

## AN OPEN RANDOMIZED STUDY COMPARING DISULFIRAM AND ACAMPROSATE IN THE TREATMENT OF ALCOHOL DEPENDENCE

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**Abstract** — **Aims:** To compare the efficacy of acamprosate (ACP) and disulfiram (DSF) for preventing alcoholic relapse in routine clinical practice. **Methods:** One hundred alcoholic men with family members who would encourage medication compliance and accompany them for follow-up were randomly allocated to 8 months of treatment with DSF or ACP. Weekly group psychotherapy was also available. The psychiatrist, patient, and family member were aware of the treatment prescribed. Alcohol consumption, craving, and adverse events were recorded weekly for 3 months and then fortnightly. Serum gamma glutamyl transferase was measured at the start and the end of the study. **Results:** At the end of the trial, 93 patients were still in contact. Relapse (the consumption of >5 drinks/40 g of alcohol) occurred at a mean of 123 days with DSF compared to 71 days with ACP ( $P = 0.0001$ ). Eighty-eight per cent of patients on DSF remained abstinent compared to 46% with ACP ( $P = 0.0002$ ). However, patients allocated to ACP had lower craving than those on DSF ( $P = 0.002$ ). **Conclusion:** DSF is superior to ACP for preventing relapse in alcohol-dependent men with good family support. Further comparisons between these two drugs in different treatment settings and populations are warranted.

### INTRODUCTION

Two anti-craving agents, acamprosate (ACP) and naltrexone (NTX) are now widely available for the long-term management of alcoholism. However, they are more expensive than older alcohol-deterrent drugs like disulfiram (DSF) and few studies comparing the effectiveness of the two classes of medication have been done.

Pooled analysis of ACP trials confirms its efficacy in the maintenance of abstinence in alcohol dependence (Lesch *et al.*, 2001; Slattery *et al.*, 2003; Mann *et al.*, 2004; Verheul *et al.*, 2004) ([www.docs.scottishmedicines.org/docs/pdf/Alcohol%20Report.pdf](http://www.docs.scottishmedicines.org/docs/pdf/Alcohol%20Report.pdf)). However, this efficacy is relatively modest with an average effect size of only 0.26 (Berglund *et al.*, 2003) and some subsequent studies have not shown efficacy (e.g. Namkoong *et al.*, 2003). ACP reduces the severity of relapse in alcoholics undergoing abstinence-oriented treatment (Chick *et al.*, 2003), and may even be effective in the management of alcohol-dependent adolescents (Niederhofer and Staffen, 2003). It is the only anti-craving agent so far with good cost effectiveness ratings in the management of alcoholism (Schadlich and Brecht, 1998; Foster and McClellan, 1999).

DSF is an alcohol deterrent that inhibits acetaldehyde dehydrogenase. The resulting increase in acetaldehyde levels in the body leads to the characteristic DSF–ethanol reaction that includes a sense of uneasiness, flushing, nausea, and vomiting (Savas and Gullu, 1997). Several reviews support the efficacy of DSF, if supervised, in the treatment of alcohol dependence (Brewer, 1992; 1995; Berglund *et al.*, 2003; Slattery *et al.*, 2003).

We reported a comparison of DSF and NTX and found DSF considerably more effective in reducing the frequency and severity of relapse (De Sousa and De Sousa, 2004). However, there have been no studies so far comparing DSF and ACP, though Besson *et al.* (1998) found that, in a study where there was random allocation to placebo or ACP, patients who had

chosen to take DSF did particularly well compared to patients who had not chosen DSF whether on placebo or ACP. The aim of this study was to compare DSF and ACP in patients with pure alcohol dependence. As with our comparison of DSF and NTX, an open trial design was chosen, partly because it would have been difficult to maintain compliance and blinding in a long trial and partly because the patients' awareness that they are taking DSF is an important factor in DSF's effectiveness.

### SUBJECTS AND METHODS

The setting of this open, randomised study was typical of routine clinical practice in India. The subjects were alcohol-dependent men undergoing detoxification in a private psychiatric hospital in the large city of Mumbai. The list for randomisation was provided by a qualified statistician. Treatment was allocated by the clinic's staff according to the serial number on the list.

#### Inclusion criteria

- (i) Age between 18 and 65 years.
- (ii) DSM-IV criteria for alcohol dependence.
- (iii) Patients were required to have a stable family environment so that the family could ensure to maximize treatment compliance and provide regular follow-up information.

#### Exclusion criteria

- (i) Presence of other substance abuse disorders (excluding nicotine dependence).
- (ii) Presence of any co-morbid psychiatric disorder.
- (iii) Any medical condition present that would interfere with treatment compliance or be a contraindication to ACP or DSF.
- (iv) Any of the routine liver function test values more than three times above the normal value.
- (v) Previous treatment with DSF and/or ACP.

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After completing detoxification, either in hospital or as an out patient, subjects were informed about the objectives and duration of the study and the nature of the two drugs. Their mechanisms of action, side effects, and the importance of maintaining compliance were discussed. Patients were also told that the drug given to them would be chosen at random but they would know which drug they were receiving. They were told that relapse or non-compliance would lead to their exclusion from the trial, as would the absence of regular follow-up with a family member. They were free to leave the study at any time.

#### Assessment procedure

After signing the informed consent declaration, subjects completed:

- (i) The Addiction Severity Index (McLellan *et al.*, 1980).
- (ii) The Severity of Alcohol Dependence Scale (Stockwell *et al.*, 1983).
- (iii) A scale to measure the three parameters of craving i.e. frequency, duration, and intensity (Anton *et al.*, 1995).

They were given a calendar to record any alcohol consumption during the follow-up. Baseline aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), and serum bilirubin were done.

Following randomisation, patients received either 250 mg of DSF or 1998 mg of ACP per day. DSF was given as a single daily dose after breakfast while ACP was given as 666 mg thrice daily after meals. The importance of family members observing patients when they took medication to enhance compliance was emphasised. Only the non-dispersible form of DSF is available in India.

Patients were followed up weekly for the first 3 months and then fortnightly until the end of the trial. At each follow-up, they were assessed for craving and adverse effects along with compliance and alcohol consumption. Self-reports were checked against reports of family members. All patients were offered weekly supportive group psychotherapy during the trial. It was probably less structured than in classical treatment programmes. Abstinence was positively reinforced. Patients also received symptomatic treatment for depression (escitalopram 10 mg/day) or insomnia (zolpidem 5–10 mg at night), when required. Benzodiazepines were not prescribed.

#### Outcome measures

The following outcome measures were assessed:

- (i) Accumulated days of abstinence.
- (ii) Days until the first relapse (defined as the consumption of >5 alcoholic drinks/40 g of alcohol in 24 h).
- (iii) Number of drinks consumed per typical week.
- (iv) Number of drinks consumed per typical occasion.
- (v) Craving measures.
- (vi) GGT measured every 3 months.
- (vii) Discontinuation of treatment.
- (viii) 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. Since she was on the staff of the clinic, she was not blinded to the treatment group in all cases.

Table 1. Variables at the entry into the study

	ACP (N = 50)		DSF (N = 50)	
	Mean	SD	Mean	SD
Mean age	41.7 years		42.6 years	
Marital status	48 (96%)		47 (94%)	
Employment	32 (64%)		36 (72%)	
Secondary education	47 (94%)		49 (98%)	
Severity of alcohol dep. scale	27	6	26	4
Addiction severity index	0.73	0.11	0.72	0.13
Composite craving score	54	18	51	19
Days of drinking in last 6 months	83	17	86	21
Typical no. of drinks per day	10.3	4.7	11.6	5.3
Serum GGT	124	86	114	89
Serum ALT	79	38	72	32
Serum AST	56	23	59	21
Days of abstinence	18	8	21	11

#### Statistical analysis

Chi square test and Student's *t*-test were used in the statistical analysis. All outcome analyses were conducted on an 'intention to treat' principle. Drop-outs were considered as relapses. The number of drinks consumed per week, number of drinks consumed at a time, and the serum GGT were analysed using the analysis of covariance (ANCOVA).

## RESULTS

A total of 167 patients were screened and 104 met the criteria. Of these, the first 100 (in serial order) were chosen for the study. Fifty patients were randomized to each group. During the study, three dropped out of the ACP group due to irregular attendance while four dropped out of the DSF group—three due to side effects (neuropathy) and one due to stoppage of medication.

Table 1 shows that there were no significant differences between the treatment groups in terms of baseline socio-demographic or clinical variables.

All the six patients who dropped out from the study did so in the first month. Table 2 shows that by the end of this 8-month study, 88% of DSF group had not relapsed, compared with 46% in the ACP group ( $P = 0.0001$ ). Mean survival time until the first relapse was significantly greater with DSF (123 days) than with ACP (71 days) ( $P = 0.0001$ ). Craving scores of patients on ACP were lower than for those on DSF.

Only two patients received escitalopram. Zolpidem was given to 28 patients for insomnia. Side effects were uncommon. Nausea was experienced equally in both groups (ACP 3%, DSF 4%), but side effects abated in the first week of the study.

## DISCUSSION

Compared with ACP, DSF was associated with a large and significantly greater reduction in relapse and significantly more abstinent days. This study adds to the evidence that supervised DSF is a very effective component of alcoholism treatment and is significantly more effective than either ACP or NTX.

Table 2. Outcomes at the end of 8 months

	ACP		DSF		P-value
	N = 50	%	N = 50	%	
Completed the study	47	94	46	92	0.16
Withdrawn due to irregularity	3		0		
Withdrawn due to side effects	0		3		
Stopping medication	0		1		
Tried to abandon treatment	2	4	2	4	
Abstinent since the last assessment	23	46	44	88	0.0002
Relapsed during therapy	27	54	6	12	0.0003
Given escitalopram	1	2	1	2	
Given zolpidem	13	26	15	30	
Psychotherapy sessions attended	35	4	31	3	0.707

  

	N = 47		N = 46		P-value
	Mean	SD	Mean	SD	
Days to first alcohol intake	48	28	112	24	0.0001
Days to first relapse	71	27	123	19	0.0001
Number of drinks taken	3	11	3	4	
Days of abstinence	169	101	201	145	0.2034
Craving severity	10.9 (N = 47)	9.3	17.2 (N = 46)	10.6	0.0021
Serum GGT	79 (N = 47)	34	111 (N = 46)	52	0.0004

It does not seem to be sufficiently recognized that DSF generally has no specific effect unless it is monitored and supervised by family members or professionals (Brewer, 1986; Fuller and Gordis, 2004). It is of theoretical and practical interest that although ACP reduced craving significantly more than DSF, there were no comparable reductions in relapse or alcohol intake. This is the first published comparison between these two drugs in a relatively large number of patients but even larger studies in diverse treatment settings are clearly needed. Family support is typically strong in India. Wives monitored medication in ~90% of subjects. In the remainder, parents monitored it. Another point of importance in an Indian context is that DSF is cheaper than ACP and much cheaper than NTX. We nominated one family member to take responsibility for monitoring and encouraging compliance and the same person was invited to accompany the patient at follow-up.

### LIMITATIONS

This was an open study and the investigators were not blinded. At the start of the study, the investigators had no firm indication as to which treatment would be more effective but as the study progressed, better outcomes were noted with DSF. This may have resulted in the investigators making more efforts to ensure better compliance in this group and could have introduced some bias. The assessment of compliance was based on family reports. It would have been helpful if more use had been made of laboratory markers. Most patients in this study had supportive families. This may partly account for the low drop-out rate compared with many other studies. Nevertheless, we conclude from this study that DSF is more effective than ACP for preventing relapse in alcohol dependence.

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