Brief Communication

Correlates of Baclofen Effectiveness in Alcohol Dependence

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ABSTRACT

Alcohol dependence is a global concern. Baclofen has shown promise as an anti-craving agent but its efficiency remains to be settled. We reviewed 549 male cases diagnosed with alcohol dependence who received Acamprosate (201) or Baclofen (348). 'Time to first drink' was compared between two groups and multiple regression analysis was done in baclofen group to identify correlates of effectiveness. There was a significant difference in outcome measure between Baclofen ($M = 4.44$, $SD = 3.75$) and Acamprosate group ($M = 3.73$, $SD = 2.19$); $t(547) = 2.45$, $P = 0.01$. Initial regression analysis with six predictor variables (average daily alcohol units, current age, age at onset of dependence, family history, duration of dependence and dose of baclofen in mg/day) showed significant correlation of outcome variable with only two predictor variables — dose of baclofen and average daily intake. Using the hierarchical method it was found that 'dose of baclofen' and 'average alcohol intake' explain a significant amount of variance in 'time to first drink'. [$F(1, 345) = 182.8$, $P < 0.001$, $R2 = 0.52$, $R2_{adjusted} = 0.51$]. This information can be used to select patients in long term longitudinal studies and may explain variable results seen in clinical trials of baclofen done earlier.

Key words: *Alcohol, anticraving, Baclofen, correlates, effectiveness*

INTRODUCTION

Alcohol dependence represents a global health problem with high morbidity and mortality.[1] Approved pharmacological treatments include a deterrent agent (Disulfiram) and two anti-craving agents; Acamprosate and Naltrexone. Recent reviews show that both anti-craving agents have similar[2] and moderate effects.[3,4] Multiple other drugs with different mechanisms of action are being investigated as anti-craving agents.[5]

Patient characteristics and genetic factors contribute to variable treatment response to a specific agent. For instance, positive family history, high craving predict good response to Naltrexone while late age of onset, protracted withdrawal predict good response to Acamprosate.[5] Thus there is a movement towards patient oriented treatment plan.[6]

The potential of Baclofen as a maintenance treatment for alcohol dependence has been highlighted in case reports, case series, open label studies and randomised trials.[7] However, there is also the contradictory finding as one double blind randomised controlled trial failed to detect any difference between Baclofen and placebo.[8] This raises the important question on whether heterogeneity in patient characteristics and drug dosing may be responsible for these findings. Specifically, in the study published by *Garbutt et al.*,[8] severity of alcohol dependence was lower than Italian

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studies.[9] Another factor that needs investigation is optimal dose. Post-hoc data analysis of International Baclofen intervention study (IBIS) indicates superiority of 60 mg/day dose over 30 mg/day dose.[10] High dose baclofen therapy is being used as an off-label treatment in some parts of world, with encouraging results.[11,12] To sumarise, optimal dosing and patient related factors are important factors that need investigation to improve patient selection in future trials and in clinical practice.

We report a review of outcome with use of baclofen as an anti-craving drug in alcohol dependent patients voluntarily seeking out-patient services at a specialized de-addiction center. Our aim is to study relationship between patient related factors (age, age at onset of alcohol dependence, and family history), addiction severity (average daily alcohol intake and duration of dependence) and treatment response to baclofen (time to first drink).

MATERIALS AND METHODS

Setting

The study was carried out at the Centre for Addiction Medicine (CAM), a tertiary care de-addiction center of South India attached to the National Institute of Mental Health And Neurosciences (NIMHANS), Bangalore, India. Patients attending the CAM out-patient services are evaluated using a 166 item semi-structured questionnaire. The questionnaire contains information on socio-demographic details, substance use profile and other clinically relevant details. Diagnosis of alcohol dependence (ADS) is made based on self-report and interview of a family member by a consultant psychiatrist using ICD-10 criteria.[13] Alcohol use is quantified using frequency and quantity taken on a typical occasion (operationalised as units of alcohol 1 unit = 10 grams of alcohol).

Sample

1.1 For the current study we reviewed case records of out-patients who received a diagnosis of ADS and selected cases based on following criterion:

- First contact with de-addiction services during a period of one year (January 2013 to January 2014).
- Absence of any other substance use disorder (except nicotine dependence), psychiatric disorder, serious medical disorder including seizure disorder.
- Complicated withdrawal requiring in-patient admission.
- Baclofen/Acamprosate having been started as an anti-craving agent.
- Compliance with prescribed dose of anti-craving till outcome event of first drink (patients who

stopped anti-craving or reduced dose prior to this were excluded).

Outcome measure

Time to first drink in months (irrespective of quantity) as reported by patient and family member during the follow up period was taken as an outcome measure.

Statistical analysis

Data was analysed using Statistical package for social sciences version 17 (SPSS 17). All variables except family history are continuous variables. Family history was coded as 0-absent and 1-present. A comparison was done between patients who received baclofen and those who received Acamprosate. Age at onset, duration of dependence, family history average daily intake and time to first drink were compared. Further, in baclofen sub-group, multiple linear regression was done with 'time to first drink' as dependent variable and six predictor variables: Average daily alcohol units, current age, age at onset of dependence, family history, duration of dependence and dose of baclofen in mg/day. Initial analysis was done using 'forced entry' and variables with significant ($P < 0.05$) correlation were then used to construct final regression model. Standardized residuals and Cook's distance was checked for outliers and influential cases. Correlation between predictor variables was checked for colinerarity.

RESULTS

A total of 755 case records were reviewed, 206 cases (100 baclofen and 106 Acamprosate) were excluded as they stopped or reduced dose of anti-craving prior to first drink. In a study sample of 549 cases, 348 cases received baclofen while 201 cases received Acamprosate. All subjects were men, with mean age of 38.8 years ($SD = 10.27$). Mean age at onset of alcohol dependence was 25.4 years ($SD = 8.20$) and mean duration of dependence was 12.6 years ($SD = 8.9$) at the time of first consultation. Family history of alcohol dependence in first degree relatives was present in 344 (62.6%) cases. Mean daily intake of alcohol in this sample was 15.1 units ($SD = 8.03$) where 1 unit was taken as equivalent to approximately 10 grams of ethanol. Mean dose of Baclofen in mg. per day was 50.76 ($SD = 21.67$). Mean time to first drink was 4.2 months ($SD = 3.28$). Median time to first drink was 3.5 months and Interquartile range was 1.5-6 months. ($SD = 3.75$).

Baclofen ($N = 348$) and Acamprosate group ($N = 201$) were similar in terms of age of the patient, duration of dependence, age at onset, average daily intake and positive family history *(P = 0.6, 0.08, 0.10, 0.38 and 0.5 respectively)*. An independent sample *t*-test

was conducted to compare mean time to first drink in Baclofen and Acamprosate group. There was a significant difference between Baclofen (*M = 4.44, SD = 3.75*) and Acamprosate group (*M = 3.73, SD = 2.19*); *t* (547) = 2.45, *P* = 0.01.

Further analysis to explore correlates of baclofen efficiency was done on baclofen group (*N* = 348). Initial regression analysis with 6 predictor variables (average daily alcohol intake, current age, age at onset of dependence, family history, duration of dependence and dose of baclofen in mg/day) showed significant correlation of outcome variable with only two predictor variables — dose of baclofen and average daily alcohol intake. Final model included these as predictor variables and results are summarised in Table 1. Using the hierarchical method it was found that 'dose of baclofen' and 'average daily alcohol intake' explain a significant amount of variance in 'time to first drink'. (*F* (1, 345) = 182.8, *P* < 0.001, R^2 = 0.52, $R^2_{adjusted}$ = 0.51).

Colinearity between dose of baclofen and average daily alcohol use was not found (*r* = 0.45, *P* = 0.2). There were no outliers or influential cases.

DISCUSSION

A preliminary comparison between baclofen and an approved anti-craving agent, Acamprosate showed superiority of baclofen in this sample. This was followed by analysis of variability in response.

This study shows that variability in effectiveness of baclofen as an anti-craving agent could be because of various factors. In this sample 52 % variance in baclofen response was explained by dose of baclofen and average alcohol intake. This represents a moderate effect.[14] Model has good statistical generalisability (R^2 -$R^2_{adjusted}$ = 0.01 that is. a 1% shrinkage if model was used on a different sample).[14]

There are multiple outcome measures used in addiction research like cumulative abstinence rates, time to relapse to heavy drinking and various biochemical parameters. We used 'time to first drink' as an outcome measure as patients had completed detoxification, and were abstinent at the time of baclofen initiation. Self-reported 'time to first drink' has been used in earlier studies.[8] Subjects included in this review had severe alcohol dependence reflected by an average intake of 14 units (140 grams of ethanol) per day and mean duration of dependence of 13 years. As per World health Organization (WHO) guidelines this represents 'at high risk' drinking.[15] Patients requiring other psychotropic or anti-epileptic drugs or having multiple substance use were excluded as it has been shown to confound outcome.[9]

This study supports earlier contention that Baclofen may be more effective in patients with severe alcohol dependence and higher daily intake.[9] In the current sample 25% variance in outcome measure was explained individually by quantity of alcohol intake.

Further a dose-response relationship was confirmed in this sample as earlier speculated.[10] Subjects in this review received a flexible dose unlike in trials and thus no optimal dose can be deduced. However, difference in dose accounted for around 26% of variance in outcome. This supports some case series and open label studies using high dose Baclofen.[12] No relationship was found between current age of subjects, family history of alcohol dependence, age at onset of dependence or duration of dependence with outcome measure. Earlier studies have also not found any such relationship.[5,7] This distinguishes Baclofen from other anti-craving agents like Acamprosate, Naltrexone and Topiramate that have differential efficacy based on 'typology of alcoholism'[5,16]

This study has a number of limitations like, retrospective design and lack of biomarkers to evaluate abstinence and a biased sample as only patients who came for treatment after detoxification were studied. However it has a good sample size and is adequately powered to study correlates of treatment response in short-term.

To summarize, present study shows a strong correlation between doses of baclofen used, average alcohol intake and time to first drink in a selected sample with severe alcohol dependence. Further long term, randomised study are needed to establish factors associated with optimal response to Baclofen.

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Table 1: Correlates of baclofen effectiveness

Model and Parameters	B	Standard Error	Beta-coefficient
Model 1			
constant	−0.07	0.44	
Dose of Baclofen	0.09	0.01	0.51
Model 2			
constant	−3.44	0.43	
Dose of Baclofen	0.85	0.01	0.49
Average Alcohol Intake (In units per day)	25	0.02	0.05

Model 1 – R^2 = 0.264, $R^2_{adjusted}$ = 0.262, F (1,346) = 124.2, *P* < 0.001; Model 2 – R^2 = 0.519, $R^2_{adjusted}$ = 0.516, F (1,345) = 182.8, *P* < 0.001

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