reduce the likelihood of relapse to heavy drinking. The primary efficacy variable was the time to first episode of heavy drinking, as assessed by the Time-Line Follow-Back (TLFB) method (Sobell and Sobell, 1992). An episode of heavy drinking was defined as five drinks on a single occasion for men and four drinks for women. (One 'drink' is defined as that amount of beverage containing 13 g ethanol, corresponding to the USA tradition, which was used in this study to permit comparison with the previous naltrexone trials, rather than the UK unit system where 1 'unit' is that amount containing 8 g ethanol.) This was chosen as the primary efficacy variable, first, because it has clinical meaning, in that it is heavy drinking which causes problems, and, second, because it was the outcome variable used in the two previous studies (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992). Secondary effectiveness measures included time to first drink, overall alcohol consumption, number of abstinent days, craving as measured by the Obsessive–Compulsive Drinking Scale (OCDS; Anton *et al.*, 1995, 1996), a physician rating of global severity ('need for treatment') from an abbreviated version of the Addiction Severity Index (aASI; McLellan *et al.*, 1991), and changes in serum gamma-glutamyl transferase (GGT), ALT and AST (Rosalki and Rau, 1972; Chick *et al.*, 1981; Salaspuro, 1986). Urine was collected at each visit. Safety was assessed by observed or volunteered adverse clinical events (ACE) and laboratory test results. All clinical laboratory determinations were performed by a central laboratory. (The markers carbohydrate-deficient transferrin and mean red corpuscular volume were not used.) The above measurements were made at baseline and repeated at 2, 4, 6, 8, 10 and 12 weeks.

Compliance with medication was assessed by counting returned tablets. For the naltrexone group, compliance was also assessed by identification of the presence in urine of 6-β-naltrexol, a metabolite of naltrexone with a half-life of 14–18 h (Cone *et al.*, 1974). Urinary 6-β-naltrexol concentration of 1 µg/ml was set as the limit for detecting those who actually took their dose during the preceding 24 h (Pieniaszek *et al.*, 1996). No comparable biological marker of placebo compliance was used.

Statistical analysis

Based on the assumption that 50% of patients treated with placebo relapse to heavy drinking, compared to 25% of patients treated with naltrexone during a 12-week period, 75 patients per treatment arm were needed to obtain 80% power when testing at the 5% significance level. All statistical analyses were performed using the Statistical Analysis System package, version 6.08 (SAS Institute, Cary, NC, USA). A result was deemed statistically significant when the statistical test yielded a two-tailed probability (*P*-value) of ≤0.05. Baseline was defined as the last observation obtained prior to initiation of study medication. Endpoint was defined as the last observation available during the 12-week treatment period for each patient.

Survival analysis methods (Kaplan–Meier estimates and log-rank test) were used to analyse the time-to-event variables. For continuous variables, differences in means between groups were tested using an analysis of variance model (ANOVA). Changes from baseline were tested within each treatment group using a paired *t*-test. Biochemical test results were not normally distributed, so median changes from baseline were compared between treatment groups using the Kruskal–Wallis test. Discrete variables were compared between treatments using χ^2-test or Fisher's exact test. Adverse clinical events were classified and summarized according to World Health Organization Adverse Reaction Terms (WHOART; WHO, 1992)

Initial analyses were carried out on an intention-to-treat basis, including all patients who received at least one dose of study medication. Drop-outs were assigned to the heavy-drinking category. The analysis plans detailed in the study protocol identified *a priori* that compliance with study medication would be used to identify subgroups of patients for further analyses. For these analyses, a patient was considered compliant if at least 80% of the scheduled medication was consumed, as documented on the basis of tablet counts, and all appointments had been attended.

RESULTS

Of the 175 patients entering the trial, 85 were randomized to receive placebo and 90 to receive naltrexone (Fig. 1). No significant differences between the naltrexone and placebo groups were observed for any baseline variable (Table 1). Overall, patients tended to lack social support: only 40% were married or in a permanent relationship, 26% lived alone and only 27% were in full-time employment. During the week prior to study entry, the mean attendance at an intervention session or a 12-step meeting was 3.1 (±5.5) times for the naltrexone group and 2.4 (±3.2) times for the placebo group.

Forty-nine (58%) patients randomized to placebo (P) and 53 (59%) randomized to naltrexone (ntx) discontinued the study before the end of the 12-week treatment period because of: adverse clinical events (P 11, ntx 13), protocol violations including starting other medicines (P 12, ntx 18), withdrawal of consent (P 9, ntx 3), poor compliance (P 1, ntx 2) and loss to follow-up (P 16, ntx 17).

Of the 73 patients (P 36, ntx 37) who completed the study, 70 (P 35, ntx 35) attended all follow-up appointments and showed 80% compliance based on tablet counts. In this completed and compliant subgroup, patients randomized
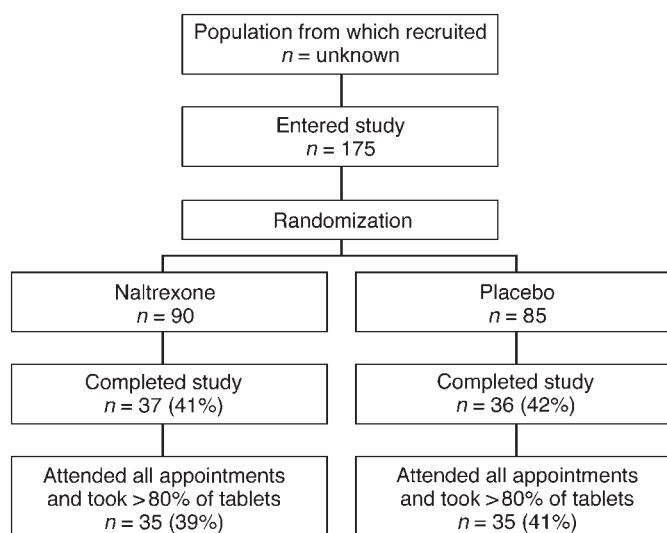
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┌─────────────────────────────────┐
│  Population from which recruited  │
│         n = unknown               │
└─────────────────────────────────┘
                 │
┌─────────────────────────────────┐
│          Entered study            │
│            n = 175                │
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│         Randomization             │
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        │                 │
┌───────────────┐   ┌───────────────┐
│   Naltrexone   │   │    Placebo     │
│    n = 90      │   │    n = 85      │
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│ Completed study│   │ Completed study│
│  n = 37 (41%)  │   │  n = 36 (42%)  │
└───────────────┘   └───────────────┘
        │                 │
┌─────────────────┐ ┌─────────────────┐
│Attended all      │ │Attended all      │
│appointments      │ │appointments      │
│and took >80% of  │ │and took >80% of  │
│tablets           │ │tablets           │
│ n = 35 (39%)     │ │ n = 35 (41%)     │
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Fig. 1. Recruitment, randomization and retention in study.

to naltrexone or placebo were still matched with respect to demographic and baseline characteristics (Table 1).

Analysis of urinary concentrations of 6-β-naltrexol revealed that naltrexone patients who discontinued the trial during the first 6 weeks of the study had substantially higher rates of non-compliance with study medication than those who remained in treatment for more than 6 weeks. Thus, for example, at the 2-week visits, 78 urine specimens were tested and 40% of those who completed 6 or more weeks in the study were compliant with their naltrexone medication, compared to only 5% of those who subsequently dropped out before the 6th week.

Efficacy results: intention-to-treat analyses

Alcohol consumption. Alcohol consumption data for patients who received at least one dose of randomized study medication were available for 164 patients (79 placebo and 85 naltrexone) for some or all of the 12-week study period. Overall, no significant differences between treatments were observed in the time to first heavy drinking episode or the time to first drink (Fig. 2). Complete abstinence for the entire study period was achieved by 19% of placebo patients and 18% of naltrexone patients. The number of drinks consumed during the last 4 weeks of the study was lower in the naltrexone group (mean ± SEM: 49 ± 12.0) than in the placebo group (mean ± SEM: 86 ± 15.4) but this difference was not significant.

Biochemical markers. In the 76 patients for whom more than baseline biochemical test results were available, significant decreases in serum GGT activities were observed in both treatment groups at all time points. In these patients, there had been no difference at baseline in median serum GGT, AST or ALT activities between the treatment groups. The median reduction in serum GGT activity for the naltrexone group was significantly greater than in the placebo group at week 8 ($P < 0.05$). Reductions in serum AST and ALT activities did not discriminate between the groups (data not shown).

Craving. Significant mean decreases from baseline in total OCDS score were observed at all time points in the naltrexone group, compared to a significant decrease from baseline only at week 6 for the placebo group. The reduction in total OCDS score in the naltrexone group was significantly greater ($P < 0.05$) than in the placebo group at weeks 10 and 12.

Physician's global assessment. The alcohol component of the aASI assesses the patient's 'need for treatment for alcoholism' as a global measure of severity. A significantly greater percentage of patients in the naltrexone group than in the placebo group (64% versus 45%; $P < 0.05$) were characterized as 'needing less treatment' at week 12, than at baseline.

Table 1. Demographic and alcohol history

	All patients		Completed and compliant	
Variable	Placebo ($n = 85$)	Naltrexone ($n = 90$)	Placebo ($n = 35$)	Naltrexone ($n = 35$)
Age (years; mean ± SD)	43.9 ± 9.7	43.1 ± 8.3	43.9 ± 11.0	43.9 ± 8.0
Gender: male (%)	66 (78)	65 (72)	27 (77)	27 (77)
Length of drinking (years; mean ± SD)	25.9 ± 10.6	22.9 ± 8.7	25.4 ± 10.8	22.2 ± 8.8
Average intake (drinks/day)[a] (mean ± SD)	10.3 ± 7.5	10.1 ± 9.1	9.2 ± 5.0	11.4 ± 12.3
Abstinence before study initiation (days; median, range)[b]	11 (0–30)	10 (0–30)	11 (0–30)	11 (3–29)
DSM-III-R criterion: alcohol dependence (%)	82 (97)	87 (97)	35 (100)	34 (97)
Alcohol abuse (%)	3 (4)	3 (3)	0	1 (3)
Serum GGT (U/l; median) (reference range 7–64)	36	45	54	52
Serum ALT (U/l; median) (reference range 8–48)	24	26	26	28
Serum AST (U/l; median) (reference range 6–37)	22	22	34	27
Not married/cohabiting (%)	52 (59)	53 (59)	18 (52)	16 (49)
Living alone (%)	26 (31)	20 (22)	8 (23)	6 (17)
Employed full time (%)	18 (21)	29 (32)	9 (26)	13 (37)

[a]During the 90 days preceding the first day of the study, based on the Time-Line Follow-Back method.
[b]The actual range differs from that specified in the protocol (5 to 30) because of protocol violations.
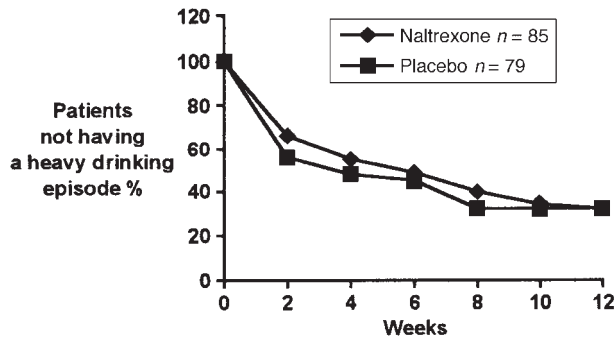ALT, alanine aminotransferase; AST, serum aspartate; GGT, gamma-glutamyl transferase.

Fig. 2. Time to first episode of heavy drinking: intention-to-treat analysis.

Fig. 3. Time to first episode of heavy drinking: completed and compliant patients.

Fig. 4. Mean alcohol consumption during periods between assessments: completed and compliant patients.
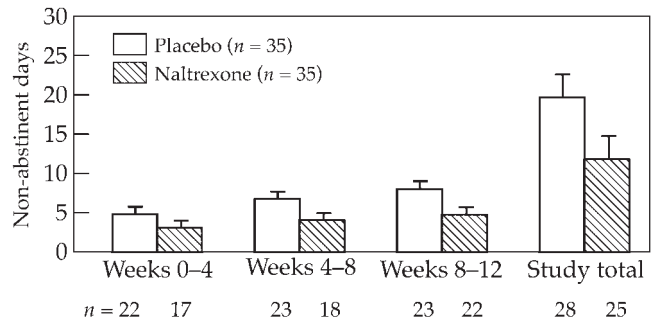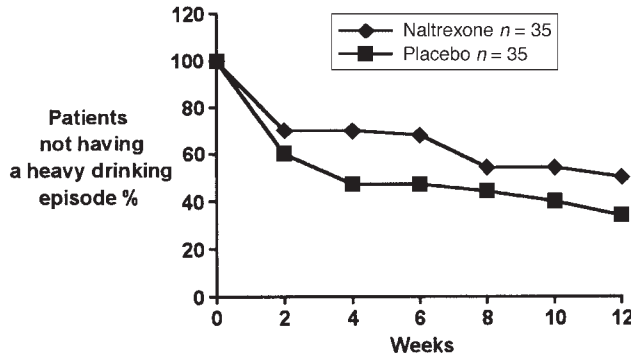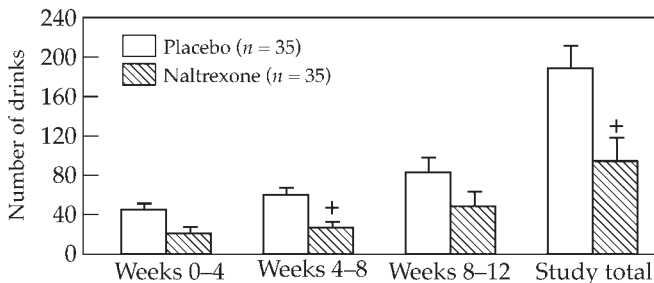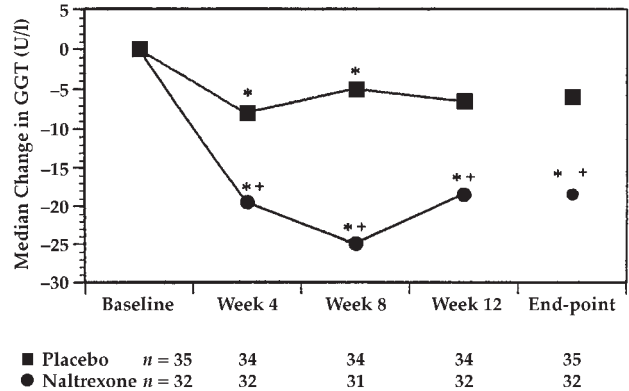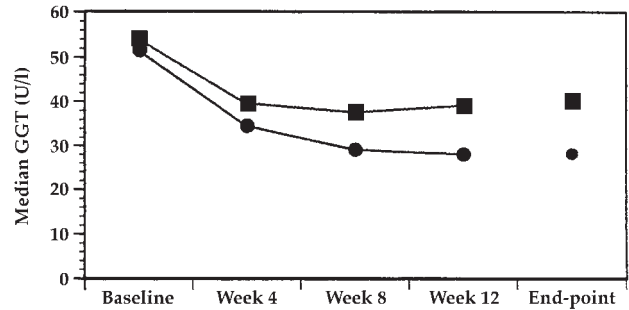Bars show means + SE. +$P \leq 0.05$.

Fig. 5. Mean number of non-abstinent days during periods between assessments: completed and compliant patients.
Bars show mean + SE. The differences are not significant.

Fig. 6. Median, and median change from baseline, in serum gamma-glutamyl transferase (GGT) activities (U/l): completed and compliant patients.
*Statistically significant change from baseline $P \leq 0.05$; +statistically significant difference between groups $P \leq 0.05$. 'Endpoint' is the last result available for each patient.

Efficacy results: completed and compliant patients

Alcohol consumption. In the completed and compliant subgroup, there was no significant advantage of naltrexone over placebo in time to first episode of heavy drinking or time to first drink (Fig. 3). The naltrexone patients consumed, on average, half the total amount of alcohol consumed by placebo patients, during weeks 4–8 ($P < 0.05$) and cumulatively over the whole study ($P < 0.05$) (Fig. 4). The number of non-abstinent days accruing in each of the 4-week periods is shown in Fig. 5. There was a trend suggesting that naltrexone patients had fewer non-abstinent days (i.e. more days of abstinence) than placebo patients but this did not reach significance.

Biochemical markers. The median decrease in serum GGT activity in the naltrexone group was greater than that in the placebo group at all time points ($P < 0.05$) (Fig. 6). Median reductions in serum GGT activity ranging from 19 to 25 U/l were observed for the naltrexone group throughout the study period, compared to median reductions ranging from 5 to 8 U/l in the placebo group. Significant decreases from baseline in serum GGT activity were observed at all time points for the naltrexone group and at weeks 4 and 8 for the placebo group. A similar trend which reached significance at 12 weeks, of a greater median reduction in the naltrexone patients than
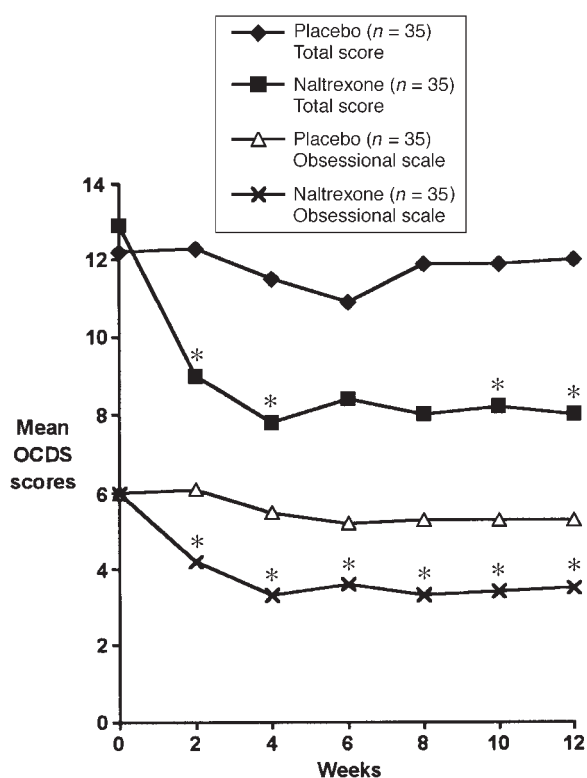
Fig. 7. Mean Obsessive–Compulsive Drinking Scale (OCDS) total score and obsessive subscale score: completed and compliant patients. *$P \leq 0.01$.

placebo patients, was seen for serum AST, but not for serum ALT, activities (data not shown).

Craving. There were significant mean decreases from baseline in total OCDS scores in the naltrexone group at all visits. No significant mean changes from baseline in total OCDS scores were observed in the placebo group. Significant between-group differences in total score favouring naltrexone were observed at all time points, except week 6 and over the whole 12-week study period ($P < 0.01$) (Fig. 7). Because there is a component of the total score which measures alcohol consumption itself, a separate analysis of the scale without the consumption items, the obsessive subscale, was conducted. There was a significantly greater reduction in the obsessive subscale in the naltrexone patients than the placebo patients over the 12-week period ($P < 0.01$) (Fig. 7).

Physician's global assessment. Global benefit of naltrexone was observed in the alcohol component of the aASI: a significantly greater percentage of patients in the naltrexone group than in the placebo group (69% versus 43%; $P \leq 0.05$) were characterized as 'needing less treatment' at week 12 than at baseline.

Safety

Safety results were based on data for all patients who received at least one dose of study medication (P $n = 83$; ntx $n = 90$). The most frequently reported adverse clinical event was headache (P 51%, ntx 44%) (Table 2). Significant differences between treatments were observed for the incidences of nausea, pain, dyspepsia and anorexia. Dyspepsia occurred more frequently in the placebo group than in the naltrexone group. Nausea, pain and anorexia occurred more frequently in the naltrexone group. Although events classified by the non-specific WHOART term 'pain' occurred more often in the naltrexone group, incidences of other 'pains' such as

Table 2. New-onset adverse clinical events with an incidence of ≥10%: all patients

Adverse clinical event	Placebo		Naltrexone	
	n	(%)	n	(%)
Total no. of patients evaluated[a]	78		85	
Total no. of patients with an ACE	71	(91)	81	(95)
Headache	40	(51)	37	(44)
Upper respiratory tract infection	17	(22)	29	(34)
Nausea	13	(17)	27[b]	(32)
Insomnia	15	(19)	14	(16)
Vomiting	11	(14)	15	(18)
Depression	13	(17)	13	(15)
Somnolence	7	(9)	15	(18)
Dizziness	11	(14)	10	(12)
Diarrhoea	9	(12)	11	(13)
Anorexia	1	(1)	8[b]	(9)
Abdominal pain	9	(12)	11	(13)
Arthralgia	12	(15)	8	(9)
Anxiety	7	(9)	12	(14)
Fatigue	9	(12)	10	(12)
Back pain	10	(13)	9	(11)
Pain	3	(4)	13[b]	(15)
Coughing	3	(4)	9	(11)
Dyspepsia	9	(12)	2[b]	(2)

[a]Excludes patients who withdrew before adverse clinical events could be reported.
[b]Significant difference between treatment groups, $P \leq 0.05$. In addition to the events in this table, the incidence of anorexia was significantly higher in the naltrexone group than the placebo group (9% vs 1%).
ACE, adverse clinical events.

headache, back pain, abdominal pain, and arthralgia were comparable in the two groups.

Eleven (14%) placebo patients and 13 (15%) naltrexone patients discontinued the study because of adverse clinical events, the most common being nausea. One placebo patient discontinued the study because of deteriorating liver function presumed to be alcohol-related. There were no deaths during the study. No scale of depressive symptoms was used in this study. Depression did not emerge as commoner in patients taking naltrexone.

DISCUSSION

An attrition rate in excess of 50% within the first month of treatment for alcohol is common (Stark, 1992). The discontinuation rate in the present study was higher than in the previously published naltrexone trials. High discontinuation rates have been a feature of multicentre alcoholism treatment studies in the UK (e.g. Chick *et al.*, 1992, 2000).

As in many currently published controlled trials, no attempt was made to assess whether the blindness of patients or staff to the treatment allocated had been maintained (Moncrieff and Drummond, 1998). In the present study, the comparability of the incidence of side-effects makes it unlikely that side-effects would have significantly disturbed the blindness.

The analyses of the completed and compliant subpopulation in this study were performed to elucidate more clearly the treatment effects of naltrexone in patients motivated to stay in treatment and to comply with study medication, the rationale being that naltrexone will only benefit patients who take it. In the subgroup defined by full attendance and tablet count, greater reduction in total alcohol consumption reported by the naltrexone patients was corroborated by improvements in serum GGT activities, improvements in physicians' global rating of alcoholism severity, and by greater reduction in craving.

However, a statistically significant advantage in the primary efficacy variable, time to first heavy drinking episode, was not seen, although there was a trend in favour of naltrexone. Thus, the study has not replicated the results of the previous clinical trials. One possible explanation could be that the psychosocial treatment offered at these six UK sites was in general much less intensive and was not specified, compared to that offered in previous studies. (This was not intended in the design, but resulted from the real-life National Health Service environment of the research.) In samples of patients where few are likely to sustain complete abstinence, structured coping skills training possibly interacts with the use of naltrexone to help prevent major relapse. This is suggested in the studies of O'Malley *et al.* (1992) and Anton *et al.* (1999) and the preliminary report of a Swedish study (Balldin *et al.*, 1997), and the nalmefene study of Mason *et al.* (1999). It could, however, also be argued from this UK study that, at least in compliant patients, some benefits from naltrexone can be seen with varied and non-intensive psychosocial treatment.

Our findings with respect to compliance are similar to those seen previously in studies in the USA. O'Brien *et al.* (1996) found that the size of the naltrexone treatment effect among compliant patients was substantially greater than that in the less compliant. In a different outpatient population, Volpicelli *et al.* (1997) found large naltrexone treatment effects for highly compliant subjects, but no naltrexone effect for the less compliant.

Mechanism of action

Our result, that in compliant patients naltrexone helped reduce alcohol intake, without an unequivocal reduction in number of drinking days, would be consistent with the hypothesis that naltrexone reduces the loss of control which some dependent drinkers experience when they start to drink (Volpicelli *et al.*, 1995*b*) or that naltrexone reduces the amount consumed by reducing the euphoric effect or inducing an aversive effect of drinking alcohol (e.g. Swift *et al.*, 1994; Davidson *et al.*, 1999). Although all patients recruited to the study had been advised to abstain, less than 20% did so. Many of the therapists at the centres where the studies were carried out would have been prepared to continue working towards a modified goal of 'safer drinking' with some patients who gave up aiming for total abstinence, and perhaps naltrexone helped here.

Craving appeared to be reduced by naltrexone, and yet abstinence was not enhanced. At first, this appears to be a discrepancy. However, craving may result from heavy drinking as well as being a stimulus to start drinking. Patients taking naltrexone drank less heavily and this could be a partial explanation of why they reported less craving.

In summary, efficacy, as defined in the protocol's primary measures, was not demonstrated in the whole study population. In those patients who complied with medication and attended appointments, naltrexone over a period of 3 months helped patients reduce their alcohol consumption, reduced their perceptions of craving and improved their global recovery as assessed by their physician, and was accompanied by a reduction in serum markers of alcohol consumption.

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