Original Article

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Comparison of Disulfiram and Naltrexone in Cases of Alcohol Dependence Syndrome

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ABSTRACT

Background: Relapse prevention in alcoholism is recognised as an important component of management. Use of pharmacotherapies to prevent relapse in combination to psychological intervention is emerging. Disulfiram and Naltrexone are two of three FDA approved drugs for pharmacotherapy. The aim of the study is to compare the effectiveness of these two drugs in preventing relapse in alcohol dependence syndrome cases.

Methods: A prospective crossectional study was conducted to compare disulfiram and naltrexone in alcohol dependent patients in tertiary institution. Cases of alcohol dependence syndrome were diagnosed based on ICD-10 DCR presenting to psychiatry department of Tribhuvan University Teaching Hospital, over the period of 6 months. After detoxification and fulfillment of inclusion criteria, semi structured proforma, Severity of alcohol dependence questionnaire, Stages of change readiness and treatment eagerness scale, Obsessive compulsive drinking scale were applied. Drug allocation was based on simple random method and on subsequent follow ups done at 2nd, 4th, 8th, 12th week semi structured proforma, Obsessive Compulsive Drinking Scale were completed and psychological intervention continued. After data collection, analysis and final results were computed.

Results: Both drugs reduced craving ($p<0.001$) and amount of alcohol intake ($p<0.001$). Relapse was more in naltrexone group but was not statistically significant ($p>0.05$). Side effects were more with disulfiram ($p<0.001$) whereas dropout was more in naltrexone group, ($p<0.01$).

Conclusions: Disulfiram and Naltrexone were equally effective in reducing craving, reducing amount of alcohol intake, and preventing relapse in 12 weeks follow up period. Naltrexone was found to be better in tolerability whereas disulfiram was better in terms of dropout from treatment.

Keywords: Alcohol dependence; disulfiram; naltrexone; relapse

INTRODUCTION

Alcohol dependence syndrome (ADS) is defined as a cluster of behavioural, cognitive, and physiological phenomena that develop after repeated alcohol use.[1] Alcohol use ranks among the top five risk factors for disease, disability and death throughout the world.[2] About 80-90% cases of ADS relapse even after years of abstinence . Use of pharmacotherapies to prevent relapse in combination to psychological intervention is emerging, as upto 70 percent of cases relapse after psychosocial treatment alone. [3-6]

Relapse prevention strategies in Nepal are in quiescent stage. Among three FDA approved anticravings, only Disulfiram (DSF) and Naltrexone (NTX) are available and they differ cost wise. Previous researches have focused mainly on epidemiology of alcohol related problems. Thus, comparing two available anticravings would provide evidence regarding their effectiveness and compare our findings with previous studies.

The aim of this study was to compare the effectiveness of disulfiram and naltrexone in preventing relapse in ADS cases. The specific objectives being to assess reduction in craving, reduction in amount of alcohol intake, compare tolerability and dropout for each agent.

METHODS

This was a prospective cross-sectional study conducted in psychiatry department of Maharajgunj Medical Campus, Tribhuvan University Teaching Hospital, Kathmandu, Nepal. Cases that were diagnosed as alcohol dependence

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syndrome from the ward and OPD were included. Follow up visits were done at 2nd, 4th, 8th and 12th week. The total duration of study was one year.

The study protocol and consent were approved by Research board Tribhuvan University Teaching Hospital and all other considerations were followed. The decision to take medication was taken with active participation of the patient as well as a family member after explaining about advantages and the disadvantages of taking or not taking treatment, about side effects and cost of treatment. The consent was taken from participants after they were informed that the information they would provide were used only for research purpose.

The inclusion criteria were- i. age 16 to 65 years ii. fulfilling diagnostic criteria for alcohol dependence syndrome according to ICD 10 DCR within last one month. The exclusion criteria were - i. Co-morbid substance use except nicotine ii. Another current psychiatric diagnosis iii.Co-morbid physical disorders such as diabetes mellitus, hypertension, alcoholic cirrhosis, renal impairment, other systemic illnesses iv. Pregnancy v. No informed consent vi. Poor family support for supervision

The sample size was calculated using standard formula with the least sample size needed in each group to be N= 21. The sampling method was purposive with odd-numbered participants assigned to one group and even-number assigned to another group. There were total of 78 participants who met criteria in the study with 39 participants allocated in each group.

After enrolment in the study, medication was started. In disulfiram group, participant were given disulfiram 500mg orally once daily for one week followed by 250 mg once daily thereafter and in naltrexone group, naltrexone 50mg was given orally once daily.

The follow up visits were done at 2nd, 4th, 8th and 12th week. Patients were called for next follow up giving them the precise date and were also reminded few days prior via phone. All patients who came during follow up were taking medication regularly. Patients who did not take medication or left in between or missed two regular follow ups were considered dropout. Among those who resumed alcohol few were only considered as relapse. Cases that relapsed and came back for treatment were treated following our guidelines, first detoxification followed by relapse prevention (Anticravings with motivational interviewing) but were not included in study again.

The following tools were used to assess patient at enrolment: Semi structured proforma, Severity of Alcohol Dependence Questionnaire (SADQ) which was developed by the Addiction Research Unit at the Maudsley Hospital. It is Self administered questionnaire with 20 items. It is a measure of the severity of dependence: Score of below 16 usually indicates mild physical dependency, 16 -30 indicates moderate dependence and 31 or higher indicates severe alcohol dependence. Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) which was designed to assess readiness for change in alcohol abusers. Three subscale scores are obtained. a. Recognition: high scorers directly acknowledge that they are having problems related to their drinking, tending to express a desire for change. b Ambivalence: high scorers say that they sometimes wonder if they are in control of their drinking, are drinking too much, and/or are alcoholic. c. Taking steps: high scorers report that they are already doing things to make a positive change in their drinking, and may have experienced some success in this regard. Obsessive Compulsive Drinking Scale (OCDS) which was developed to reflect obsessionality and compulsivity related to craving and drinking behavior.It is Self administered 14 items scale: Obsessive Subscale which sum items 1 to 6 and Compulsive Subscale which sum items 7 to 14. It is sensitive as monitoring tool and increasing scores may predict relapse drinking.

At each follow up assessment included following tools: Semi structured proforma (follow up) and OCDS. The obtained data were fed and analysed by SPSS 18. Mean ± standard deviation, median, range, percentage; Chi-squared test, t- test and other appropriate tests with 95% confidence intervals were used in statistical analysis.

RESULTS

Table 1. Sociodemographic variables within two groups.

	Naltrexone n=39	Disulfiram n=39	P value
Mean age	39.56 years	39.41 years	0.94
Gender	M: 39(100%) F: 0	M: 34(87.2%) F: 5 (12.8%)	0.021
Marital status	Married: 37(94.9%)	Married: 36(92.3%)	0.602
Ethnicity			0.74
Brahmin	10(25.6%)	5 (12.8%)	
Chhetri	9(23.1%)	9(23.1%)	
Newar	6 (15.4%)	6 (15.4%)	
Magar	3(7.7)	6 (15.4%)	
Tamang	4(10.3%)	4(10.3%)	
gurung	1(2.6%)	2(5.1%)	

Limbu	0	1(2.6%)	
tharu	0	1(2.6%)	
others	6(15.4%)	5(12.8%)	
Education			0.022
Illiterate	3(7.7%)	0	
Literate	1(2.6%)	7(17.9%)	
Primary	7(17.9%)	12(30.8%)	
secondary	14(35.8%)	10(25.6%)	
Slc and intermediate	8(20.4%)	9 (23.1%)	
Graduate and PG	6(7.7%)	1(1.3%)	
Occupation	Service and sale workers: 9(23.1%)	Agriculture, forestry and fishery: 12(30.8%)	0.620
Income	22851-45750: 12 (30.8%)	11451-17150 and 22851-45750: 10 (25.6%) each	0.021
Religion	Hindu 35(89.7%)	Hindu 37(94.9%)	0.395

As shown in Table 1, there were no significant differences between treatment groups in terms of baseline socio-demographic variables except in gender wise distribution, education level, and income.

Table 2. Clinical variables between two groups".

	Naltrexone n=39	Disulfiram n=39	P value
Admission of participant			0.65
OPD	20(51.3%)	22(56.4%)	
ER	19(48.7%)	17(43.6%)	
Diagnosis: Uncomplicated withdrawal	15(38.5%	19(48.7%)	0.07
Family history	24(61.5%)	28(71.8%)	0.337
Age of initiation of alcohol intake			0.313
mean (SD) years	16.26 (5.78)	18.64(5.86)	
Median (range)	15(5-34)	17(5-32)	
Duration of intake: median (range)	23 years (5-55)	20 years (6-49)	0.186
Duration of ADS: Median (range)	5 years (1-30)	5 years (1-27)	0.955
Drinks per day :units\day	10-19: 14 (35.9%)	10-19 and 20-29: 15 (38.5%) each	0.461
Last intake of alcohols ,days			0.196
Mean (SD)	12.44 (4.83)	13.72 (3.78)	
Median (range)	12 (5,25)	13 (7,25)	
Serum AST U\L	197 (140)	186 (129)	0.72
Serum ALT U\L	163 (113)	148 (131)	0.60
Serum GGT U\L	412 (350)	572 (384)	0.058
Severity of alcohol dependence: Moderate (16-30)	24 (61.5%)	25(64.1%)	0.78
SOCRATES score	82	85	0.054

Table 2 shows there were no significant differences between treatment groups in terms of baseline clinical variables.

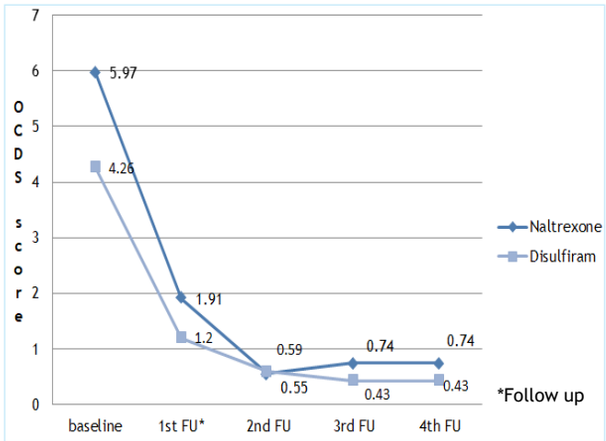

Figure 1. Comparison of OCDS score.

As shown in figure1, in both the groups craving was reduced at each follow up visits compared to baseline and this reduction was highly significantly ($p<0.001$) whereas the OCDS score were similar between the two groups, ($p>0.05$).

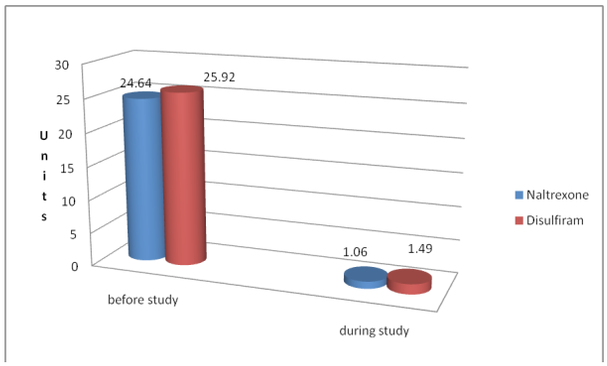

Figure 2. Alcohol intake (Units) before and during study beween two groups.

Figure 2 shows the difference in mean (SD) amount of alcohol consumed before and during the study period was highly significant ($p<0.001$) in both the groups whereas there was no significant difference between the groups ($p>0.05$).

Proportion of Participants who resumed alcohol during study period were more in Disulfiram group [11(28.2%)] than in Naltrexone group [8(20.5%)]. In 7(17.9%) participant from disulfiram group and 2(5.1%) participants from naltrexone group whether they were abstinent or not could not be determined. The median (range) days to alcohol consumption was 20 (5, 87) days and 16.5 (3, 50) days in respective groups.

Relapse cases were more in Naltrexone group {4(10.3%)} than in Disulfiram group [2(5.1%)]. Lapse or relapse could not be determined in 8(20.5%) participant from naltrexone group and 2(5.1%) participants from disulfiram group. The mean days to relapse was 43.75 days and 32.50 days in respective groups.

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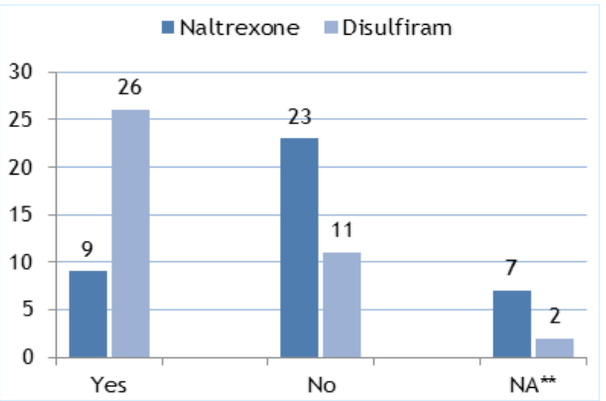

Figure 3. Side effects between two groups.

As shown in figure 3 side effects were more in disulfiram group than in naltrexone group and the difference was highly significant ($p<0.001$).

Table 3. Side effects between two groups.

	Naltrexone	Disulfiram	Total
Nausea\ vomiting	1(2.5 %)	8(20.51%)	9
headache	4(10.25%)	16 (41.02 %)	20 (51.25%)
dizziness	0	14 (35.89%)	14
fatigue	0	3 (7.69%)	3
Decrease appetite	2 (5.12%)	5 (12.82%)	7
palpitation	1(2.5 %)	5(12.82%)	6
Sedation\ disturbed sleep	0\2 (0/5.12%)	1\3 (2.5\7.69%)	1\5
Chest pain\ breathless	0	4(10.25%)	4
restlessness	2(5.12%)	0	2
Others	bodyache: 1(2.5%)	Bodyache: 6	10
		epigastric pain:1	
		Tinglingsensation & diarrhoea:1	
		alter taste:1	

The major side effect was headache in both the groups. It was followed by dizziness, nausea and vomiting in disulfiram group and restlessness and decrease appetite in naltrexone group. Alcohol disulfiram reaction occurred in 5 (12.82%) patients.

Most dropouts were due to lost follow up [NTX- 10(71%), DSF- 2 (50%)], followed by Craving [NTX- 4 (28.6%), DSF- 2(50%)], and left medication (compliance issue) [NTX-3 (21.4%), DSF-2(50%)].There are no dropouts due to side effects. The median (range) days to dropout was 45 (3, 90) days and 18 (14, 30) days in Naltrexone group and Disulfiram group respectively.

DISCUSSION

Concept of alcoholism had evolved as chronic disease condition with frequent cravings and relapses. There were evidences of neurobiological basis as etiology and pharmacological agents were used targeting at craving and enhancing abstinence, improving drinking behavior, and preventing relapse.[7,8] In this study comparison between two FDA approved drugs- Naltrexone and Disulfiram with regard to above outcomes and along with them tolerability of the drugs and dropout from the treatment were also considered as primary outcome. The results of this study were mixed with similarities and differences when compared with the previous outcomes.

This study was similar to comparative studies done in India in 2004[9] and 2008[10] but with shorter duration of follow up period i.e. 12 weeks due to limitation of time period.

In terms of sociodemographic variable, there was significant difference in terms of gender, education level and income whereas in terms of clinical variables there was no significant difference between two groups.

In both the studies done in India, naltrexone had a better

outcome in terms of reduction in craving.[9,10] Whereas in another study in 2005, the disulfiram treated subjects reported lower levels of craving than the naltrexone treated subjects.[11] In a comparative trial done in 2007 between acamprosate, naltrexone and disulfiram there was significantly reduction in craving and disulfiram was superior to others.[12] Similarly, in this study there was significant reduction in craving ($p<0.001$) at each follow up compared to the baseline but with no significant difference between two groups ($p> 0.05$).

In two separate trials, there was significant reduction in amount of alcohol intake in all the drug groups and the reduction in amount was more in disulfiram group than others.[9, 12] In this study, there was significant reduction in amount of alcohol intake ($p<0.001$) during treatment in both the groups with no significant difference between the groups ($p>0.05$). Proportion of participants who resumed alcohol intake were more in disulfiram group [11(28.2%)] than in naltrexone group [8(20.5%)] but with no significant difference between the two groups, p value > 0.05.

In previous comparative trials, the average days to first drink was variable, in naltrexone group: (i) 44 days (ii) 16 days iii) 67days, in disulfiram group: (i) 103 days (ii) 30days (iii) 70 days respectively.[9,11,12] Disulfiram was significantly effective in maintaining abstinence in first two of three trials. In this study the median (range) days to first alcohol consumption was 16.5(3, 50) days and 20(5, 87) days in naltrexone group and disulfiram group respectively with no significant difference between two groups at 0.05 level and this was similar to study in 2007 with 12 week follow up period.

In a trial done in 2004 with 1 year follow up, relapsed cases were 56% in naltrexone group and 14% in disulfiram group with days to relapse [mean(SD)] 63(33) days and 119(21) days respectively.[9] Similarly, another trial in 2008 with 6 month follow up, relapsed cases were 21% in naltrexone group and 4 % in disulfiram group with days to relapse 51 days and 84 days respectively.[10] In another comparative trial done in 2007, days to relapse in naltrexone group was 22(22) days and in disulfiram group was 47(27) days.[12] In all these studies disulfiram was superior to naltrexone in relapse prevention. Similarly, in this study proportion of participants who relapsed were more in NTX group [4(10.3%)] than in DSF group [2(5.1%)] and the mean days to relapse being 44 days and 33 days respectively but with no significant difference between two groups. However undetermined cases [NTX: 8(20.5%), DSF: 2(5.1%)] are not included as relapse and if so done the difference would had been significant.

In various comparative trials, tolerance of these two drugs showed variable results. In trial conducted in India in 2004 side effects were more common in the naltrexone group than in the disulfiram group, in the form of nausea (33% and 5%), drowsiness (12%and 1%), abdominal pain (10%and 1%) and diarrhoea (8%and 1%) respectively. All these side-effects were present only within first two weeks of initiating therapy.[9] Whereas in another similar trial done in 2008 no side effects were reported.[10] In another study 31.1% in disulfiram group and 39.8% in naltrexone group reported side effects. The most common adverse effects reported in disulfiram group were tiredness and headache and in naltrexone group were nausea, headache and tiredness.[12] Whereas in the other trial subjects on disulfiram were more likely to experience fever and on naltrexone were more likely to experience nervousness or restlessness.[11] In this study side effects were more in Disulfiram group and highly significant ($p<0.001$). Overall the most common side effect was headache (NTX: 10%, DSF: 41%).In disulfiram group other side effects were: dizziness 36%, nausea 20%, bodyache 15%, decrease appetite\palpitation 13% each, chest pain\breathless10%, epigastric pain\ Tingling sensation\diarrhoea in 5% each and altered taste in 2.5%. Alcohol disulfiram reaction occurred in 5 (12.82%) but all were mild in intensity and self limiting. In naltrexone group other side effects were decrease appetite\disturbed sleep\restlessness:5% each, along with nausea, palpitation and bodyache in 2.5% each.

In a trial done in India in 2004, dropped out cases in disulfiram group was 4% (2 subjects), one due to side effects and other due to stopping medication. In the naltrexone group dropout was 2% and it was due to irregular follow up. Another similar study in 2008 had 7% (2 subjects) dropouts from each group due to stopping treatment.[9,10] In another study in 2005, dropout subjects were 35%.[11] In the trial in 2007 at the end of the first twelve-week study period, the total drop-out rate was 25.1% (29.3% in ACA, 25.9% in DSF and 20.0% in NTX).The most common reason was poor compliance or protocol violation (change of medication).[12] In this study disulfiram was superior to naltrexone in terms of retention in regular treatment. Dropouts were more in naltrexone group than in disulfiram group: 14(35.9%) vs 4(10.3%). In naltrexone group majority 10(71%) were due to lost to follow up followed by craving (28%) and stopping medication (21%) whereas in disulfiram group 2 subject(50%) each dropped out for each reasons. This difference in dropout between two groups was significant ($0.001>p<0.01$) at 5% level. One of the reasons

for more dropouts in naltrexone group may be its high cost. Dropouts due to side effects were not present in both the groups. The median days to dropout was 45 days and 18 days in naltrexone group and disulfiram group respectively and the difference was statistically significant.

Supervised use of disulfiram was recommended for the treatment of alcoholism by several authors.[13-16] Supervision was considered for both the groups as to avoid bias in treatment outcome. Supervision and follow up with family member was encouraged. Psychological intervention based on approaches of Cognitive-behavioural therapy and motivational interviewing was carried out at each follow up.

This was an open label study and the investigator was not blinded. Knowing cost difference between the drugs may have affected allocation of clients in each group. Estimation of alcohol consumed in terms of units cannot be made with certainty as concentration of different types of locally brewed alcohol could not be ascertained well. The reliability of information at follow up regarding compliance and alcohol use was from the report made by a family member rather than client him\ herself and this may have had some negative impact in rapport. The brief psychological intervention that was carried out to each participant though structured its evaluation was not done.

CONCLUSIONS

Disulfiram and naltrexone were equally effective in reducing craving, reducing amount of alcohol intake, and preventing relapse in 12 weeks period. Naltrexone was better in terms of tolerability whereas disulfiram was better in terms of dropout and retention in treatment.

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