Alcohol & Alcoholism Vol. 39, No. 6, pp. 528–531, 2004 doi:10.1093/alcalc/agh104

A ONE-YEAR PRAGMATIC TRIAL OF NALTREXONE VS DISULFIRAM IN THE TREATMENT OF ALCOHOL DEPENDENCE

ALAN DE SOUSA and AVINASH DE SOUSA*

Get Well Clinic and Nursing Home, 33rd Road, Off Linking Road, Bandra, Mumbai- 400050, India

(Received 18 *August* 2003*; first review notified* 23 *September* 2003*; in revised form* 23 *August* 2004*; accepted* 23 *August* 2004*)*

Abstract — Aims: To compare the efficacy of naltrexone and disulfiram in preventing an alcoholic relapse in routine clinical practice in an Indian metropolis. **Methods:** Hundred alcohol-dependent men, for whom a family member would accompany the patient to follow-up appointments, were randomly allocated to a year of treatment with either naltrexone or disulfiram. Patients, the accompanying family member and the treating psychiatrist were aware of the nature of treatment given. Alcohol consumption, craving and adverse events were recorded weekly for the first three months, then fortnightly for the rest of the year, by the treating psychiatrist. Serum gamma-glutamyl transferase (GGT) was measured at the start and the end of the study. **Results:** At the end of the year, 97 patients were still in contact. Relapse, the consumption of >5 drinks (40 g of ethanol) in a 24 h period, occurred at a mean of 119 days with disulfiram and at 63 days with naltrexone ($P = 0.020$). Mean serum GGT, which had not differed between the two groups initially, was 117 U/l with naltrexone and 85 U/l with disulfiram ($P = 0.038$) at the end of the study. Eighty-six per cent of the patients remained abstinent throughout the study with disulfiram compared to 44% with naltrexone ($P = 0.0009$). However, patients allocated to naltrexone had significantly lower craving than those allocated to disulfiram. **Conclusions:** Disulfiram is superior to naltrexone in preventing a relapse among alcohol-dependent men with family support. Comparison between these treatments in other settings and in different types of alcoholics is warranted.

INTRODUCTION

For many years, the pharmacological treatment of alcohol dependence was limited to the withdrawal period. Deterrent agents such as disulfiram and naltrexone may be of use in the long term (Fuller and Gordis, 2004).

Naltrexone is an opioid receptor antagonist with a proven history in reducing euphoria, alcohol intake and reducing the risk of relapse in alcoholic patients (Kranzler and Van Kirk, 2001; Streeton and Whelan, 2001). This action is thought to be due to the blockade of mu-opioid receptors. This antagonism prevents the release of endogenous opioids that would, on consumption of alcohol, produce a dopamine surge in the reward centre of the nucleus accumbens of the medulla (Benjamin *et al*., 1993; Catafau *et al*., 1999). Naltrexone's efficacy has seldom been evaluated in a 12-month study to date. One such was a multi-centre study where 675 patients were recruited and 209 were offered treatment with naltrexone for a 12-month period. However, the study did not support the efficacy of naltrexone (Krystal *et al*., 2001). Naltrexone has been compared with acamprosate (calcium acetylhomotaurinate), another anti-craving agent, in a one-year study, which showed that naltrexone was superior to the latter in preventing a relapse (Rubio *et al*., 2001).

Disulfiram inhibits acetaldehyde dehydrogenase, by blocking the further metabolism of acetaldehyde, which is an intermediate metabolic product of alcohol in the body. The resulting increased acetaldehyde levels in the body lead to the characteristic disulfiram–ethanol reaction (DER) that includes a sense of uneasiness, flushing and a feeling of nausea and vomiting (Savas and Gullu, 1997).

The only published study that compared the efficacy of naltrexone with disulfiram was a pilot study in patients with both alcohol and cocaine dependence, in which disulfiram had a superior effect (Carroll *et al*., 1993). The aim of the present study was to compare their efficacy in the treatment of pure alcohol dependence. A double-blind design was not chosen because there would have been excessive resistance to treatment compliance in a long blinded trial. Moreover, the patient's awareness that he is under disulfiram treatment is an important factor towards its efficacy.

SUBJECTS AND METHODS

This study was designed as an open randomized trial of naltrexone versus disulfiram. The conditions that pertained to the study were similar to those found in routine clinical practice. The subjects were alcohol-dependent males who were undergoing detoxification in a private psychiatric hospital in the city of Mumbai, India. The list for randomization was provided by a qualified statistician. Patients were allocated by the clinic staff according to a serialwise number on the list.

Inclusion criteria

The inclusion criteria were as follows: (1) age between 18 and 65 years; (2) DSM-IV criteria for alcohol dependence and (3) patients were required to have a stable family environment so that the family could ensure treatment compliance and provide information on regular follow-up.

Exclusion criteria

The exclusion criteria were: (1) other substance use and dependence excluding nicotine dependence; (2) any comorbid psychiatric disorder that met DSM-IV criteria excluding nicotine dependence; (3) any medical condition that would interfere with treatment compliance is a contraindication for the drugs used in the study; (4) liver function tests elevated

*Author to whom correspondence should be addressed: Dr Avinash De Sousa. E-mail: avides999@rediffmail.com. Tel: +91 22 26460785; Fax: +91 22 26462672

above three times the normal value and (5) previous treatment with naltrexone and/or disulfiram.

After the completion of detoxification treatment either in the hospital setting or on an out-patient basis, the subjects were informed about the objectives of the study. They were informed about the duration of the study and the nature of the two drugs to be used in the study (naltrexone and disulfiram), their mechanisms of action, their side-effects profile and the importance of maintaining proper compliance. They were also informed that the drug given to them would be chosen at random but that they would know about the drug that they were receiving. They were told that a relapse or non-compliance would lead to their exclusion from the trial. They were also told that they would be dropped from the trial in the absence of a regular follow-up with a family member. They were given the freedom to choose to leave the study at any time.

Procedure and assessments

After signing the informed consent declaration, the subjects completed questionnaires that pertained to: (1) the Addiction Severity Index (McLellan *et al*., 1980); (2) severity of Alcohol Dependence Scale (Stockwell *et al*., 1983); (3) a scale to measure the three parameters of craving i.e. frequency, duration and intensity (Anton *et al*., 1995); (4) a calendar to record any alcohol consumption during the follow-up and (5) a baseline investigation in all patients to evaluate serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and bilirubin.

After randomization, the patients received either 50 mg of naltrexone or 250 mg of disulfiram daily. Both the drugs were given as a single daily dose in the morning after breakfast. Compliance was enhanced by asking the family members to observe the patient when he takes the medication. (Only the non-dispersible form of disulfiram is available in India.)

They were followed up weekly for the first three months and then fortnightly till the end of the trial. They were assessed at each follow-up for craving and adverse effects along with compliance and alcohol consumption, which was checked against the reports made by family members. All the patients were offered supportive group psychotherapy once a week during the trial on a weekly basis and this was less structured than would be in a classical deaddiction programme. Abstinence was positively reinforced. The patients also received symptomatic treatment, for depression (sertraline 50–100 mg/day) or insomnia (zolpidem 5–10 mg at night) when required. Benzodiazepines were not permitted.

Outcome measures

The following outcome measures were assessed:

Accumulated days of abstinence; days until the first relapse — (relapse was defined as the consumption of >5 alcohol drinks in 24 h i.e. 40 g of alcohol); number of drinks consumed per typical week; number of drinks consumed at a typical drinking occasion; craving measures; serum GGT measured once in three months; discontinuation of pharmacological treatment; and drop out from the study.

To improve the consistency and independence of the ratings, the final outcomes were rated by a psychologist independent of the study. However, because she was on the staff of the clinic, she was not necessarily blinded to the treatment group in all cases.

Statistical analysis

Chi-squared test and the Student's *t*-test were used in the statistical analysis. All outcome analyses were conducted under the principle of intention to treat — drop-outs were considered as those who relapsed. The analysis of number of drinks consumed per week, number of drinks consumed at a time and the serum GGT were analysed by analysis of covariance (ANCOVA).

RESULTS

A total of 182 patients were screened for the study out of whom 114 met the criteria. Of these, 105 patients gave consent, but before randomization four had found employment outside the area and were not admitted to the study, and one changed his mind about the role played by his family member in the treatment study. Fifty patients were randomized to each group. During the study, one patient dropped out in the naltrexone group due to irregular attendance whereas two dropped out of the disulfiram group — one due to side-effects and one due to stopping of medication.

There were no significant differences between the treatment groups in terms of sociodemographic or clinical variables that were measured at baseline (Table 1).

The mean days of abstinence at the start of the trial was 22 days (range 16–30). Three patients dropped out from the trial of whom two were in the first month of treatment and one in the fourth month (Table 2).

At the end of the year, the number of patients in the disulfiram group that remained abstinent was twice that of the naltrexone group. Survival time until the first relapse was greater for disulfiram than for naltrexone. At the end of the study, 86% of the disulfiram group had not relapsed compared

Table 1. At the entry into the study

	Naltrexone $n = 50$		Disulfiram $n = 50$	
Mean age	45.6 years		43.2 years	
Marital Status	46 (92%)		48 (98%)	
Employment	38 (76%)		39 (78%)	
Secondary education	44 (88%)		47 (94%)	
	Mean	SD	Mean	SD
Severity of alcohol dependence scale	29	5	28	6
Addiction severity index	0.70	0.14	0.71	0.12
Composite craving severity score	52	19	51	22
Days of drinking in the last 6 months	87	20	87	22
Typical number of drinks per day	12.5	5.0	12.2	5.1
Serum GGT U/l	110	98	105	102
Serum ALT U/l	81	21	84	19
Serum AST U/l	64	30	67	31
Days between last drink and start of the study	15	6	16	10

There were no variables for which the groups were statistically significantly different.

Table 2. Outcomes at 1 year

	Naltrexone		Disulfiram		
	n	%	*n*	%	*P*
Completed the study	49	98	48	96	0.14
Withdrawn due to irregularity	1		0		
Withdrawn due to side effects	0		1		
Withdrawn due to stopping medication	0		1		
Abstinent since last assessment	22	44	45	90	0.0002
Given sertraline	2	4	1	2	0.9
Given zolpidem	9	18	14	28	0.6
Tried to abandon treatment	0	0	1	2	0.21
Relapsed during therapy	28	56	7	14	0.0009
	Mean	SD	Mean	SD	
Number of psychotherapy sessions attended	32	6	34	5	0.01
Days to first alcohol consumption	44	36	103	26	0.34
Days to the first relapse	63	33	119	21	0.02
Number of drinks taken at a time	4	12	3	5	0.01
Number of days of abstinence	243	115	306	180	0.03
Composite craving severity	11.3	10.1	16.3	11.2	0.01
Serum GGT U/l	107	90	85	56	0.038

with 44% of the naltrexone group. In terms of the composite score for craving, the patients had lower scores with naltrexone than with disulfiram (Table 2).

Sertraline was prescribed to three patients because depressive episodes emerged. Zolpidem was prescribed to 23 patients because they complained of insomnia. Side-effects were more common in the naltrexone group than in the disulfiram group, in the form of nausea (33 and 5%, respectively), drowsiness (12 and 1%, respectively), abdominal pain (10 and 1%, respectively) and diarrhoea (8 and 1%, respectively). All these side-effects disappeared within 15 days of the start of the study.

DISCUSSION

Disulfiram was associated with a greater reduction in relapse, and more cumulative days of abstinence. Patients on disulfiram had a greater reduction in the number of drinks consumed at a given time. Disulfiram appears to be the more effective drug in terms of control over drinking though its use by clinicians is patchy and often misunderstood (Brewer, 1995). Previous studies have shown that the outcome is best when the administration of disulfiram is monitored under family supervision (Brewer, 1986; Fuller and Gordis, 2004). Naltrexone however had a better outcome in terms of reduction in craving. It is difficult to compare these results with that of other studies as this is perhaps the first published study that compares these two drugs in such a large number of patients. In terms of tolerability, the group treated with naltrexone experienced more side-effects, but these were limited to the first 15 days of the study and did not influence the incidence of drop-outs from the study.

In about 75–80 cases the patient's spouse monitored the treatment whereas in the rest either the parents (mother or father) or a brother/sister monitored the same. In India there are more joint families than nuclear and hence there is usually more than one member of the family willing to monitor the supervised medication, therefore we assigned one member to take the responsibility and the same member was advised to be with the patient at the time of follow-up.

Limitations of the study

This was an open study and the investigators were not blinded. At the start of the study the investigator was not aware as to the type of treatment that would be more effective. But as the study progressed, there was a better outcome noted with disulfiram that may have resulted in the investigators making more efforts to ensure better compliance in that group. This could have, hypothetically, introduced a bias. However, there was also greater improvement seen in the disulfiram group in terms of the levels of serum GGT; this provides an objective corroboration of the self-report made by the patient and investigator-rated measures. The assessment for compliance was obtained from the report made by a family member. It would have been more accurate if a laboratory marker was in use to determine this measure. In this study, all the cases had very good primary support groups that may have led to better compliance and fewer drop-outs than seen in other published works. From this study we conclude that disulfiram has superiority over naltrexone in preventing a relapse in alcohol dependence, but further investigation in different types of alcoholics and various treatment settings is warranted.

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