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A RANDOMIZED, MULTICENTRE, OPEN-LABEL, COMPARATIVE TRIAL OF DISULFIRAM, NALTREXONE AND ACAMPROSATE IN THE TREATMENT OF ALCOHOL DEPENDENCE

E. LAAKSONEN[1], A. KOSKI-JÄNNES,[4] M. SALASPURO,[2,3] H. AHTINEN,[5] and HANNU ALHO[2,3]*

[1]University of Turku and Turku Health Centre
[2]National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki
[3]Research Unit of Substance Abuse Medicine, Helsinki University
[4]Department of Sociology and Social Psychology, University of Tampere, Finland
[5]Medikalla Oy, Medfiles, Turku, Finland

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Abstract — Aim: To compare the effects in alcohol-dependent patients of three pharmacotherapies, disulfiram (DIS), naltrexone (NTX), and acamprosate (ACA), when used with a brief manual-based cognitive-behavioural intervention. **Method:** We conducted a randomized, open label, multicentre naturalistic study in two phases; first, a 12-week continuously supervised medication, followed by targeted medication (TM) up to 52 weeks in addition to a 67-week follow-up period; altogether 119 weeks (2.5 years), in 243 voluntary treatment-seeking alcohol-dependent adult outpatients. Subjects were randomized 1:1:1 to receive supervised NTX, ACA or DIS, 50, 1998, or 200 mg, respectively, per day, plus a brief manual-based cognitive-behavioural intervention. The patients were met in the second and sixth weeks, and then after 3, 6, and 12 months. The primary outcome measures were the time (days) to first heavy drinking day (HDD), and time during the first 3 months to the first drinking day after medication started. Secondary variables were abstinent days/week (0 drinks/day), average weekly alcohol intake, Alcohol Use Disorder Identification Test (AUDIT), Severity of Alcohol Dependence Data (SADD), and quality of life (QL) measures. **Results:** All three study groups showed marked reduction in drinking, from baseline to the end of the study. During the continuous medication phase, treatment with DIS was more effective in reducing HDDs and average weekly alcohol consumption, and increasing time to the first drink, as well as the number of abstinent days. During the TM period, there were no significant differences between the groups in time to first HDD and days to first drinking, but the abstinence days were significantly more frequent in the DIS group than ACA and NTX. There were no differences between the NTX and ACA groups in either phase of the study of drinking outcomes. However, SADD scores improved more in the NTX group than the ACA group. **Conclusions:** Patients allocated to ACA, NTX and DIS combined with brief manual-based cognitive behavioural intervention significantly reduce their alcohol consumption and report improved QL. Supervised DIS appeared superior, especially during the continuous medication period, to NTX and ACA.

INTRODUCTION

According to several systematic reviews and meta-analyses, the effectiveness of psychosocial treatment of alcohol dependence can be significantly improved by some pharmacological agents (Garbutt *et al*., 1999; Kranzler and Van Kirk, 2001; Srisurapanont and Jarusuraisin, 2002; Berglund *et al*., 2003; Bouza *et al*., 2004). These include supervised administration of an aldehyde dehydrogenase inhibitor disulfiram (DIS), the opioid antagonist naltrexone (NTX), and the noncompetitive N-methyl-D-aspartate (NMDA)-receptor blocker acamprosate (ACA). However, only a few controlled studies have compared the effectiveness of these pharmacotherapies with each other (Anton *et al*., 1999; von Bardeleben *et al*., 1999; Kiefer *et al*., 2003).

Psychotherapy is an important part of successful treatment, but randomized trials have only rarely been able to pinpoint the form of intervention which is most effective in combination with pharmacotherapy (Anton *et al*., 1999; Chick *et al*., 2000; Berglund *et al*., 2003; Morley *et al*., 2006). The interpretation of the treatment results is also hampered by the fact that the various pharmacological treatments have seldom been based on structured manuals for comprehensive treatment. There is, however, some evidence suggesting that, for instance, NTX medication should be combined with cognitive behavioural or coping skills therapy (O'Malley *et al*., 1996; Heinala *et al*., 2001).

The aim of this randomized study was to compare the effectiveness of NTX, ACA and DIS in the treatment of alcohol dependence when combined with structured psychological intervention based on specific manuals. Accordingly, the study had two objectives: (i) to develop three different manuals with treatment aims matching the medication, and (ii) to compare the effectiveness of these pharmacotherapies used in conjunction with these structured interventions.

METHODS

Study participants

The study subjects screened were men and women aged 25–65 years, who were voluntarily seeking outpatient treatment for alcohol problems at three different A-clinics in Helsinki, Tampere, and Turku, and three different occupational and health care units, two in Turku and one in Naantali from 2000 to 2005. Patients with a history of heavy drinking, and who accepted the study protocol, were recommended for screening. For inclusion, the patients had to meet the criteria of alcohol dependence (ICD-10). Detoxification was not required and at least 1 month had to have elapsed since the last date of that treatment. The exclusion criteria were clinically significant symptoms of alcohol withdrawal, significant recently diagnosed psychiatric disease (psychosis, personality

*Author to whom correspondence should be addressed at: National Public Health Institute, Department of Mental Health and Alcohol Research, 00251 Helsinki, Finland. Tel: +358-9-47448123; Fax: +358-9-47448133;
E-mail: hannu.alho@ktl.fi

disorder, or suicidal tendency that appeared during the initial interview), current psychiatric disease demanding special treatment or medication including DSM-IV-determined drug dependence other than alcohol or nicotine dependence, current use of any opioids within the 4 weeks before screening, significant brain, thyroid, kidney disease, uncompensated heart disease, clinically significant liver disease (cirrhosis, alcoholic hepatitis or alanine transaminase (ALAT) >200), pregnancy, nursing, or women who refused to use a reliable birth control method.

Ethics

The study protocol, written information for subjects, and consent form were approved by the independent Helsinki and Uusimaa Hospital District Ethical Committee (# 23.2.2000), the Turku Health Care Organization Ethical Committee of (DNO 6-2000), and the Finnish National Medical Agency of (KL# 052/2000). The study was conducted according to the principles of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice and the 1964 Helsinki Declaration. The study was registered at the National Public Health study registry (# KTL-175-1) and clinicalTrials.gov (#NCT00435435). All subjects had to be able to read and understand the patient information sheet and sign the informed consent. All participants were free to finish the study medication whenever they wanted, and were not paid or reimbursed for their participation.

Study protocol and design

Study enrollment began in September 2000 and the last subject completed the study in April 2005. The study lasted for 52 weeks and the patients were contacted, on average, 67 weeks after study completion (follow-up), altogether 119 weeks (2.5 years). One doctor screened, enrolled, and treated all subjects at each study centre. After providing written consent, subjects underwent screening procedures including the recording of demographic and medical history, physical examination, ALAT and gamma-glutamyltransferase (GGT) analyses were performed by the independently accredited VITA-Health Services Ltd, Helsinki, Finland). A set of questionnaires including Severity of Alcohol Dependence Data (SADD) (Davidson and Raistrick, 1986), European Quality of Life (EQ-5) (EuroQol Group, 1990), the Koskenvuo Quality of Life Scale (KQL) (Koskenvuo, 1979), the Visual Analogue Scale (VAS) (Scott and Huskisson, 1976) on the quality of life (QL) and the Alcohol Use Disorder Identification Test (AUDIT) (Saunders *et al*., 1993) were filled in by each subject. The quantity of alcohol consumption and the use of study medication during the preceding 52 weeks were assessed by a retrospective drinking diary (Poikolainen and Karkkainen, 1983).

All patients meeting the inclusion criteria were randomly assigned by an independent person in a 1:1:1 ratio ($N = 81 + 81 + 81$) to ACA, DIS or NTX groups by using random permuted blocks (Vassar Statistic randomizing algorithm). The study medications were purchased from medical companies: DIS, Antabus, from Dumex-Alpharma, NTX, ReVia, from Bristol-Myers Squibb, and ACA, Campral, from Merck. Eligible subjects were randomly allocated to receive either 50 mg of NTX once a day, 666 mg of ACA three times a day (1998 mg/day, or if the patient's weight was less than 60 kg, then 1333 mg/day), or 100–200 mg of DIS once a day or 2 tablets (400 mg) twice a week. The DIS dose for each patient was decided by the study doctor basing on body weight, patient's earlier experience with DIS medication (any adverse events) and/or patient logistics (i.e. not possible for daily supervised dosing); the dosing was for 17 patients with 100 mg, and 16 patients with 200 mg daily, and for 27 patients with 400 mg twice a week. All patients were requested to provide the name of a person responsible for supervising the intake of the study medication, which was not being supervised by the study doctor or the clinic staff. The daily pharmacotherapy was to continue uninterrupted for the first 3 months (12 weeks). During weeks 13–52 targeted medication period, (TM), patients were to take the medication (daily dose) in a 'craving situation', that is, when patients perceived that their propensity to drink was high. During the follow-up period patients could continue their individual medication in a craving situation, but this medication was no longer provided without charge by the study centre. The psychosocial part of the intervention was based on cognitive behavioural principles in all groups. Treatments were aimed at matching the medications used, which were reduction of heavy drinking, or abstinence with ACA and NTX, and total abstinence with DIS. Preventing relapse was regarded as important in all of these. On the first visit, patients received a booklet that they were instructed to follow during the study. The booklet contained motivational components based on self-assessment and goal-setting as well as relapse prevention, life-style change and problem-solving components aimed at maintaining the change over the longer run. These components and assignments were discussed at each of the four initial visits with the doctor. The title of the booklet was 'Winning at last—defeating the drinking problem'. Even though three separate manuals, one for each medication, were used in the study, these have been compressed into one English language manual with three alternative medications (http://alcalc.oxfordjournals.org).

During the 52-week treatment period, the subjects were asked to return a diary on their alcohol consumption and use of medication to the study centre at weeks 2, 6, 12, 26 and 52. At each study visit, medication intake, alcohol use (standard drink of 12 g), and other information since the previous visit were recorded in the drinking diary, AUDIT (0, 12, 26 and 52 weeks), SADD (0, 6, 12, 26 and 52 weeks), EQ-5, KQL and VAS (0, 12 and 52 weeks). During the follow-up period, the patients were advised to continue the drinking diary. Any possible adverse events were elicited at each visit and recorded by patients in the drinking diary. Clinical laboratory tests (ALAT, GGT) were repeated at weeks 0, 6 and 52.

At the end of the follow-up period (week 119) patients received a set of questionnaires by mail (AUDIT, SADD, EQ-5, KQL and VAS) and an opportunity to visit the study doctor and laboratory was offered.

Patients were free to attend alternative facilities such as Alcoholics Anonymous or other support groups. Relapse did not lead to the exclusion of the patient from the treatment. When necessary, the patient was directed to detoxification.

Outcome measures

The primary outcome measures were the time (days) to the first heavy drinking day (HDD) during the first 3 months, and the time of the first drinking day after medication started. The secondary variables were abstinent days/week (0 drinks/day) and average weekly alcohol intake, AUDIT, SADD and QL measures. A HDD was defined as a day with consumption of five or more drinks for men and four drinks for women, or being intoxicated during the study visit. An abstinence day was defined as a day with no drinks. A standard drink was defined as approximately 12 grams of absolute alcohol (one standard bottle of beer (350 cl) in Finland, one standard glass of wine (12 cl), or a shot of strong liquor (4 cl)).

Statistical analysis

All primary and secondary outcome statistical analyses were performed by an independent source (Medikalla Oy, Medfiles, Turku). Intent-to-treat populations, (ITT) which included all randomized patients, were used in all tables and analyses of primary outcomes. In the ITT populations, the missing data were accepted and no imputations were done with this population. Abstinence days (0 drinks/day), average alcohol intake/week, AUDIT, SADD, QL and laboratory variables (GGT, ALAT) were analysed using a per-protocol analysis that included all the patients who completed the study.

Descriptive statistics were calculated for all variables. Categorical variables were listed in frequency tables (PROG FREQ in SAS) (number of cases and percentages) by treatment. The numerical variables were tabulated by treatment (PROG UNIVARIATE in SAS).

Baseline variables were analysed by logistic regression or analysis of variance (ANOVA). Primary outcome measures: (i) Time (days) to first HDD after medication started (during the first 3 months) and (ii) Time of the first HDD after beginning the medication (during the first 3 months) were analysed with the Kaplan–Meier curves and Log-rank (PROG LIFETEST).

Secondary outcome measures: (i) Abstinence days (0 drink/day) by group, and (ii) Average alcohol intake (weekly by group). Abstinence days (0 drinks/day) by group, and average alcohol intake, weekly by group, were both subjected to ANOVA for repeated measures when treatment and the time were in the model (PROC MIXED). All statistical evaluations utilized the SAS procedures in SAS system for Windows (Version 8.2).

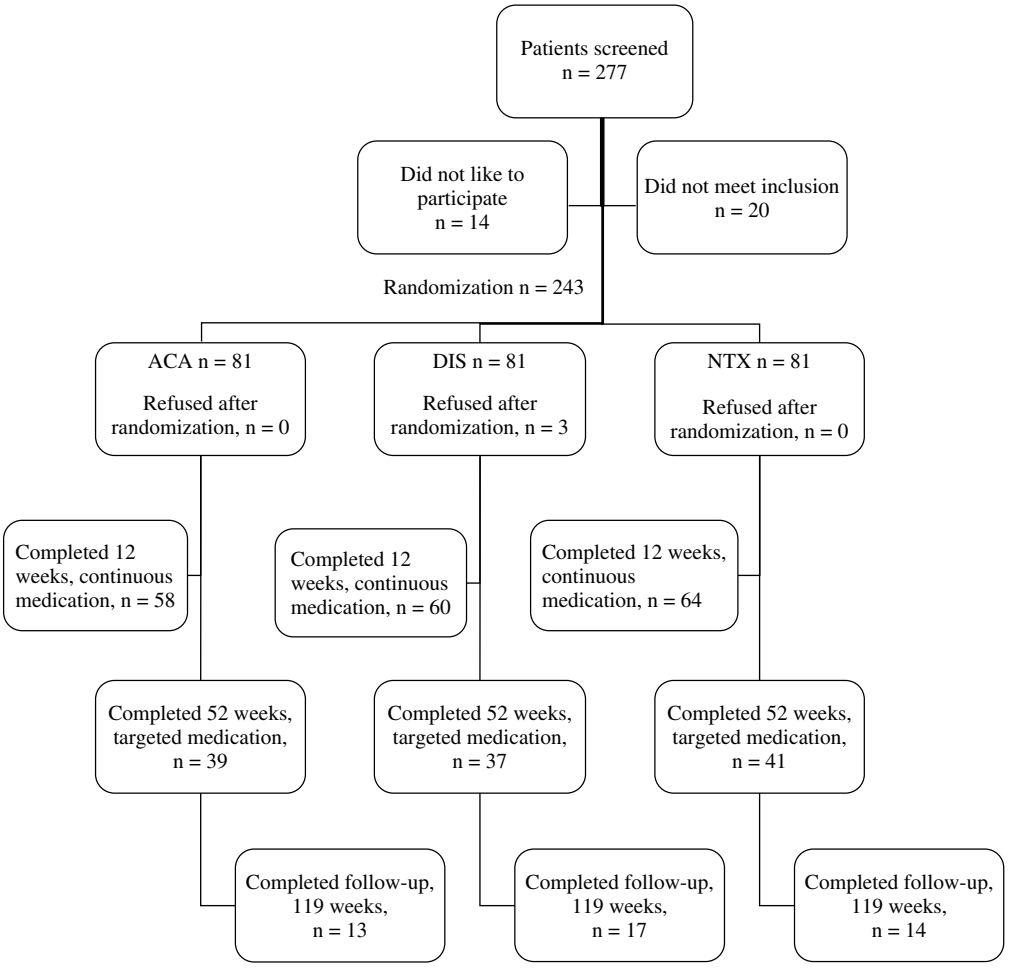

Fig. 1. Consort flow chart, recruitment, randomization and retention in study. Patients completing 80% of the per-protocol tasks (visit, survey and laboratory) are considered compliers.

RESULTS

Subject disposition

Two hundred and seventy-seven subjects were initially screened for the study; 14 subjects refused to participate, 20 did not meet the inclusion criteria, and 243 subjects entered the study. Three patients in the DIS group refused to continue the study and were considered as drop-outs in the analysis (Fig. 1). By the end of the first twelve-week study period (continuous medication), the total drop-out rate was 25.1% (29.3% in ACA, 25.9% in DIS and 20.0% in NTX), and by the end of the study period (52 weeks) 51.8% (51.9% in ACA, 54.3% in DIS, 49.4% in NTX). There was no significant difference in study completion between the groups. The most common reason for premature discontinuation was poor compliance, or protocol violation (change of study medication, six patients); however, there were no significant differences between the study groups. At the end of the follow-up period (119 weeks) 103 (42.4%) subjects returned the mailed surveys but only 44 (18%) of them visited the study doctor and/or gave a blood sample (Fig. 1).

Baseline and demographic characteristics

All subjects were Caucasians. The mean age was 43.1 ± 8.6 years. In all, 70.8% were males, 56% married, 59% living with their families and 66% employed (Table 1). The treatment groups did not differ significantly with regard to demographic characteristics, drinking or smoking behaviour, except for the more frequent incidence of coronary heart disease in the ACA group ($P = 0.01$ compared to NTX) and less smokers in the ACA group ($P = 0.01$ compared to NTX).

Study drug use and compliance

The consumption of drugs was checked by pill count at each study visit and was recorded by the patient in the drinking diary to evaluate the use of study medication and compliance with treatment. Since subjects were instructed to take medication in the second phase of the study (after 12 weeks of daily continuous medication) only on those days when the propensity to drink was high, the evaluation of the later phase compliance is unequivocal. During the initial 12-week study period, 76.4% took the study medicine daily and there was no significant difference between the study groups (DIS 67.5%, $N = 54$; NTX 82.5%, $N = 66$; ACA 79.3%, $N = 65$). During the following 13–52 weeks (TM) 87.0% (DIS 92.1%; NTX 81.4%; ACA 87.5%) took the study medication at least once a week and there was no statistical difference between the groups in the intake of study drugs (calculated as one tablet corresponding to the stipulated daily dose of each medication, e.g. six tablets/day

Table 1. Sociodemographic characteristics

Study medicine groups	Disulfiram	Naltrexone	Acamprosate	Total
Age (years), mean ± SD	43.2 ± 8.6	41.5 ± 8.6	44.6 ± 8.4	43.1 ± 8.6
Gender, *N* (%)				
Male	56 (69.1)	58 (72.5)	58 (70.7)	172 (70.8)
Marital status, *N* (%)				
Married	45 (62.5)	45 (58.4)	37 (48.0)	127 (56.2)
Living conditions, *N* (%)				
Together with family	45 (62.5)	48 (64.0)	40 (51.9)	133 (59.4)
Employment, *N* (%)				
Employed	50 (70.4)	43 (56.6)	55 (71.4)	148 (66.1)
Education, *N* (%)				
Secondary school or less	54 (79.6)	61 (82.4)	51 (69.9)	169 (77.6)
College or university	13 (19.4)	13 (17.6)	22 (30.1)	48 (22.4)
Diseases, *N* (%)				
Diabetes, thyroid	8 (10.8)	4 (5.2)	5 (6.3)	17 (8.1)
Psychological	26 (35.1)	25 (32.5)	28 (35.4)	79 (38.0)
Elevated blood press.	15 (20.3)	8 (10.4)**	24 (30.4)	47 (22.6)
Asthma and allergy	7 (9.5)	2 (2.6)	6 (7.6)	15 (7.2)
Other	19 (22.3)	17 (22.1)	14 (17.8)	32 (24.0)
Previous alcohol treatments *N* (%)				
None	22 (29.3)	20 (26.3)	22 (28.9)	64 (28.2)
Detoxification	7 (9.3)	2 (2.6)	7 (9.2)	14 (6.2)
Therapy at A-clinic	20 (26.7)	20 (26.3)	20 (26.3)	60 (26.4)
Institution therapies	2 (2.7)	1 (1.3)	0	3 (1.3)
Several treatments	21 (28.0)	33 (43.4)	27 (35.5)	81 (35.7)
Alcohol consumption at baseline (g/ethanol/week)	591.2	561.8	570.8	1,723.8
Min	120	132	240	120
Max (*N*)	1,848 (69)	1,680 (75)	2,520 (71)	2,520 (215)
Smoking at baseline, *N* (%)				
Yes	44 (55.7)*	58 (72.5)*	42 (51.9)	144 (60.0)

No statistically significant differences between the groups except in smoking. (* $P < 0.0001$ DIS compared to NTX and $P < 0.0005$ DIS vs ACA and $P < 0.0001$ NTX vs ACA) and CVD (** $P = 0.01$ NTX compared to ACA).

for ACA).The weekly tablet consumption was not recorded during the follow-up phase, week 53–119.

Drinking outcomes

During the *continuous medication period* (1–12 weeks), DIS was significantly better than NTX and ACA in time to first HDD (Table 2; Fig. 2), days to first drinking (Table 2; Fig. 3), abstinence days (Table 2) and average weekly alcohol intake (Table 3).

During the *TM period* (13–52 weeks), there were no significant differences between the groups in time to first HDD and days to first drinking after TM (Table 4), but the abstinence days (Table 4) were significantly more frequent in the DIS group than in the ACA and NTX groups. The average alcohol consumption in all groups remained significantly below the baseline (Table 3). During the whole study period (1–52 weeks) the time to the first drink (in days) by Kaplan–Mayer survival analysis demonstrated that DIS was significantly better than the two other groups (Fig. 4).

At the end of the *follow-up period* (53–119 weeks), 42.4% (103) of the subjects returned the mailed surveys, but only 18% (44) (ACA 16%, DIS 18%, NTX 20%) visited the study doctor and/or gave a blood sample. Among all those who complied, the average mean weekly alcohol consumption (ACA: 216 g, DIS: 168 g, and NTX: 240 g) remained under the baseline values, as well the SADD and AUDIT scores (Table 5). In the ACA and NTX groups, the serum concentrations of GGT and ALAT had decreased ($P = 0.05$) as compared to the baseline, while in the DIS group the serum concentrations were at the baseline level (Table 6).

Degree of severity of alcohol dependence

Severity and dependence indicators measured by SADD and AUDIT scores during the study and follow-up periods indicated significant reduction in both AUDIT and SADD scores. However, at the middle of the TM (week 26), the NTX group had significantly better SADD scores than ACA and DIS (Table 5).

Quality of life measures

QL was estimated by EQ-5, KQF and VAS scores. Total EQ-5 scores in the ACA group increased from the baseline of 51.4 to 63.5 (52 weeks), DIS from 49.4 to 60.9 and NTX from 47.3 to 67.8; the KQF score increased in ACA from 11.9 to 13.7, DIS from 11.9 to 14.0 and the NTX group from 11.9 to 14.0. In VAS, ACA went from 52.1 to 60.1, DIS from 47.3 to 66.6 and NTX from 50.5 to 64.2. The improvement in the QL

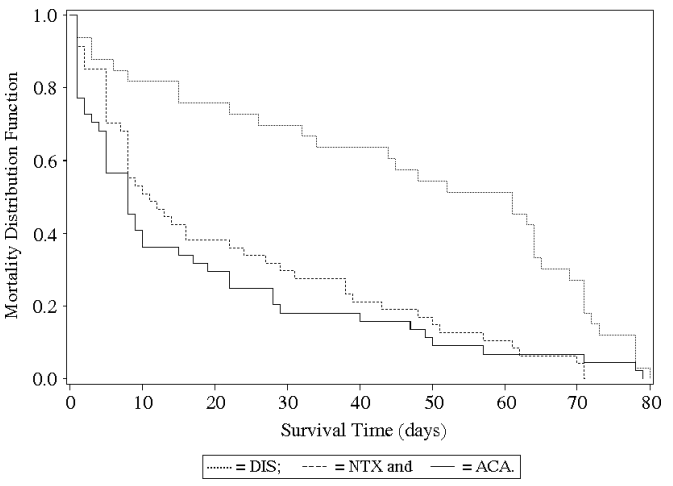

Fig. 2. Time to first heavy drink (days) during the continuous medication period (1–12 weeks). Kaplan–Meier survival analysis on the start of heavy drinking. Significant difference between DIS ($P = 0.001$) and others.

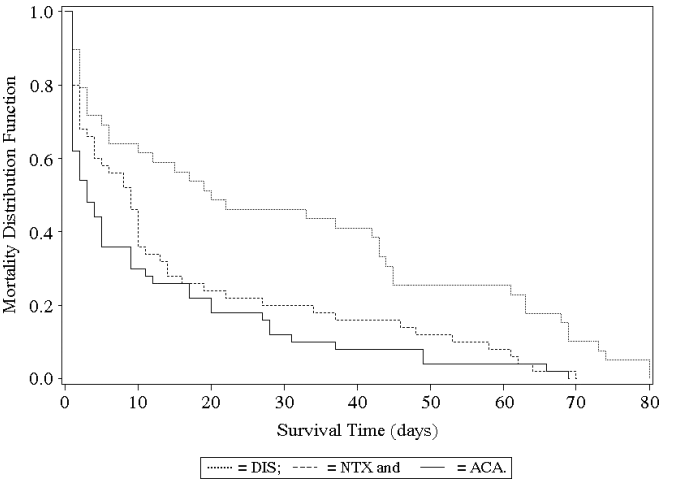

Fig. 3. Time to first drink (days) during the continuous medication period (1–12 weeks). Kaplan–Meier survival analysis when the first drinking started. Significant difference between DIS ($P = 0.0002$) and others.

Table 2. Drinking outcomes during continuous medication period (up to 12 weeks)

	ACA	DIS	NTX
Time (days) to first HDD, mean ± SD (n)	17.6 ± 22.0 (44)	46.6 ± 27.5 (33)**	22.0 ± 22.0 (47)
Time (days) to first drinking, mean ± SD (*N*)	11.4 ± 17.0 (50)	30.4 ± 27.8 (39)*	16.2 ± 20.2 (50)
Abstinence days/week, mean ± SD (*N*)	4.5 ± 2.1 (52)	6.3 ± 0.9 (54 ***)	4.6 ± 2.0 (53)

* Significance DIS > NTX and ACA; $P = 0.0002$.
** Significance DIS > NTX and ACA ($P < 0.0001$).
*** Significance DIS > NTX and ACA ($P < 0.0001$); difference between weeks ($P = 0.001$).

Table 3. Average alcohol (g/ethanol per week) intake during the study period (0–52 weeks)

	ACA	DIS	NTX
Baseline, mean ± SD (*N*)	570.8 ± 333.8 (71)	591.2 ± 325.8 (69)	561.8 ± 286.2 (75)
Continuous medication (weeks 1–12), mean ± SD (*N*)	203.2 ± 180.2 (58)	52.0 ± 90.7 (60)*	183.7 ± 174.1 (64)
Targeted medication (weeks 13–52), mean ± SD (*N*)	194.9 ± 148.4 (39)	109.2 ± 103.7 (37)**	229.3 ± 199.6 (41)

Significant reduction in alcohol intake in all groups between the baseline and weeks 1–12 and 13–52.
* Significance DIS > NTX and ACA ($P < 0.0001$).
** Significance DIS. > NTX ($P = 0.0005$) and ACA ($P = 0.0097$).

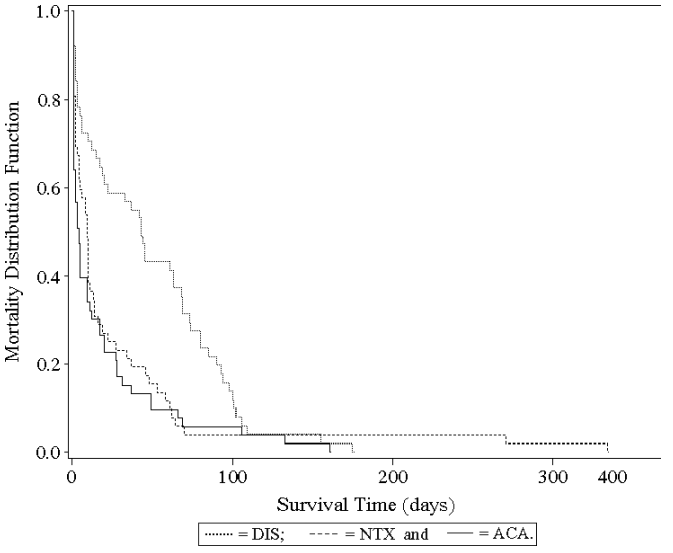

Fig. 4. Time to first drink (days) during the whole study period (1–52 weeks). Kaplan–Meier survival analysis of the first drink (days) during the whole study period (1–52 weeks). DIS significantly better than NTX and ACA ($P = 0.001$).

scores over the whole study period (52 weeks and follow-up) was statistically significant ($P < 0.0001$) with no difference between the groups.

Biochemical markers

In the NTX group, the serum concentrations of liver enzymes decreased significantly ($P = 0.058$ GGT and $P = 0.043$ ALAT) during the study period and were at the same level at the end of the follow-up period. In the ACA group, a significant reduction was observed at the end of the follow-up period and only in ALAT. In the DIS group, GGT decreased significantly in weeks 1–6; $P < 0.0001$ and weeks 1–52; $P = 0.0125$. There were no significant group differences (Table 6).

Safety and tolerability

One-third of subjects reported at least one adverse event during the study period, 29.1% in ACA ($N = 26$ symptoms), 31.1% in DIS ($N = 31$ symptoms) and 39.8% in NTX ($N = 41$ symptoms). There were no significant differences between the study groups in reporting AEs (Table 7). The most common AEs reported in ACA were diarrhoea and dermatological problems; DIS: tiredness and headache; NTX: nausea, headache and tiredness. Five serious adverse events (SDEs) were reported, four in ACA and one in DIS (see Table 7). These events were considered by the study coordinator (HA) not to be related to the study treatment based on clinical evaluation and forensic autopsy reports on each case. During the continuous medication phase in the DIS group, ALAT values were elevated >200 in six patients. The DIS dose was halved for three of these patients, while in the other three cases it was discontinued, and the values returned to normal in 2–3 weeks.

Table 4. Drinking during targeted medication (TM) period (up to 13–52 weeks)

	ACA	DIS	NTX
Time (days) to first HDD after continuous medication, mean ± SD (*N*)	110.7 ± 23.2 (9)	105.5 ± 17.0 (17)	128.8 ± 22.5 (4)
Abstinence days/week, mean ±SD (*N*)	4.4 ± 1.9 (48)	5.6 ± 1.2 (43)*	4.2 ± 2.1 (44)

* Significance DIS > NTX ($P = 0.0006$) and ACA ($P = 0.0015$). The table indicates only new HDDs (during the TM period and thus the low *N*).

Patient satisfaction

At the end of the study (week 52), subjects filled a survey about their subjective feelings: 72% felt that the treatment was useful, 64.6% felt that the study medication was useful, 79.4% felt that the therapy was useful and 62.6% that the therapy booklet was useful, no difference being observed between the groups.

DISCUSSION

Understanding alcoholism as a chronic disorder with craving, relapses and remissions has led to a better understanding

Table 5. Severity and dependence indicators measured by SADD (Severity of Alcohol Dependence Data) and AUDIT (Alcohol Use Disorder Identification Test) scores during the study period and follow-up

	Week	SADD mild % (*N*)	AUDIT normal % (*N*)
ACA	0	11.8 (9)	0.0 (0)
	6	45.8 (27)	N.A
	12	45.5 (25)	25.5 (14)
	26	50.0 (22)	16.3 (7)
	52	52.4 (22)	19.0 (8)
	119	45.2 (14)	22.6 (7)
DIS	0	5.7 (4)	0.0 (0)
	6	76.8 (43)	N.A
	12	67.9 (36)	46.9 (23)
	26	54.1 (20)	27.0 (10)
	52	42.9 (15)	14.3 (5)
	119	47.2 (17)	28.9 (11)
NTX	0	2.6 (2)	0.0 (0)
	6	40.4 (23)	N.A
	12	48.1 (25)	26.5 (13)
	26	63.4* (26)	29.3 (12)
	52	42.9 (18)	14.6 (6)
	119	46.7 (14)	23.3 (7)

SADD: Mild = SADD score less than 10. All groups showed significant difference compared to baseline ($P < 0.0001$).
* Significant difference NTX > ACA and DIS ($P = 0.0164$). AUDIT: Normal = AUDIT score less than 8 in women and 10 in men. No difference between groups, in all groups, and at all time points significant difference compared to baseline ($P < 0.0001$). N.A = data not available, survey not in protocol at this time point.

Table 6. Biochemical markers

	Week	*N*	ALAT	GGT
ACA	0	75	49.8 ± 50.8	91.6 ± 146.5
	6	64	45.4 ± 48.1	78.7 ± 113.6
	52	38	47.5 ± 51.0	91.7 ± 156.2
	119	13	30.9 ± 18.7*	35.4 ± 18.9**
DIS	0	72	48.3 ± 36.6	96.1 ± 109.2
	6	62	47.6 ± 53.9	49.5 ± 54.1***
	52	32	41.7 ± 30.7	63.7 ± 51.6†
	119	14	49.6 ± 47.3	111.0 ± 181.5
NTX	0	74	55.5 ± 83.6	78.6 ± 95.3
	6	55	35.6 ± 22.1*	55.4 ± 64.6††
	52	34	38.7 ± 33.4	64.4 ± 91.0
	119	17	34.3 ± 21.4*	43.6 ± 29.3††

Serum alanine aminotransferase and gamma glutamyl transferase values (U/l, mean ± SD, *N*) during the study and follow-up periods. No difference between the groups; * $P = 0.043$ compared to baseline; ** $P = 0.043$ compared to baseline, *** $P < 0.0001$; † $P = 0.0125$ compared to baseline; †† $P = 0.058$ compared to baseline.

Table 7. Adverse events: % reporting (*N*) during the whole study period (52 weeks) by study groups

% of AEs (*N*)	ACA	DIS	NTX
GI, nausea, vomiting	17.1 (14)	11.1 (9)	21.3 (17)
Skin symptoms	8.5 (7)	2.5 (2)	2.5 (2)
Headache, dizziness	4.9 (4)	24.7 (20)	22.5 (18)
Sexual dysfunction	1.2 (1)	0	5 (4)
Elevated (>200) ALAT	0	7.4 (6)[a]	0
Other	4.9 (4)[b]	1.2 (1)[c]	0

GI = gastrointestinal problem, diarrhea, nausea; SAE = serious adverse event. [a]ALAT value elevated >200, for three patients the DIS dose was halved, for the other three cases discontinued, values returned to normal in 2–3 weeks.
Other: [b]one intoxication, one suicide and two drowned, [c]one traffic accident.

of planning clinical trial aims and outcomes. Reductions in heavy drinking have begun to be an important approach in evaluation of the efficacy and effectiveness of medications and treatment therapies. Thus, the medications and aims of treatment used in this study were different—from relapse prevention to abstinence—relapsing to heavy drinking (>5 drinks/day) being selected as the common primary outcome. However, the results of this study remained the same as the other outcomes; the DIS group had more abstinence days, a longer time before the first drinking started, and lower alcohol consumption after the continuous and TM phase.

This study reports the first randomized comparison between DIS, NTX, and ACA with brief manual-based intervention therapy. The study demonstrated the efficacy of DIS as against NTX and ACA both during continuous medication (1–12 weeks), and the TM period (13–52 weeks). These findings are consistent with the previous data for both ACA and NTX. The De Sousas have compared DIS to NTX (De Sousa and De Sousa, 2004) and to ACA (de Sousa and de Sousa, 2005). In these studies DIS was superior to ACA and NTX for preventing relapse in alcohol-dependent men with good family support. Only one study has compared all these medications (von Bardeleben *et al*., 1999) which reported on a small sample size (20/group) in a 12-week study that the time to the first drink was much longer on DIS, but that there was no difference in alcohol consumption. Although supervised use of DIS is recommended for the treatment of alcoholism by several authors (Azrin *et al*., 1982; Chick *et al*., 1992; Brewer and Streel, 2003), the effectiveness of DIS has been criticized (Fuller *et al*., 1986; Fuller and Gordis, 2004) for compliance problems and possible toxic effects (Chick, 2004). However, in our study, only three patients refused to sign the consent after randomization to the DIS group, the compliance was high, drop-out rate was low, and there were few cases (six) of significant liver enzyme increase (>200) even after the 6-month study period in the DIS group. Some reasons for the good compliance may have been that the subjects were treatment-seeking patients, the motivational effect of the therapy manual as an aid in self-regulation and doctor-patient interaction.

A major reason for poor results with DIS may be the lack of compliance with the DIS regimen when patients are allowed to take it on their own. Several studies have been criticized for failing to note that the appropriate form of administration was for either the clinic staff or relatives to observe the ingestion of DIS (Brewer, 1987; Anton, 2001). Recent reviews of DIS treatment (Hughes and Cook, 1997; Anton, 2001) have concluded that unsupervised DIS administration is of limited utility, but endorse supervised DIS. In our study, DIS as well as the other medications were endorsed as supervised but not controlled at the study site—a patient was invited to give a written name and contacts for a person controlling the intake of medication. All drugs were well tolerated, the most

common side-effects in the ACA group being diarrhoea and dermatological problems, for DIS tiredness and headache, and for NTX nausea, headache, and tiredness.

One important part of successful pharmacological treatment for alcohol dependence is psychotherapy (Hunt and Azrin, 1973; Anton *et al*., 1999; Kiefer *et al*., 2003). Several studies have demonstrated the efficacy of cognitive behavioural methods, as well as the efficiency of a structured, detailed treatment format (Goudriaan *et al*., 2006). The manual used in our study, based on cognitive behavioural principles (Cunningham *et al*., 2001), was designed to be simple and usable with a primary health care physician or any doctor. The aim of the manual with its various homework assignments was to facilitate the self-regulation of drinking and to assist the patient in achieving a healthier life style. As the assignments were discussed at each visit with the doctor, the manual also included more comprehensive doctor-patient interaction, which was seen in the relatively low drop-out during the first phase of the study (25%). The aim of our study was not to evaluate the effect of the manual, and thus, no conclusions on its effects can be drawn. However, the patient rating for usefulness of the treatment indicated its value. No less than 79.4% of all patients replied that the treatment was useful, and 62.6% that the therapy booklet was useful. The study doctors considered the booklet a good and easy instrument to work with. These observations may indicate the usefulness of the manual.

The study has several limitations. One important factor is the two phases of the study. The first phase required controlled and continuous medication (weeks 1–12), and the second phase, TM, (weeks 13–52), in which the patients were instructed to take the medication in connection with craving or before an imminent relapse situation. The results were analysed separately in both phases. However, the main results were independent of the study phase. DIS was better in a majority of outcomes measuring alcohol consumption. There is some evidence of the effect of targeted usage of NTX in preventing relapsing heavy drinking among alcoholics and heavy drinkers (Heinala *et al*., 2001; Kranzler *et al*., 2003). However, there are no studies on targeted use of ACA or DIS. The intake of the study medication during the targeted phase was relatively low, 87.0% (DIS 92.1%; NTX 81.4%; ACA 87.5%) of subjects taking the study medication at least once a week. Moreover, since the exact average daily/weekly pill count is not known because the count was determined from the patient diary only, the comparison between the study groups in this phase is not well justified and limits the conclusions. However, the average weekly alcohol consumption remained at the level of the continuous medication phase except in the DIS group, where the average consumption was doubled but still remained significantly under the baseline. The third limitation is the loose control/supervision of the study medication—the intake was not controlled by the study doctors, patients being requested to name a follow-up person. Thus the results are not comparable with studies involving a rigid medication regimen or supervision control.

The main conclusions of the present study are that ACA, NTX and DIS combined with brief manual-based intervention extended in time significantly reduce heavy drinking, reduce craving for alcohol, and increase the QL. DIS was superior to the other medications and no SDEs were observed after 6 months of usage.

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SUPPLEMENTARY DATA

Supplementary data for this article are available online at http://alcalc.oxfordjournals.org/cgi/content/full/agm136/DC1.

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