

Comparing and Combining Naltrexone and Acamprosate in Relapse Prevention of Alcoholism

A Double-blind, Placebo-Controlled Study

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Background: Naltrexone and acamprosate have been shown to be effective in relapse prevention of alcoholism via different pharmacologic mechanisms. Since it remains uncertain whether both substances are equally efficient and whether a combination of both drugs potentiates the efficacy, we conducted the first published controlled study comparing and combining both compounds.

Methods: After detoxification, 160 patients with alcoholism participated in a randomized, double-blind, placebo-controlled protocol. Patients received naltrexone, acamprosate, naltrexone plus acamprosate, or placebo for 12 weeks. Patients were assessed weekly by interview, self-report, questionnaires, and laboratory screening. Time to first drink, time to relapse, and the cumulative abstinence time were the primary outcome measures.

Results: Naltrexone, acamprosate, and the combined medication were significantly more effective than placebo. Comparing the course of nonrelapse rates between naltrexone and acamprosate, the naltrexone group showed a tendency for a better outcome regarding time to first drink and time to relapse. The combined medication was most effective with significantly lower relapse rates than placebo and acamprosate but not naltrexone.

Conclusions: The results of this study support the efficacy of pharmacotherapeutic strategies in the relapse prevention of alcoholism. Naltrexone and acamprosate, especially in combination, considerably enhance the potential of relapse prevention.

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ALCOHOL INFLUENCES various neurochemical systems in the central nervous system, such as the dopaminergic, GABAergic, opioid, and glutamatergic systems.¹⁻³ Hence, based on distinct receptor mechanisms, several pharmacologic strategies on relapse prevention and craving reduction have been developed. Two compounds, naltrexone and acamprosate, have repeatedly been investigated in separate paradigms.⁴ These drugs are supposed to influence central nervous systems responsible for the positive reinforcement of alcohol intake. Although the pharmacologic actions of both substances are different and not fully understood, any effective relapse prevention strategy would give rise to great social and socioeconomic benefits.

Naltrexone, an antagonist mainly at the μ -opioid receptor, with additional antagonistic activity at the κ - and σ -opioid receptors, has been approved in the United States and other countries for the relapse prevention treatment of alcoholism. The use

of naltrexone was initially suggested by animal models demonstrating that opioid antagonists reduce alcohol drinking under a variety of conditions.⁵ It was shown that a small dose of an opioid agonist increases motivation to consume more alcohol and to initiate the intake of larger amounts of alcohol to reinstate or increase opioid activity.⁶ Since alcohol intake enhances endogenous opioid activity in the central nervous system, it has been proposed that opioid antagonists such as naltrexone reduce the risk of relapse. Up to now, the results of 10 controlled studies,⁷⁻¹⁶ with a total of approximately 1500 patients, have been published. With the exception of the results of the multicenter trial by Krystal et al,¹⁶ results revealed a superiority of naltrexone to placebo. In previous research, patients receiving naltrexone were less likely to relapse to heavy drinking and to drink fewer days. Meta-analyses by Kranzler and Van Kirk¹⁷ and Streeton and Whelan¹⁸ added additional support for an efficacy of naltrexone on abstinence rates. Consistent with the dose used for opioid addiction, 50 mg/d was shown to be effi-

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cacious. Regarding adverse effects, 15% of patients in a large, open-label safety study (N=570) terminated treatment primarily because of nausea. However, naltrexone treatment did not result in serious adverse events.¹⁹

Acamprosate, a calcium acetyl homotaurinate, is a compound that is available in most European countries and is currently being considered for approval in the United States for the maintenance of abstinence in alcoholic patients who have recently undergone detoxification. Although the precise mechanism of action or cellular targets of acamprosate are still unknown, it seems to involve primarily the restoration of a normal N-methyl-D-aspartate (NMDA) receptor tone in glutamatergic systems.²⁰ It decreases postsynaptic potentials in the neocortex²¹ and diminishes voluntary alcohol intake in alcohol-preferring rats.^{22,23} Littleton²⁴ has proposed that one of acamprosate's actions is suppressing conditioned withdrawal craving by its effects on calcium channels and NMDA receptors. Acamprosate has been investigated in 14 controlled published trials²⁵⁻³⁸ with approximately 4000 patients. Results from 7 other placebo-controlled studies across Europe show similar effects but are yet only available as a general review.³⁹ Acamprosate lengthens time to relapse, reduces drinking days, and increases complete abstinence among alcohol-dependent patients. However, 2 studies^{30,38} showed negative results. In summary, the database is markedly larger for acamprosate than for naltrexone. Acamprosate was generally well tolerated; adverse events tended to be mild and transient, primarily involving the gastrointestinal tract with diarrhea and abdominal discomfort in approximately 10% of patients.⁴⁰ The aim of both compounds is the reduction of alcohol self-administration by attenuating psychoactive effects of alcohol and reducing craving for alcohol. Both compounds do not enhance the toxic effects of alcohol and have no abuse potential. Trials with naltrexone and acamprosate are hardly comparable because of different recruitment strategies, differing duration of treatment, different inclusion and exclusion criteria, and most important, differing outcome measures. Naltrexone trials used mainly announcements for recruitment, loss of control drinking as a relapse criterion, and treatment intervals of 3 months. In contrast, acamprosate studies recruited mainly inpatients from detoxification wards, defined time to any consumption of alcohol as a main outcome criterion, and were applied between 3 and 12 months.

The aim of our study was to determine whether both compounds are equally effective and superior to placebo. In addition, we studied whether a combination of both drugs is more effective than a single therapy or placebo.

METHODS

PARTICIPANTS

Within a 2-year period from November 1, 1998, to November 30, 2000, all patients with alcoholism who were admitted to an inpatient alcohol withdrawal program at the Department of Psychiatry, University Hospital of Hamburg, and Northern Hospital of Hamburg, Hamburg, Germany, were informed about

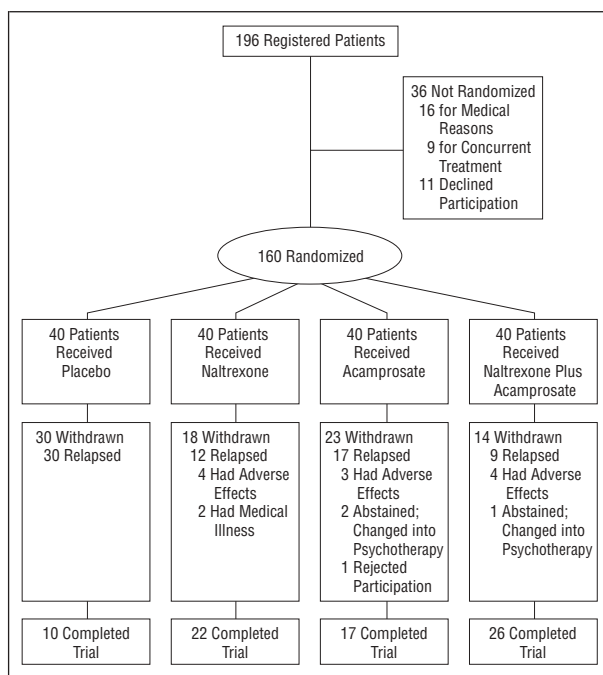


Figure 1. Profile of the randomized controlled trial applying naltrexone, acamprosate, naltrexone plus acamprosate, and placebo to patients with alcoholism. Follow-up lasted 12 weeks.

the study during an obligatory weekly information group. This action reached 782 patients with alcoholism; 196 of them were willing to be informed thoroughly about the details of the study. These patients were screened and given a structured interview for inclusion in the study (F.K., R.H.). Criteria for inclusion were as follows: (1) at least 5 DSM-IV criteria of alcohol dependence, (2) age between 18 and 65 years, (3) body weight of 60 to 90 kg, (4) complete abstinence for 12 to 15 days, (5) free of any withdrawal symptoms, and (6) drug screening test results negative for benzodiazepines, cannabinoids, barbiturates, opiates, cocaine, and amphetamines. Criteria for exclusion were as follows: (1) a current DSM-IV diagnosis of dependence or abuse on other substances except nicotine assessed by the Structured Clinical Interview for DSM-IV, (2) a current mental or psychiatric impairment or disease that required psychotropic medication or inpatient treatment on a psychiatric ward, (3) a history of opioid or cocaine abuse, (4) a history of psychosis, (5) current use of any psychotropic medication, (6) evidence of severe neurologic or physical disorders (eg, cerebral, renal, thyroid, or cardiac disease), (7) a history of cirrhosis or laboratory evidence of significant hepatocellular injury, (8) homelessness, and (9) pregnancy, nursing, or refusal to use a reliable method of birth control in women.

Of 196 participants screened, 16 were excluded for medical reasons, 9 were excluded for reasons of current treatment with psychotropic medication, and 11 declined participation. Thus, a total of 160 patients were randomized to study conditions (**Figure 1**) according to a computer-generated randomization list.

The total sample was primarily male (118 men), unmarried (73%), and employed full time (61%) and had the following characteristics (mean±SD): age, 46.2±9.3 years; number of inpatient detoxification pretreatments, 2.7±4.0; time since first alcohol-related problems, 10.1±8.4 years; and average alcohol consumption before inpatient treatment, 254.9±129.4 g/d (**Table**). The ethics committee of the General Medical Council of Hamburg approved the study, and all participants provided written informed consent. The study was conducted ac-

Baseline Data of the Patient Sample*

Characteristic	Study Group				
	Sample (N = 160)	Placebo (n = 40)	Naltrexone (n = 40)	Acamprosate (n = 40)	Acamprosate Plus Naltrexone (n = 40)
Age, y†	46.2 ± 9.3	45.6 ± 11.1	46.1 ± 8.1	46.3 ± 7.7	46.8 ± 10.3
Sex, M/F†	118/42	27/13	31/9	30/10	30/10
Married, %‡	28	30	25	23	33
Partnership, %‡	51	55	58	48	43
High school, %‡	22	20	25	23	20
Professional training, %‡	78	70	75	80	88
Unemployed, %‡	39	43	53	35	28
Violence delinquency, %‡	5	7.5	5	2.5	5
Alcohol intake, g/d†	254.88 ± 129.40	243.79 ± 143.65	257.56 ± 132.83	275.31 ± 145.70	242.81 ± 92.53
Years since first alcohol-related problems occurred†	10.14 ± 8.40	9.19 ± 7.90	11.36 ± 8.22	11.74 ± 9.27	8.31 ± 7.98
Years since first signs of withdrawal occurred‡	7.42 ± 8.09	4.90 ± 6.00	8.31 ± 8.24	9.47 ± 10.30	7.08 ± 6.72
No. of inpatient detoxifications‡	2.69 ± 4.03	2.85 ± 3.91	3.88 ± 5.86	2.18 ± 2.50	1.79 ± 2.63
Attendance at self-help groups during the last month, %‡	23.8	22.5	27.5	27.5	17.5
Intensity of withdrawal on a scale of 1-4‡	1.6 ± 2.0	1.5 ± 1.1	1.7 ± 2.0	1.7 ± 1.2	1.6 ± 0.8
Family history positive for alcoholism, %‡	45.0	42.5	40.0	47.5	50.0
No. of cigarettes per day‡	22.7 ± 15.4	20.4 ± 12.9	24.4 ± 15.8	23.7 ± 17.8	22.3 ± 14.9
SCL-90 score‡	61.3 ± 51.8	65.8 ± 54.1	61.9 ± 51.2	66.8 ± 49.2	50.6 ± 52.8
Craving (OCDS score)‡	17.6 ± 12.0	18.2 ± 12.1	17.9 ± 13.2	20.1 ± 10.6	14.1 ± 11.8
Mean craving (VAS score)‡	21.2 ± 27.3	23.7 ± 26.7	18.6 ± 27.7	23.6 ± 28.0	17.9 ± 27.7
MCV, fL‡	96.0 ± 6.3	96.6 ± 6.3	95.6 ± 4.4	97.5 ± 6.2	94.6 ± 7.7
GGT, U/L†	114.7 ± 170.2	117.9 ± 205.9	93.3 ± 132.9	162.0 ± 200.0	90.2 ± 131.3
CDT, %‡	5.7 ± 2.01	5.8 ± 2.68	5.0 ± 1.4	5.9 ± 1.4	5.9 ± 2.2

Abbreviations: CDT, carbohydrate-deficient transferrin; GGT, γ -glutamyltransferase; MCV, mean corpuscular volume; OCDS, Obsessive Compulsive Drinking Scale; SCL-90, Hopkins Symptom Checklist-90; and VAS, visual analog scale.

*Values given as mean ± SD unless otherwise indicated.

†Variables that were included as covariates in the multivariate analyses of covariance.

‡Variables without significant differences among groups.

cording to the European Good Clinical Practice Guidelines and the Declaration of Helsinki.

MEDICATION

The 160 patients received in a randomized, double-blind design naltrexone, acamprosate, naltrexone plus acamprosate, or placebo. Each treatment group had a same sample size of 40 patients. Dosages were 50 mg/d (1 capsule in the morning) for naltrexone and 1998 mg/d (2 tablets 3 times daily) for acamprosate. For each treatment group, the medication was constant throughout 12 weeks. The dosages were chosen to be consistent with prior studies and amounted to standard dosages used for subjects with a body weight of 60 kg or more. Medication was given in a double-dummy design. Original naltrexone tablets were capsuled and identical placebo capsules produced; acamprosate placebo tablets were reproduced with identical appearance of the original medication (M.B.). Allocation codes were provided in sealed envelopes for each patient at the pharmacy of the University Hospital of Hamburg, where formulation and blinding was conducted. The randomization was organized by a computer-generated list (M.B.). The medication was counted and prescribed for 14 days for each patient. At the next scheduled assessment, the unused medication was collected and counted to evaluate compliance.

The use of any concomitant psychotropic medication (antidepressants, neuroleptics, benzodiazepines, barbiturates) was not permitted. Patients started taking the medication a mean ± SD of 5 ± 1 days before discharge from inpatient treatment.

PSYCHOTHERAPY

The group therapy was conducted weekly, was abstinence oriented, and included coping skills and relapse prevention based on the cognitive behavioral model of substance abuse.⁴¹ Groups had between 8 and 14 participants, and sessions lasted 90 minutes. Patients learned to identify and handle situations that place them at high risk for the resumption of drinking. The main components of the program were as follows: screening of the week before for thoughts on alcohol intake or subjective feelings of craving, intending to identify alcohol-associated stimuli and high-risk situations, and anticipating risk situations in the week after to prepare coping strategies. If the patient used alcohol, this was addressed nonjudgmentally, and the patient was encouraged to resume abstinence. Two psychotherapy-trained psychiatrists (F.K., P.B.) and 2 cotherapists (H.H., T.T.) moderated the group.

PSYCHOPATHOLOGIC ASSESSMENTS

Patients were assessed before treatment, including a physical examination (baseline); weekly thereafter during the 12-week treatment phase; and at termination of treatment. At baseline, extensive data were collected, including information about history of addiction and sociodemographic data concerning family, social, psychological, medical, and legal problems. Drinking behavior for the 30 days before entering the detoxification ward and motivational factors for alcohol intake were assessed. Diagnosis of substance abuse and dependence was made

according to *DSM-IV*. Alcohol craving (as measured by the Obsessive Compulsive Drinking Scale [OCDS]^{42,43}) and psychopathologic symptoms (as measured by the Hopkins Symptom Checklist-90 [SCL-90]⁴⁴) were assessed at baseline. Patients were asked to complete daily a structured drinking diary recording exactly the sort and the amount of alcohol intake. Before each meeting, participants were asked to report if any alcohol was consumed, and the drinking diary was controlled for its completeness. Thereafter, an investigator (H.J.) transferred this information into standard drinks. With the help of the therapists, patients completed an adverse effect checklist, rating each adverse effect for its presumed association with the study medication. Individual symptoms were clustered in 7 categories: gastrointestinal, dermatologic, muscular, neurologic or psychological, genitourinary or sexual, sleep or activation, and others. Patients were asked about attendance at self-help groups or any other additional treatment.

Participants' self-rated craving (OCDS) was assessed each week, and the SCL-90 was used additionally at weeks 4, 8, and 12. After termination of the medication, patients were asked what kind of medication they thought they had received.

CLINICAL CHEMISTRY MEASURES

Blood was drawn at baseline and at weeks 4, 8, and 12 to assess erythrocyte, total white blood cell, and platelet counts; packed red blood cell volume; hemoglobin and prothrombin concentrations; and serum concentration of sodium, potassium, chloride, calcium, phosphate, urea, creatinine, blood glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, cholesterol, triglycerides, and albumin. Additionally, mean corpuscular volume (MCV), γ -glutamyltransferase (GGT), and carbohydrate-deficient transferrin (CDT; Roche Diagnostics, Mannheim, Germany) values were measured to gain additional data on possible relapse. Breath alcohol concentrations and urinary drug screens were randomly registered (3 to 4 times for each patient during treatment).

OUTCOME ASSESSMENT

Data on drinking outcome were collected independently. At each assessment, the patient was classified by the therapist as abstinent or relapsed according to his or her self-report. If there was any hint of nonabstinence (eg, a patient skipping a visit), the patient, a collateral, or the general practitioner was contacted to obtain information about drinking behavior and any attempted returns to the treatment program. Depending on the course of illness, collaterals and general practitioners were contacted between 2 and 5 times during the study by 3 of the authors (F.K., T.T., H.H.) (minimum at onset and after dropout). Drinking diary, laboratory measures, and interviews of collaterals were compared for consistency and were used to justify abstinence, lapses, and relapses (D.N., K.W.). For the patient to be considered abstinent, these criteria had to be concordant. If not, patients were deemed not to be abstinent. Patients who missed a visit but attended the next one were able to continue the study if they took their coded medication and were able to return abstinent to the community within 1 week. The study was also continued for patients who had a *lapse* (ie, the first alcohol intake) but who did not *relapse*, which was defined as 5 or more drinks per day for men and 4 or more drinks per day for women or at least 5 drinking days per week according to the criteria of Volpicelli et al.⁷ Patients who relapsed were removed from the study and had the opportunity to participate in an ambulant setting without study conditions. In these cases, all assessments were discontinued as well.

STATISTICAL ANALYSIS

Baseline characteristics, except for those considered in the analysis of covariance described herein, were compared among groups using a multivariate analysis of variance for continuous variables and the χ^2 test for categorical variables. The main efficacy analysis was performed on an intent-to-treat basis. Survival analyses (ie, the life table method of Kaplan and Meier and the Breslow test) were applied to receive the time-dependent survival (unrelapse) probabilities of the treatment groups and to compare their courses. Survival analyses were also applied for lapses. The possibility of later improvement during the treatment period was ignored in the analyses.

In addition to the survival analyses, multivariate analyses of covariance (MANCOVAs) with the time to the various events and the cumulative abstinence (ie, the total number of days of abstinence) as dependent variables, group as the independent variable (between-subjects influence factor), and sex, age, GGT level, duration of addiction, and amount of alcohol consumed daily as covariates were performed first to test the significance of the group effect of the periods and second to clear it of possible influences of the aforementioned covariates. Although in the survival analyses the 17 participants who dropped out and were abstinent (Figure 1) were considered as censored; in the analyses of variance and covariance, they were excluded. When significant group effects were found in MANCOVA, univariate F tests followed to identify those variables that contributed significantly to the effects. For those variables, tests with contrasts were additionally performed to locate the group pairs with significant differences in the means of those variables. An α level of .05 was accepted as a nominal level of significance (type I error). Multivariate analyses of variance of the total sample were applied to compare the medication groups with regard to the craving scores obtained by the OCDS and visual analog scale (VAS). All post hoc tests (univariate F tests and tests with contrasts) were performed at a reduced level of significance (Bonferroni corrected level) to keep the type I error to less than or equal to .05. All analyses were 2-tailed, with significance levels at $P < .05$. Using a completely randomized design for the study, an α level of .05, and sample sizes equal to 40, for each group the power of the study (ie, the probability of rejecting the zero hypotheses when they are false) is more than 0.98 for medium and 0.99 for large effect sizes.

RESULTS

SOCIODEMOGRAPHIC DATA

After unblinding the randomization code, in view of sociodemographic characteristics and alcohol-related baseline data, treatment groups were homogeneous. No differences among the 4 groups emerged for the indicated variables (Table). No baseline testing was performed for the variables sex, age, GGT level, duration of addiction, and the amount of alcohol consumed daily, since these variables had been selected before the analysis as covariates of the MANCOVA. Results are presented as mean \pm SD.

PRIMARY OUTCOME

Concerning drinking outcome, we obtained the following results: 75 (46.9%) of the 160 randomized patients completed the 3-month, double-blind treatment abstinent, 17 (10.6%) were abstinent at the time they dropped, and 68 (42.5%) relapsed. Eleven participants

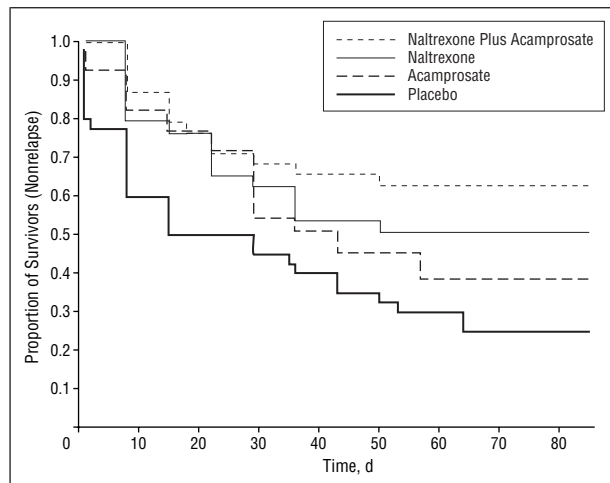


Figure 2. Curves of the survival probabilities toward the event “relapse” for each of the treatment groups (Breslow test: $t_3=13.87$, $P=.003$). Significant differences emerged between naltrexone and placebo ($P=.02$), between acamprosate and placebo ($P=.05$), and between the combined medication and placebo ($P=.008$). In addition, the combined medication was more effective than acamprosate ($P=.04$).

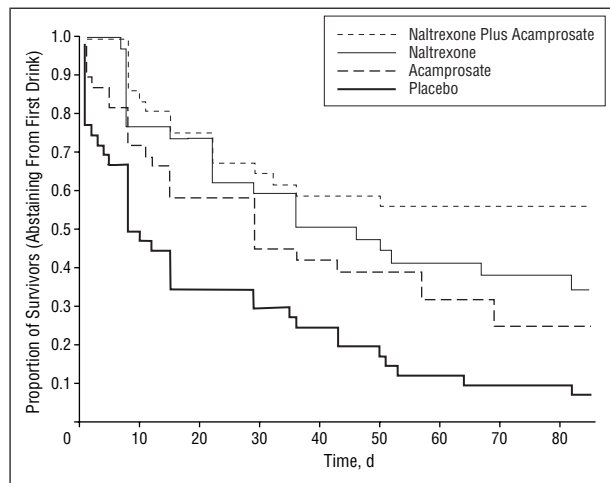


Figure 3. Curves of the survival probabilities toward the event “first alcohol intake” (lapse) for each of the treatment groups (Breslow test: $t_3=29.25$, $P<.001$). Significant differences emerged between naltrexone and placebo ($P=.03$), between acamprosate and placebo ($P=.04$), and between the combined medication and placebo ($P=.002$). In addition, the combined medication was significantly more effective than acamprosate ($P=.04$).

withdrew their consent because of intolerable physical disabilities interpreted as adverse effects, 3 participants withdrew consent to attend an inpatient psychotherapeutic program, and 1 withdrew consent without giving any reason. Two participants were withdrawn from the study because of additional medical illness, 1 with acute depression and 1 with an indication for surgery (Figure 1).

SURVIVAL ANALYSES TOWARD RELAPSES AND LAPSES

Survival analyses were completed examining the courses of the nonrelapse rates to heavy drinking for the 4 treatment groups (**Figure 2**). The differences among the groups were statistically significant (Breslow test:

$t_3=13.87$, $P=.003$). Significant differences emerged between naltrexone and placebo (Breslow test, $P=.02$), between acamprosate and placebo (Breslow test, $P=.05$), and between the combined medication and placebo (Breslow test, $P=.008$). There was no significant difference in the course of nonrelapse rates between naltrexone and acamprosate. However, the combined medication was more effective than acamprosate ($P=.04$) but not than naltrexone.

Application of survival analyses on the lapse events (ie, first alcohol intake) also revealed statistically significant differences among the treatment groups (Breslow test: $t_3=29.25$, $P<.001$; **Figure 3**). Significant differences emerged between naltrexone and placebo (Breslow test, $P=.03$), between acamprosate and placebo (Breslow test, $P=.04$), and between the combined medication and placebo (Breslow test, $P=.002$). There was no significant difference in time to first drink between naltrexone and acamprosate. The combined medication was significantly more effective than acamprosate (Breslow test, $P=.04$) but not than naltrexone.

GROUP COMPARISONS IN THE 3 PRIMARY OUTCOME VARIABLES CONTROLLED OVER SOME COVARIATES

Performing a MANCOVA with the time to lapses, time to relapses, and the total number of abstinent days as dependent variables, we found a significant treatment effect (Wilks multivariate test of significance; effect of treatment: $F_{9,284}=2.51$, $P=.009$) attributed to all dependent variables (univariate F test, $P<.05$). There was also a significant effect of the covariates of the groups ($F_{9,284}=2.11$, $P=.03$) caused mostly by the covariate age. Pairwise testing of the group differences in the dependent variables showed that the combined therapy differed significantly from placebo (test with contrast, $P=.02$) and the acamprosate therapy (test with contrast, $P=.05$).

CRAVING

There was a marginal significant difference among the medication groups on the OCDS and VAS craving measures (average, maximum, and frequencies) comparing mean craving during treatment (Wilks multivariate test of significance; effect of group: $F_{18,257}=1.61$, $P=.05$), attributed to the differences in the VAS maximum scores, which were lower during the study in the combined medicated group than in the placebo group (**Figure 4**). Baseline craving (OCDS and VAS) was significantly higher than craving during treatment independent of the treatment modality (Wilks multivariate test of significance; effect of treatment: $F_{2,111}=111.39$, $P<.001$).

SAFETY AND TOLERABILITY

No serious medical adverse drug experiences were reported. Eleven participants stopped treatment prematurely because of adverse events (Figure 1). One complained of fatigue, 1 of a rash, 1 of itching, 2 of abdominal bloating, 1 of diarrhea, 2 of pruritus, and 3 of nausea. The 4 treatment strategies showed no reasonable differ-

ences between the single evaluated adverse effects (7 clusters), with the exception of diarrhea (placebo, 6.7%; naltrexone, 0.6%; acamprosate, 6.7%; combined medication, 13.8%) and nausea (placebo, 0.4%; naltrexone, 2.5%; acamprosate, 0.6%; combined medication, 5.6%), which seemed to receive higher values under the combined medication. The SCL-90 scores decreased significantly during the study without significant group effects (week 12: placebo, 28.1 ± 27.4 ; naltrexone, 39.0 ± 38.2 ; acamprosate, 34.0 ± 36.4 ; combined medication, 23.9 ± 29.9).

LABORATORY PARAMETERS AND COMPLIANCE

Final GGT values at week 12 were significantly decreased compared with baseline, with no significant differences across treatment groups (placebo, 30.9 ± 44.0 U/L; naltrexone, 11.5 ± 5.3 U/L; acamprosate, 21.2 ± 13.6 U/L; combined medication, 22.2 ± 28.0 U/L). The CDT values and MCV also did not differ among groups. Also, the last available GGT value during treatment before drop-out revealed no significant differences (placebo, 32.4 ± 33.9 U/L; naltrexone, 12.7 ± 8.1 U/L; acamprosate, 21.0 ± 9.7 U/L; combined medication, 15.1 ± 11.0 U/L). Medication compliance was similar across treatment groups, with an overall mean rate of 81.1% based on returned capsule or tablet count. Urinary drug screens for illicit drugs showed no positive results. Of the 68 patients counted as having relapsed, 61 primarily discontinued participation. Contact with patient collaterals confirmed that the patients had relapsed. However, 7 of 68 patients were withdrawn from the study, since elevated levels of CDT, GGT, or MCV were suggestive of a relapse. In these cases, the participant was confronted with this information and a collateral was asked for the drinking behavior of the participant. We had no case of increases in CDT, GGT, and MCV values without positive drinking information.

Regarding compliance, there were no differences in attendance among the groups (89.7% mean attendance until dropout). After completion of the study, patients were asked for the identity of the double-blind treatment to test the integrity of the double-blind administration. A total of 34% guessed having received placebo, 34% guessed receiving real medication, 30% stated having no idea what they received, and 2% of answers were missing. There was no significant association between patient's guess and the identity of the given medication.

COMMENT

Relapse prevention treatment with both naltrexone and acamprosate was superior to placebo, with a tendency for a better outcome in the naltrexone group compared with the acamprosate group in maintenance of abstinence. Additionally, we observed a significant superiority of the combination of both compounds in relation to acamprosate monotherapy and placebo. Relapse rates of approximately 43% during anticraving monotherapy in our study and lapse rates of approximately 68% are comparable with recent naltrexone and acamprosate studies. O'Malley and colleagues⁸ found that approximately 50% of patients treated with naltrexone and coping skills relapsed to heavy drinking within 12 weeks, whereas

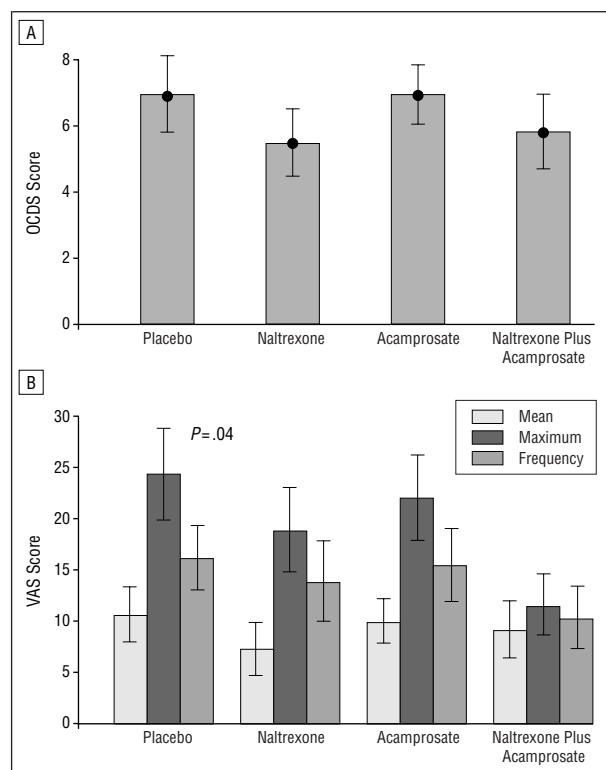


Figure 4. Mean craving during treatment according to the treatment groups. A, Craving assessed with the Obsessive Compulsive Drinking Scale (OCDS). B, Craving assessed with visual analog scales (VASs) concerning mean and maximum cravings and frequency. Error bars indicate SEM ($P < .05$). There was a significant difference comparing maximum craving between placebo and combined treatment ($P = .04$).

Whitworth et al³¹ found that with acamprosate treatment approximately 60% lapsed between weeks 1 and 12. Conservative outcome definitions were used in our trial: nonattending patients were classified as treatment failures. This might lead to an overestimation of relapses but might reflect the course of alcohol dependence.⁴⁵

Although up to now no controlled study directly compared the efficacy of both anticraving drugs, efforts to this matter have been made by meta-analyses of controlled single-drug trials^{17,46} and by a recently conducted open study with a better outcome in the naltrexone group.⁴⁷

In our sample, the combined medicated group had a relapse rate of nearly 25%, which is much lower than in most comparable trials. Although a recent preclinical study showed no additive effect of a combined treatment with naltrexone and acamprosate on alcohol intake in rats,⁴⁸ our data imply that both compounds seem to act additively, improving drinking outcome in a clinical sample. Since no serious adverse effects occurred during combined treatment, this treatment seems to be a highly effective and safe therapeutic strategy in relapse prevention of alcoholism.

Although previous studies found naltrexone to be mainly effective in nonabstinent patients with alcoholism,^{7,49} our results concerning time to first drink show that naltrexone also exerts its effects during controlled abstinence and independent of alcohol consumption. This

might support the hypothesis that alcohol-associated stimuli lose their reinforcing property with naltrexone treatment.^{50,51} Cues associated with drinking are known to act like a priming dose of alcohol and to elicit an appetitive motivational response through conditioned endogenous opioid release. This response in anticipation or actual receipt of alcohol is effectively blocked by naltrexone. In line with the early results of the study by O'Malley et al,⁸ our results show that naltrexone works in maintaining abstinence and, moreover, seems to be superior to acamprosate. Anton et al⁹ also added support to the hypothesis that naltrexone might be efficacious in the maintenance of abstinence, and moreover, this hypothesis was reinforced by the results of the meta-analyses by Kranzler and Van Kirk¹⁷ and Streeton and Whelan.¹⁸ Craving as one possible target of drug effects plays a crucial role in understanding pharmacologic relapse prevention in patients with alcoholism. However, the relationship between craving and relapse has not been definitively elucidated,⁵² and results concerning anti-craving compounds and self-rated craving are inconsistent. We found an inverse relation of craving during treatment and abstinence times. Regarding the different treatment groups, we detected a significant reduction of mean craving in the combined medicated group and a tendency to reduce craving in the naltrexone group compared with placebo.

The mechanisms of action of anticraving drugs are poorly understood, and the literature rarely gives hypotheses for predictability of treatment response. Based on the neurobehavioral model by Anton et al,⁵³ a 3-dimensional psychobiological model of craving was proposed.⁵⁴ Following this, the reward craving results from either opioidergic or dopaminergic dysregulation, with a high sensitivity to rewarding events. Relief craving with the desire for the reduction of tension was thought to result from a glutamatergic or GABAergic dysregulation, and obsessive craving was defined as lack of control of intrusive thoughts about drinking, resulting from a serotonin deficiency. Hence, it was hypothesized that naltrexone most likely reduces reward craving, whereas acamprosate decreases relief craving. Such a dimensional model might have the potential to relate treatment interventions with specific drug effects to distinct neurobiological dysfunctions. In our study, most patients described both "reward" and "relief" as important motivational factors for their alcohol intake. Hence, further studies are warranted on the basis of more specific identification of these distinct subgroups. The enhanced efficacy of the combined treatment might already result from tackling both alterations.

Because of the recruitment strategy, our sample is homogeneous and representative regarding baseline data and not biased by inclusion in the study. A sample of 279 patients who denied further information about the study did not show any differences in drinking behavior or sociodemographic data (R.H., unpublished data, June 28, 2000). One shortcoming of the study might eventually be the limited duration of treatment. However, survival analyses of our data show main effects during weeks 1 to 8 and a steady state of relapse rates during the third month. The optimal duration of treatment with either nal-

trexone or acamprosate remains to be determined. Additionally, the effect of beginning pharmacotherapy in an inpatient setting remains unexplored, since the opportunity to drink is limited during inpatient treatment. One might speculate whether the treatment in patients without a sustained period of abstinence might lead to comparable results, since Chick et al¹⁰ found acamprosate not to be efficacious in a sample of patients with alcoholism without continuous abstinence. Another problem might derive from the interpretation of the interactions of pharmacotherapy with psychotherapy, since there is evidence that psychotherapy may reinforce the effects of medication.⁵⁵ All patients of our study received behavioral therapy. The skills to avoid or cope with drinking triggers learned in therapy may have contributed to the reduction of drinking and self-reported craving severity across treatment groups. Certainly, further research is needed concerning the interactions between psychosocial interventions and pharmacotherapy.

Our results surmise the notion that pharmacotherapy effectively supports abstinence therapies. Both naltrexone and acamprosate are superior to placebo. By combining both drugs, a considerably enhanced efficacy can be achieved. Further studies are necessary to identify those patients who respond favorably to the distinct pharmacotherapeutical interventions.

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