ORIGINAL ARTICLE

An open label comparison of efficacy of low dose topiramate with naltrexone in preventing alcohol relapse

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Abstract

Introduction: *Alcohol use disorder is a relapsing and remitting disorder. Preventing alcohol relapses has been a difficult task. The available drugs do not have adequate outcome in diverse needs. Topiramate, a GABAergic anticonvulsant, has been useful for the prevention of alcohol relapse as demonstrated in western studies. We compared the efficacy of Topiramate at 100mg with Naltrexone 50 mg in preventing relapse among Nepalese alcohol dependence patients.*

Methods: *Following an inpatient alcohol detoxification, 37 patients taking Topiramate 100 mg and 41 patients taking Naltrexone 50 mg were followed up as outpatients at 1, 4, 8 and 12 weeks in order to monitor their abstinence period, craving for alcohol and alcohol use pattern.*

Results: *At the end of 12 weeks follow up, Topiramate is as good as Naltrexone 50 mg in terms of maintaining abstinence (27% vs 31.7%, p=0.651) and reducing the daily alcohol intake. Topiramate is better than Naltrexone in decreasing craving at 12 wks (p=0.015).*

Conclusion: *Topiramate 100 mg is equally efficacious to Naltrexone 50 mg in reducing alcohol craving and maintaining abstinence.*

Keywords: Topiramate, Naltrexone, Relapse Prevention

INTRODUCTION

Alcohol use disorder is now regarded as a chronic relapsing and remitting disorder. Worldwide about 4% of all deaths are attributed to alcohol, which is more than the deaths caused by HIV/AIDS, violence or tuberculosis.[1] It is the leading risk factor for death in males ages 15–59, mainly due to injuries, violence and cardiovascular diseases. It is the third highest risk for disease and disability, after childhood underweight and unsafe sex. Yet, the alcohol use disorder remains a low priority in public health policy[1].

Use of alcohol is universal phenomenon in Nepalese society, as the traditional sanctions and caste-bound restraints have disappeared. Many people drink alcohol as required in cultural rituals. People make alcohol at home. The local wines (Chhyang, Tongba, Jand etc.) are included in the daily meals. In a community survey, 60 % of the Nepalese population have experienced alcohol and 41% have taken it

during the last 12 months and 10 per cent are daily users of alcohol.[2] Another community based study in the eastern city of Dharan showed that the prevalence of alcohol dependence was 25.8% by CAGE questionnaire.[3] With the increasing use of alcohol in the society, alcoholism is producing a huge health care cost directly or indirectly.

Alcohol use disorder is now regarded as an illness with robust biological basis. Alcohol alters the brain's structure and function which remains even after alcohol use has stopped. This is the reason people are at risk for relapse even after abstinence. Relapse rate is very high after abstinent attempts.

Food and Drug Administration (FDA), USA, has approved Disulfiram, Acamprosate and Naltrexone for relapse prevention in alcohol dependence. Only Disulfiram and Naltrexone are available in Nepal. But, these drugs are not adequate for the need of the diverse group of people. Topiramate, FDA approved drug for seizure and migraine, is found to be useful in relapse prevention. Topiramate facilitates the GABA signal and inhibits the Glutamate neurons, which decreases the dopamine level in reward circuit resulting in the decrease in euphoric effect of alcohol.[4] The efficacy in reducing alcohol relapses has been seen in the placebo controlled trials. [5-8] Topiramate also reduces the relapses induced by the cues[9] and the first drink following abstinence[7] thus blocking the mechanisms of relapse of alcohol. When compared with standard anticraving agent naltrexone, topiramate at 300 mg/day is as good as or even better than naltrexone in preventing alcoholic relapses[10, 11]

There is an interesting observation that topiramate even at dose of 100 mg/day was significantly better than placebo [8, 12] and useful in maintaining abstinence and preventing relapses. [13, 14] This can have several implications. If clinical usefulness can be demonstrated at lower dose, dose related side effects would be fewer and treatment becomes less costly. However, we need more evidences to support these observations. Moreover, the studies in South Asian countries are scarce to get the inferences for the population. Thus, we compared the efficacy of Topiramate 100 mg with Naltrexone in Nepalese alcohol dependent individuals. We expected that the findings will be useful in guiding clinicians and adding the evidences in the field of anticraving agents.

MATERIAL AND METHOD

Type and Design of study:

This is a prospective naturalistic open level comparison of Topiramate with Naltrexone.

Participants and context:

This study was conducted at Psychiatry OPD and De-addiction ward, Maharajgunj Medical Campus, Teaching Hospital, Kathmandu, Nepal. This is the oldest University Teaching Hospital of Nepal. It is a tertiary care hospital where patients all over the country get referred for the treatment. All patients who came to the hospital during this 8 months period for alcohol related problems were screened. The participants were recruited from the in-patient and out-patient clinics from Nov 2012 to Aug 2013.

Sample:

It consists of men and women between 15 to 65 years of age and fulfilling the diagnostic criteria for Alcohol Dependence Syndrome according to ICD 10 Diagnostic Criteria for Research. Subjects with co-morbid substance use problem except Nicotine were excluded. Similarly, those with another current Psychiatric diagnosis except personality disorder, those with the clinical history of mental retardation, those who with renal impairment, renal stones, seizures, or unstable hypertension and those not willing for the informed consent were excluded.

Procedure:

All 173 alcohol dependent patients presented to the hospital during study period were screened for possible enrollment in the study. After exclusion, the remaining 120 patients receiving inpatient detoxification and 11 receiving detoxification on out-patient basis were discussed about the anticraving medications. Eighty five clients chose to take Naltrexone or Topiramate. Only 76 of them agreed for the informed consent. They were then assessed with Semi-structured Proforma, Readiness to Change Questionnaire[15]and Obsessive-Compulsive Drinking Scale (OCDS). [16]

Patients in the Naltrexone group were prescribed a 50 mg tablet once daily with no further escalation. Patients in Topiramate group was given a 25 mg tablet in the evening which was increased to 25 mg bid in second week, and then was increased at 25mg per week up to

100mg. The participants were followed up at 0, 1, 4, 8, 12 wks. The follow up assessment was done with OCDS along with semi structured proforma. The comparison will be done between Naltrexone and Topiramate based on these outcome measures.

Outcome measure:

The outcome of the research is based on the abstinence period (The duration when there was no alcohol intake reported), and the proportion of participants abstinent at 12 weeks, the amount of alcohol consumed after the enrolment in the treatment, and the craving as shown by total OCDS score.

Tools:

The semi-structured Performa:

The semi-structured Performa was used to study the socio-demographic profile and other relevant information of the patients like duration of alcohol intake, duration of alcohol dependence, average amount of alcohol intake in atypical day, previous attempts to quit alcohol if any, any co-morbid medical problems or medical problems related to alcohol use and the family history of alcohol dependence. The semi-structured Performa for follow up included the duration of abstinence, the amount and the frequency of drinking if restarted.

Readiness to Change Questionnaire:[15]

The Readiness to Change Questionnaire (RCQ) is a short and useful measure to find out the drinkers stage of change based on the model developed by Prochaska and DiClementel. It is a 12-item instrument. All items are scored on a 5-point rating scale ranging from: -2 (Strongly disagree),-1(Disagree) 0 (Unsure), +1 (Agree), +2 (Strongly agree). To derive the readiness to change score, the combined contemplation and action stages score were added with the precontemplation score with reverse sign (- changed to + and + changed to -).

Obsessive-compulsive drinking scale (OCDS): [16]

The OCDS is a modified version of the Yale-Brown Obsessive Compulsive Scale (Modell JG et al 1992). The scale is a valid instrument to measure craving for alcohol. It measures various aspects of craving like the urge to drink alcohol, thoughts about alcohol and the struggle to control the urge. It consists of 14 items which takes about five minute to fill up.

Statistical analyses:

Thus obtained data was fed into the computer and a master sheet was produced in the Windows Excel 2010. Further analyses were done in SPSS 17.0. The abstinence period is presented in median, the amount of alcohol consumed after the enrolment in the treatment is presented in median with interquartile range.

Ethical issues:

The approval for the research was taken from the Ethical Review Board of the Institute. The participants were well informed about the advantages and the disadvantages of taking or not taking medicines, including the cost of the treatment. The decision to take medication was taken with the active participation of the patient as well as family member. The informed consent was taken from all the participants. They knew that they can withdraw the consent anytime during the study and that the withdrawal from the study will not affect patient care in the days to come.

RESULT

Table 1: Socio demographic and clinical characteristics of participants (N=78)

Characteristic	Mean ±SD , Median (Interquartile range), Number(%)
Age of the participants (years)	41.60±8.55
Age of initiation of alcohol consumption (years)	19.56±5.18
Duration of dependence on alcohol (years)	5.50 (3,10)
Diagnosis at presentation	
Uncomplicated withdrawal	34(43.6%)
Withdrawal seizures	8(10.3%)
Delirium tremens	30(38.5%)
Alcohol Induced Psychotic Disorder	2(2.6%)
Withdrawal Seizures and Delirium tremens	4(5.1%)
Education	
Illiterate	8(10.3%)
School level	62(79.5%)
College and above	8(10.3%)

Sample characteristics:

As shown in Table 1, the mean age of the participants is 41.60±8.55 years with mean age of initiation of alcohol intake of 19.56±5.18 years. The median duration of established alcohol dependence was for 5.5 years.

More than half of the participants had developed complicated withdrawal (38.5% had Delirium Tremens, 10.3% had withdrawal seizure, 5.1% had both). Most of the participants had education up to school level and above.

The socio-demographic variables (Table 2) like mean age of the participants, education, ethnicity, occupation were equally represented in both the groups taking Topiramate and Naltrexone. Similarly, clinical variables like family history of alcohol use disorder, mode of presentation, and the longest abstinence duration in the past were also similarly represented in both the groups.

Main efficacy results:

At the end of 12 weeks, there is no significant difference in the proportion of the participant that remained abstinent [27% for Topiramate and 31.7% for Naltrexone; p=0.651] (table 3). The median abstinence duration after the start of the study was 65 days for Topiramate and 70 days for Naltrexone group. This is not significantly different (p=0.525). The reduction in OCDS score compared to the baseline score is highly significant in both the groups as shown in figure 1. But, the decrease in craving as shown by the OCDS total score is not different between Topiramate and Naltrexone in first (p=0.083) and second month (p=0.948). However, Topiramate is better than Naltrexone in decreasing craving for alcohol at 3rd month (p=0.015) as shown by the total OCDS score (table 4).

Table 2: Comparison of socio-demographic characteristics between the treatment groups (N=78), n (%)

Characteristic	Topiramate	Naltrexone	Total	p value
Mean (SD) age of participants (yrs)	42.97(8.2)	40.37 (8.7)		0.181**
Education				
Illiterate	5 (13.5)	3 (7.3)	8 (10.3)	0.466*
Literate	32 (86.5)	38 (92.7)	70 (89.7)	
Ethnicity				
Brahmin/Chhetri	19 (51.4)	14 (34.1)	33 (42.3)	0.055*
Newar/Gurung/Tamang	15 (40.5)	18 (43.9)	33 (42.3)	
Dalit/ Others	3 (8.1)	9 (22.0)	12 (15.4)	
Occupation				
Professional/Semiprofessional	4 (10.8)	9 (22.0)	13 (16.7)	0.113*
Clerk/Skilled/Semiskilled	18 (48.6)	21 (51.2)	39 (50.0)	
Unskilled/Unemployed	15 (40.5)	11 (26.8)	26 (33.3)	
Mode of presentation				
Outpatient	23 (62.2)	21 (51.2)	44 (56.4)	0.330*
Emergency	14 (37.8)	20 (48.8)	34 (43.6)	
Family history of Alcohol Use Disorder				
Present	13 (35.1)	18 (43.9)	31 (39.7)	0.429*
Absent	24 (64.9)	23 (56.1)	47 (60.3)	
Longest abstinence duration (days)	28 (0,560)	14 (0,364)		0.828***

** Chi square test ** Independent sample t test *** Mann-Whitney U test*

Table 3: Comparison of outcome measures between the treatment groups

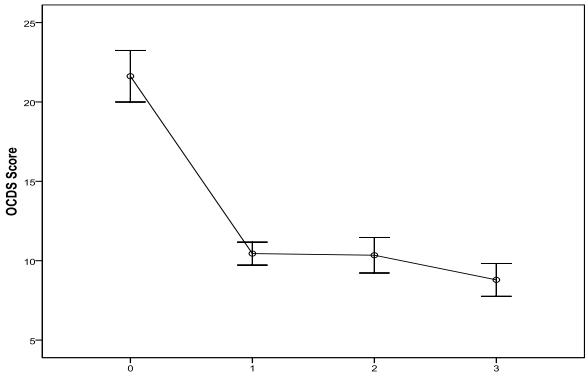
Characteristic	Topiramate	Naltrexone	p value
Abstinent days after start of study (median with interquartile range)	65 (23,90)	70 (30,90)	0.525*
Proportion of participants abstinent for 90 days	27%	31.7%	0.651**

** Mann-Whitney U test*
*** Chi square test*

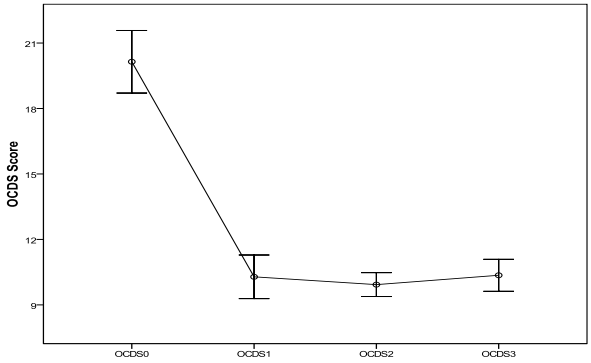
Table 4: Obsessive Compulsive Drinking Scale scores of study participants, mean (SD)

OCDS	Topiramate	Naltrexone	p value
Baseline	21.51 (4.17)	20.07 (3.83)	0.121
First month	11.47 (3.36)	10.27 (2.55)	0.083
Second month	10.34 (2.94)	10.38 (1.63)	0.948
Third month	8.79 (2.71)	10.36 (1.89)	0.015

Figure 1: Comparison of OCDS Scale at baseline and follow up visits for Topiramate (Upper panel) and Naltrexone (Lower panel)treatment groups (Error bars represent mean values with 95% Confidence Intervals) *
Paired sample t test



Topiramate:
Baseline vs First month (t=10.82, p<0.001)*
Baseline vs Second month (t=12.47, p<0.001)*
Baseline vs Third month (t=13.206, p<0.001)*



Naltrexone:
Baseline vs First month (t=16.04, p<0.001)
Baseline vs Second month (t=15.38, p<0.001)
Baseline vs Third month (t=14.53, p<0.001)

DISCUSSION:

Topiramate is a newer drug being investigated as an anti-craving agent. Since 2003, there have been several controlled clinical trials done with encouraging results. Most of the studies used Topiramate 300mg per day and reported that Topiramate is significantly better than placebo and as good as or even better than Naltrexone in reducing Alcohol relapse. We found that topiramate 100 mg is as good as naltrexone 50 mg in maintaining abstinence (27% for Topiramate and 31.7% for the naltrexone, p=0.651) at the end 12 wk among Nepalese population. Our finding is similar to the finding in the study of Danilo Antonio Baltieri which reports that at the end of their study (12th week), although the proportion of subjects completely abstinent was higher in the topiramate group, this difference was no longer statistically significant (P = 0.08).[12] However, the proportion of the subjects maintaining abstinence at the end of 12 wks is lower in our participants than in the Baltieri's sample (27% Vs 47.05%) [12] . The difference in the abstinence rate between the Baliteri group and our Topiramate group may be because our sample is hospital based and was not randomized. And we interpreted those who did not come for follow up as treatment failure. Similarly, Narayana PL have shown that the abstinence at one year among the Indian participants taking 100mg of Topiramate is as high as 76.3%. [14] Though, abstinent rate at 12 wks is not analysed

in Narayana's sample, the high rate of abstinence at 12 months may be because their study participants were all Indian army who will be invalidated of their service if they get relapse within one year of the treatment. In the analysis of Obsessive Compulsive Drinking Scale score, Topiramate is found to be significantly associated with the reduction in craving due to alcohol as the decrease in OCDS score is highly significant at 4, 8 and 12 wks (p=0.001). This is in accordance to the findings from Paparrigopolous, who used 75 mg Topiramate. [13] In this study, the reduction from the baseline OCDS score is highly significant in each follow up. Similarly in other studies [10, 12] using OCDS, the decrease in mean score is significant at the end of the study. In our participants, though topiramate is comparable to naltrexone at 1st and 2nd month, topiramate out performed Naltrexone at 3rd month (p=0.015) in reducing craving as measured by OCDS. Our observation is different from that of other similar studies. The observation by Baltieri in Brazil shows that both Naltrexone (50 mg) and Topiramate (300 mg) were similar in terms of reduction of mean scores on OCDS (F = 0.03, P = 0.97) at 12 weeks. [12] Similarly, the findings from the Spanish investigator Gerardo Flórez also reveal that Naltrexone and Topiramate were similar in terms of reducing OCDS score at the end of 12 wks (p=0.514).[10] Our finding needs to be cautiously interpreted as OCDS is not validated into Nepalese context there is non-random allocation of the medicines to the participants.

We admit that we have many limitations in this work. We conducted the study in the hospital setting and we could not allocate the medicines randomly due to ethical issues. So, the results should be interpreted cautiously. Nonetheless, our sample represents dialy clinical sample and this work has given some insight that even lower dose Topiramate is of use in the treatment of alcoholism in our patients.

CONCLUSION:

Topiramate 100 mg is as efficacious as Naltrexone 50 mg in maintaining abstinence for 12 weeks, in decreasing the daily alcohol consumption, and in reducing craving at 12 weeks. Our study contributes important new data on the efficacy of Topiramate in the treatment of Alcohol Dependence, despite few limitations. The results of the study demonstrate the response of the Nepalese population presenting with Alcohol Dependence Syndrome to Topiramate or Naltrexone as relapse prevention agent. Thus, this finding further demands the need of well-designed controlled clinical trials in our population to prove our observation.

REFERENCES:

1. *Global status report on alcohol and health 2011. WHO Press, Switzerland, page x-xi. ISBN 978 92 4 156415 1.*
2. *Dhital R, Subedi G, Gurung YB, Hamal P. Alcohol and drug use in Nepal with reference to children. Child Workers in Nepal Concerned Centre (CWIN) 2001, Kantipur Offset Press, Kathmandu, Nepal. Page 80-81.*
3. *Jhingan HP[1], Shyangwa P, Sharma A, Prasad KM, Khandelwal SK. Prevalence of alcohol dependence in a town in Nepal as assessed by the CAGE questionnaire. Addiction 2003. Mar; 98(3):339-43.*
4. *White HS[1], Brown SD, Woodhead JH, Skeen GA, Wolf HH. Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. Epilepsia 2000; 41 Suppl. 1: Poster S17-20*
5. *Johnson BA, Ait-Daoud N, Bowden CL. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 2003, 361: 1677–1685.*
6. *Johnson BA, Ait-Daoud N, Akhtar FZ, Ma JZ. Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol: dependent individuals. Arch Gen Psychiatry 2004, 61: 905–912.*
7. *Ma JZ, Daoud NA and Johnson BA.Topiramate reduces the harm of excessive drinking: implications for public health and primary care. Addiction 2006, 101: 1561–1568*
8. *Johnson BA, Rosenthal N, Capece JA. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA 2007, 298: 1641–1651.*
9. *Farook JM[1], Morrell DJ, Lewis B, Littleton JM, Barron S. Topiramate (Topamax) reduces conditioned abstinence behaviours and handling-induced convulsions (HIC) after chronic administration of alcohol in Swiss-Webster mice. Alcohol Alcohol 2007. Jul-Aug;42 (4):296-300.*
10. *Flórez G, Saiz PA, Portilla PG, et al. Topiramate for the Treatment of Alcohol Dependence: Comparison with Naltrexone. Eur Addict Res 2011, 17:29–36*
11. *B. Arbaizar, et al.. Topiramate in the treatment of alcohol dependence: a meta-analysis. Actas Esp Psiquiatr 2010, 38(1):8-12*

12. Danilo Antonio Baltieri et al. Comparing topiramate with naltrexone in the treatment of alcohol dependence. Addiction 2008, 103: 2035–2044.
13. Paparrigopoulos et al. Treatment of alcohol dependence with low-dose topiramate: an open-label controlled study. BMC Psychiatry 2011, 11:41
14. PL Narayana, AK Gupta, and PK Sharma. Use of Anti-Craving Agents in Soldiers with Alcohol Dependence Syndrome. MJAFI 2008, 64 : 320-324.
15. Rollnick S, Heather N, Gold R, Hall W. Development of a short 'readiness to change' questionnaire for use in brief, opportunistic interventions among excessive drinkers. Br J Addict 1992. May;87(5):743-54.
16. Anton RF, Moak DH, Latham P. The Obsessive Compulsive Drinking Scale: A self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. Alcohol Clin Exp Res 1995, 19:92-99.