AN OPEN LABEL TRIAL OF NALTREXONE VERSUS DISULFIRAM IN ELDERLY PATIENTS WITH ALCOHOL DEPENDENCE

Avinash De Sousa, Jyoti Jagtap

ABSTRACT

Objectives: This study aims to compare the efficacy of Disulfiram (DSF) and Naltrexone (NTX) for preventing alcoholic relapse in elderly patients in routine clinical practice.

Design: Open label trial of naltrexone versus disulfiram.

Place and duration of study: The study was conducted between December 2007 and November 2008 at a private psychiatric hospital in Mumbai.

Subjects and Methods: 32 elderly alcoholics with proper relatives or caregivers that would encourage medical compliance and would accompany them for follow up were randomly allocated to 6 months of treatment with DSF or NTX. Weekly group supportive psychotherapy was also provided. The psychiatrist, patient and family member were aware of the treatment prescribed. Alcohol consumption, craving and adverse events were recorded weekly for 2 months and fortnightly thereafter.

Results: At the end of the trial, 46 patients were still in contact. Relapse occurred at a mean of 91 days with DSF compared to 52 days for NTX ($p = 0.0001$). 81.25% patients on DSF remained abstinent compared to 43.75% with NTX ($p = 0.0001$). Patients allocated with NTX however had less craving than the DSF group ($p = 0.0022$).

Conclusions: DSF was thus found to be superior to NTX in preventing relapse in elderly alcoholics with good caregiver support. The use of DSF in the elderly population with alcohol dependence needs further exploration and research .

Key words – Disulfiram, Naltrexone, Elderly Alcoholics.

INTRODUCTION

Alcohol dependence is a leading cause of disability worldwide that is often under appreciated in the elderly population[1]. Pharmacological treatments have never played a major role in the long term management of older adults with alcohol dependence. Until recently Disulfiram was the only approved medication but was used sparsely due to adverse effect related concerns in the elderly population[2]. Elderly patients with alcohol dependence are often a tougher group for treatment due to reduced will power and poor social support accompanied by comorbid disorders[3].

Disulfiram (DSF) is a chemical deterrent drug that acts by inhibiting acetaldehyde metabolism causing increased levels of the compound leading to the characteristic disulfiram ethanol reaction accompanied by nausea, flushing, uneasiness and vomiting. There are some reports that this reaction is markedly severe in the elderly population[4-5]. Several reviews report the unparalleled efficacy of DSF in the management of alcohol dependence[6-7]. The author has reported studies where Disulfiram has been found to be superior to both Naltrexone and Acamprosate in the long term management of alcohol dependence in young and middle aged adults[8-9]. There has been a study amongst veterans that demonstrates moderate efficacy of DSF in the elderly population[10].

Naltrexone (NTX), an opioid antagonist received FDA approval for the treatment of alcohol dependence based on studies that demonstrated efficacy in middle aged patients[11-12]. The effect of Naltrexone in alcoholism is based on the interactions between endogenous endorphin activity, alcohol intake and reward[13]. A double blind randomized placebo controlled trial has demonstrated decrease in relapse amongst elderly patients with alcohol dependence[14]. Meta analytic studies have demonstrated efficacy of Naltrexone in the management of alcohol dependence in adult patients[15].

There has been to the best of our knowledge, no studies that have compared Disulfiram and Naltrexone in the management of alcohol dependence in the eld-

Avinash De Sousa, Consultant Psychiatrist, Carmel, 18, St. Francis Avenue, Willingdon Colony, Off S.V. Road., Santacruz (West), Mumbai – 400054.
E-mail: avinashdes999@yahoo.co.uk Mumbai

Jyoti Jagtap, B.Sc (Occupational Therapy), Consultant Occupational Therapist, Mumbai

Correspondence:

Dr. Avinash De Sousa

erly population (age > 60 years). This study aimed to fill that void. An open trial design was chosen due to difficulties in compliance and blinding that would arise due to the length of the study and due to the fact that the patient's awareness of being on DSF is an important factor in enhancing its efficacy.

SUBJECTS AND METHODS

The setting of this open randomized study was similar to routine clinical practice in India. The subjects were elderly alcohol dependent patients that successfully underwent two weeks of detoxification at a private psychiatric hospital in Mumbai. The randomization list was provided by the statistician and the treatments were allocated as per the list.

Inclusion Criteria for selection for the study –

1. Age greater than or equal to 60 years.
2. DSM-IV criteria for alcohol dependence.
3. Patients were expected to have good social support or a stable family environment to ensure treatment compliance and correct follow up information. (A fixed relative or caregiver was assigned for the same).

Exclusion Criteria –

1. Presence of other substance use disorders (excluding Nicotine Dependence).
2. Presence of any other co-morbid psychiatric disorder (Ruled out by screening via clinical interview).
3. Any medical condition that would interfere with treatment compliance, lead to drug interactions with the drugs concerned in the study or be a contra-indication for the drugs being studied.
4. Routine liver function test values more than three times the normal value.

After successful completion of detoxification the subjects and their relatives / caregivers were informed about the objectives and scope of the study. They were also informed about randomization, nature of the two drugs in the study, their mechanism of action and the need to maintain regular follow up and treatment compliance. Patients were told that despite randomization, they would be informed about the drug being given to them. They were informed that relapse or non compliance or absence of regular follow up with a relative / caregiver would lead to exclusion from the trial. They were free to drop out from the study at any point of time.

ASSESSMENT PROCEDURE

After an informed and valid consent declaration the subjects were administered –

1. The Addiction Severity Index [ASI][16].
2. The Severity of Alcohol Dependence Scale[17].
3. A scale to measure parameters of Craving[18].

The subjects were asked to record any alcohol consumption during the trial. Baseline aspartate aminotransferase (AST), alanine aminotransferase (AAT) and gamma glutamyl transferase (GGT) were recorded. Following randomization, the patients received non dispersible DSF at a dose of 250mg once a day in the morning while NTX was administered at a dose of 50mg twice a day. Relatives and caregivers were asked to monitor consumption of the medication.

Patients were followed up weekly for the first 2 months and then fortnightly till the end of the trial which lasted totally for 6 months. Craving, compliance and alcohol consumption if any was assessed at each follow up. Self reports were checked against the reports of relatives or caregivers. All the patients attended weekly supportive group psychotherapy during the trial. They were educated about alcohol dependence as a disorder. They were encouraged to talk about their problems with alcohol and causes of their relapses in the past. They were educated about the medications used in the study while their role in their families and interpersonal issues if any were addressed. The sessions were less structured as in classical treatment programmes. The sessions were conducted by the first author and traveling allowance was provided as an incentive for the patient to attend the weekly sessions. Patients also received symptomatic treatment for depression (Duloxetine 20-40mg / day) and insomnia (Zolpidem 5-10mg at night). Benzodiazepines were not prescribed during the study.

The following outcome measures were assessed –

1. Accumulated days of abstinence.
2. Days until the first relapse (defined as consumption of more than 5 alcohol drinks / 40gm of alcohol in 24 hours).
3. Number of drinks consumed per typical week.
4. Number of drinks consumed per occasion.
5. Craving measures.
6. GGT measured every 3 months.
7. Discontinuation of treatment.
8. Drop out from the study.

To improve consistency of the ratings and to eliminate ratings the final outcomes at the end of the study was done by a research assistant (author 2) who was recruited specially for the study and was blinded to the treatment groups.

STATISTICAL ANALYSIS

Chi square test and student t test were used in the statistical analysis. All the outcome analyses were assessed on an intention to treat principle. Drop outs were considered as relapses. The number of drinks per week, number of drinks per day and GGT were analyzed using analysis of covariance.

RESULTS

A total of 48 patients were screened and 32 met the inclusion criteria. 16 were randomized to each group as per the list provided by the statistician. During the study 4 dropped out from the NTX group while 2 dropped out from the DSF group. Table 1 shows that there were no significant differences between treatment groups on entry into the study. 6 patients received Duloxetine while 25 patients were given Zolpidem during the trial. Side effects were uncommon. 7 patients in the DSF group developed peripheral neuropathy in the legs that subsided on its own during the 1st 2 weeks of the trial. The drop out patients left the study in the 1st month itself.

Table 2 shows that at the end of the study 81.25% of the DSF group had not relapsed compared to only 43.75% in the NTX group (p = 0.0001). Mean survival time until first relapse was greater with DSF (91 days) compared to NTX (52 days) (p = 0.0001). Craving scores however were significantly lower in the NTX group (p = 0.0022).

Table 1: Variables at the Entry into the Study

Variable	DSF (N = 16)		NTX (N = 16)	
Mean age	66.9 years		65.3 years	
Marital Status	15 (93.75 %)		16 (100%)	
Employment	02 (12.5%)		03 (18.75%)	
Secondary education	16 (100%)		16 (100%)	
	Mean	**SD**	**Mean**	**SD**
Severity Alc. Dep Scale	28	4	29	5
ASI	0.81	0.09	0.78	0.06
Craving Score	55	11	57	13
No. of drinks / day	12.6	4.5	13.1	5.9
Serum GGT	114	49	118	45
Serum ALT	88	29	82	28
Serum AST	83	32	86	26
Days of abstinence	19	5	21	7

Table 2: Outcome at the end of 6 Months

Variable	DSF (N = 16)		NTX (N = 16)		P value
Completed the study	14 (87.5%)		12 (75%)		
Irregular follow up	0		0		
Side effects	0		0		
Stopped medication	2		4		
Abstinent since last assessment	13 (81.25%)		07 (43.75%)		0.0001
Relapsed during therapy	01 (6.25%)		05 (31.25%)		0.0001
Given Escitalopram	4		2		
Given Zolpidem	11		14		
	Mean	**SD**	**Mean**	**SD**	
Days to 1st alcohol intake	101	21	59	23	0.0001
Days to 1st relapse	91	15	52	13	0.0001
Craving severity	20.3	6.2	13.7	5.9	0.0022
Serum GGT	77	29	75	26	

DISCUSSION

DSF was associated with greater days of abstinence and significant greater reduction in relapse than NTX. This study supports the available sparse literature that supervised DSF is a safe and effective treatment option in the geriatric population with alcohol dependence. For better efficacy and to ensure compliance it is essential that DSF therapy be stringently monitored by a relative or caregiver of the patient across all age groups[19-20]. NTX based on its opioid mechanism of action however reduced craving while failing to significantly reduce alcohol intake and relapse patterns. This is the first study, though small between these two drugs in the elderly population with alcohol dependence. Larger studies in diverse treatment settings are warranted. Alcohol dependence in the elderly is on the rise worldwide and there is need of proper medical treatments in this group[21].

There are only a few studies that provide a head on between the above drugs. An Indian study has shown Naltrexone to be superior to Disulfiram[22] while the author of this article has been involved in recent work on Disulfiram. In similar studies the author and others have shown disulfiram to be superior to naltrexone, acamprosate and topiramate in separate studies. They have also shown disulfiram to be superior to naltrexone in the management of adolescents with alcohol dependence[8-9, 23-24]. Further studies in the same line are already under progress.

We re-emphasize the role of the caregiver or relative in successful supervised DSF therapy amongst elderly patients as seen in our study. In India, DSF is a viable treatment option for alcohol dependence across all age groups as the drug is much cheaper compared to NTX and Acamprosate. The study had its limitations too. The study being an open one may have introduced some bias as it was observed that better outcomes were seen in the DSF groups as the study progressed. The assessment of compliance was based on clinical interviewing and caregiver reports while no biological parameters were assessed. Blood alcohol and DSF levels are rarely available across laboratories in India. Supportive caregivers and relatives were pivotal in the better outcome with DSF therapy. Nevertheless, DSF is safe treatment option in geriatric alcohol dependence that needs further exploration.

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