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Research Paper

Safety Profile, Compliance, and Effectiveness of Baclofen and Acamprosate in Alcohol Use Disorder- A Retrospective Cohort Study

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ABSTRACT

Background: Alcohol is the most common psychoactive substance used by Indians, about 14.6% or 16 crore Indian citizens consumes alcohol. Further, about one in five alcohol using men suffer from alcohol dependence. **Objective:** To compare the compliance, adverse effects profile, and effectiveness of baclofen and acamprosate in the management of alcohol use disorders. **Methods:** A retrospective cohort study was conducted by enrolling patients seeking treatment for Alcohol use disorder. Hospital records were reviewed for patients prescribed either baclofen or acamprosate as part of treatment. Data regarding patient demographics, compliance rates, adverse effects, and relapse rate were analyzed. **Results:** A total of 74 patients were included with 39 receiving baclofen and 35 receiving acamprosate. Compliance rates were significantly higher for patients receiving baclofen, in comparison to the acamprosate group. Adverse effects were significantly higher among patients given acamprosate, with the most common adverse effects being abdominal discomfort. A statistically significant difference was observed, with the Baclofen group (82 days) exhibiting a longer mean time to first drink compared to the Acamprosate group (66 days). Taking lower relapse of alcohol consumption as an indicator for effectiveness, baclofen was more effective than acamprosate, however, the difference between the two treatment groups was statistically insignificant ($p = 0.220$). **Conclusion:** Baclofen was better tolerated with fewer adverse effect thus contributing to higher compliance rate. However, the higher compliance rate did not result in significantly lower relapse rate. Further large scale, prospective investigations are urgently needed to determine real world effectiveness.

Keywords: *Alcohol, Addiction, Acamprosate, Baclofen*

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Safety Profile, Compliance, and Effectiveness of Baclofen and Acamprosate in Alcohol Use Disorder- A Retrospective Cohort Study

Alcohol has been an integral part of human culture for centuries, often used for social, religious, and recreational purposes(1). However, the excessive and problematic consumption of alcohol can lead to a serious medical condition known as Alcohol Use Disorder (AUD)(2). Alcohol Use Disorder, commonly referred to as AUD, is a chronic, relapsing brain disorder characterized by an impaired ability to control alcohol consumption despite adverse consequences(2). It encompasses a wide range of behaviors, from moderate to severe, that impact an individual's physical health, relationships, and overall well-being(2). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), AUD is diagnosed based on specific criteria, such as the inability to cut down on alcohol consumption, spending a significant amount of time obtaining or recovering from alcohol's effects, and continued use despite the knowledge of its negative effects(3).

According to a national level survey concluded in 2019, approximately 14.6% of the population (ranging from individuals aged 10 to 75 years) partakes in alcohol consumption. In concrete figures, this equates to around 160 million individuals within the country who engage in alcohol consumption(4). Additionally, it's noteworthy that around twenty percent of men who engage in alcohol consumption experience alcohol dependence(4). In contrast, the prevalence of alcohol dependence among women who consume alcohol is notably lower, with only about one in sixteen women being dependent on it(4). The states with the highest numbers of alcohol consumers in India are Uttar Pradesh with 42 million individuals, followed by West Bengal with 14 million individuals, and Madhya Pradesh with 12 million individuals. Roughly forty-three percent (43%) of individuals who consume alcohol engage in a pattern of consuming 'more than four drinks in a single instance,' which is indicative of 'Heavy Episodic drinking.' Additionally, a significant portion of alcohol users encounter signs of problematic consumption, such as getting into physical altercations after drinking (26.8%), consuming alcohol during daytime hours (21.2%), and being involved in road traffic accidents while under the influence of alcohol (4.1%)(4). Nationwide, approximately 2.7% of the population, accounting for around 29 million individuals, grapple with alcohol dependence. Across the entirety of the country, roughly 5.2% of the population between the ages of 10 to 75 years, encompassing around 57 million individuals, require assistance for their alcohol-related issues, indicating harmful or dependent consumption patterns. Moreover, roughly about 3 million people residing in the state of Madhya Pradesh were in urgent need for help and medical assistance for alcohol use(4).

AUD has far-reaching consequences on both physical and psychological health(5). Physically, excessive alcohol consumption can lead to liver cirrhosis, cardiovascular problems, compromised immune function, and an increased risk of certain cancers(6). Neurologically, alcohol disrupts brain chemistry, leading to cognitive impairments, memory deficits, and decreased inhibitions(7). Additionally, social consequences include strained relationships, job instability, legal issues, and isolation.

Effective treatment strategies for AUD take a holistic approach, addressing both the physical and psychological aspects of the disorder(8). Treatment plans are tailored to the individual's severity of AUD and their specific needs(8). They often include a combination of medical, behavioral, and psychosocial interventions. Medically, detoxification and medication-assisted therapy might be employed to manage withdrawal symptoms and cravings. In light of the growing concern surrounding alcohol dependence and the need for more effective pharmacological interventions, this study seeks to contribute to the existing knowledge by conducting a comprehensive comparative analysis of the safety, effectiveness (and relapse

rate) of baclofen and acamprosate as potential treatments option for patients seeking treatment for AUD. By systematically evaluating these medications within a routine outpatient clinical framework, we aim to shed light on their respective benefits and limitations, ultimately providing valuable insights that could guide clinicians and researchers in making informed decisions about the optimal management of alcohol dependence.

MATERIAL AND METHODS

Study Design: This retrospective cohort study aimed to compare the efficacy of baclofen and acamprosate in the management of alcohol dependence disorder. A retrospective cohort design was chosen to analyse the outcomes of patients who had previously received either baclofen or acamprosate treatment.

Study Duration: 6 months.

Period of data collection: 6 moths - the patient who received the treatment between the period 28/01/2023 to 28/07/2023 Period of follow up: 6 months since initiation of treatment.

Study Setting: This study was conducted at the Department of Psychiatry, LN Medical College, Bhopal. The data collection for the present study was initiated after ethical clearance from the Institute's Ethical Committee on Human Research.

Data Source: The study utilized medical records from outpatient/inpatient medical records for a period spanning. These records included detailed information on patient demographics, medical history, treatment regimens, laboratory results, and follow-up visits.

Study Population: The study population consisted of adult patients (aged 18 and above) diagnosed with alcohol dependence disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria(3). Patients who had received either baclofen or acamprosate treatment were included. *Exclusion criteria*: encompassed individuals with incomplete medical records, a history of severe liver disease, contraindications to baclofen or acamprosate, or simultaneous treatment with both medications.

Exposure: The primary exposure of interest was the use of either baclofen or acamprosate for the treatment of alcohol dependence disorder.

Outcome: The primary outcome measure was the rate of relapse, defined as the return to heavy alcohol consumption after a period of abstinence. Secondary outcomes included the duration of abstinence, and adverse events associated with each treatment(3).

Data Collection: The first author extracted relevant data from the electronic medical records using a standardized data collection form. Collected data included demographic characteristics (age, gender), baseline alcohol consumption patterns, medical and psychiatric comorbidities, initial and maintenance dosages of baclofen or acamprosate, laboratory results, and documented adverse events.

Statistical Analysis: Descriptive statistics were used to summarize demographic characteristics, baseline variables, and medication dosages. The primary outcome of relapse rates was analysed using survival analysis techniques, specifically Kaplan-Meier survival

curves and log-rank tests. Cox proportional hazards regression was employed to adjust for potential confounding variables such as age, gender, baseline alcohol consumption, and comorbidities. Secondary outcomes were analysed using appropriate statistical tests, including t-tests for continuous variables and chi-square tests for categorical variables.

Sample Size Calculation- we included all patients fulfilling the selection criteria and those who started treatment during the period specified above.

Data Analysis Software: Data analysis was performed using Stata, Version 17.0. Subgroup Analyses: Subgroup analyses were planned based on variables such as gender, age groups, and severity of alcohol dependence, to explore potential effect modification.

Sensitivity Analysis: A sensitivity analysis was conducted to assess the robustness of the results by excluding patients with incomplete follow-up data or those lost to follow-up. Results of this study should be interpreted in the context of its observational design and potential biases.

RESULTS

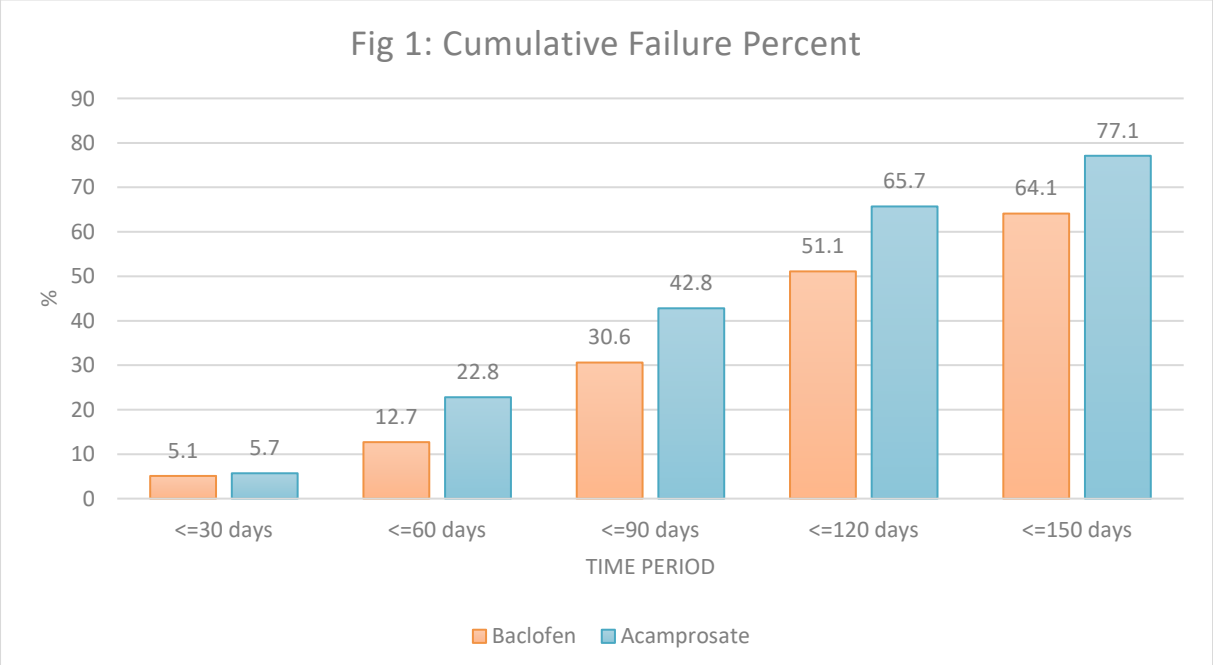
A total of 105 patient records were examined, with 31 cases were excluded to several reasons most common reason being incomplete data. In the study's analysed sample of 74 cases, 39 individuals received baclofen, while 35 were treated with Acamprosate. The entire cohort comprised males, with an average age of 34.8 years (SD=3.7). The mean age of alcohol starting alcohol consumption was 22.9 years (SD = 2.20), and the average duration of dependence was 7.6 years (SD = 2.9) at the initial consultation. A family history of alcohol dependence among first-degree relatives was noted in 50 cases (67.6%). The mean daily alcohol consumption among participants was 16.1 units (SD = 8.03), with 1 unit equivalent to around 10 ml of ethanol. The Baclofen group (n = 39) and the Acamprosate group (N = 35) displayed similarities in patient age, duration of dependence, age at starting alcohol dependence onset, average daily consumption, and positive family history ($p > 0.05$).

Table 1: History of alcohol use (n=74)

Variable	Baclofen (n=39)	Acamprosate (n=35)	P-value
Age, Mean (SD)	37.8 (3.8)	36.3 (4.3)	0.14
Duration of Dependence, Mean (SD)	7.1 (2.3)	6.8(2.7)	0.393
Age of starting alcohol, Mean (SD)	23.4 (2.1)	22.4 (1.9)	0.098
Family history (first degree relative)	26 (66.7%)	24 (68.6%)	0.719
Past attempts to quit	22 (56.4%)	27 (77.1%)	0.255
Daily Alcohol consumption	14.9	17.3	0.182

Table 2: Treatment outcome among participants (n=74)			
Variable	**Baclofen (n=39)**	**Acamprosate (n=35)**	**P-value**
Adverse effects	6 (15.4%)	12 (35.3)	0.049
Compliance	32 (82.1)	19 (55.9%)	0.015
Time to first Drink (Days)			
Mean (SD)	82 (8.45)	66 (6.23)	<0.0001
<30 days	2 (5.1%)	2(5.7%)	-
30-60 days	3 (7.6%)	6(17.1%)	
61-90 days	7(17.9%)	7(20.0%)	
91-120 days	8(20.5%)	8(22.9%)	
120-150 days	5(12.8%)	4(11.5%)	
Relapse rate	25 (64.1%)	27 (77.1)	0.220

Table 2 presents the treatment outcomes of participants (n=74) based on two different treatments: Baclofen (n=39) and Acamprosate (n=35). The table summarizes various variables related to treatment efficacy, adverse effects, compliance, time to the first drink, and relapse rates. Acamprosate had a significantly higher rate of adverse effects compared to Baclofen (p-value = 0.049). Baclofen: 6 participants (15.4%) experienced adverse effects and Acamprosate: 12 participants (35.3%) experienced adverse effects. Baclofen: 32 participants (82.1%) demonstrated compliance with the treatment and Acamprosate: 19 participants (55.9%) demonstrated compliance with the treatment. Participants on Baclofen had a mean time of 82 days to the first drink. Participants on Acamprosate had a mean time of 66 days to the first drink. The p-value "<0.0001" indicates that the difference in time to the first drink between the two treatments is statistically highly significant, with participants receiving Baclofen showing a longer time to their first drink compared to those receiving Acamprosate. A total of 25 participants (64.1%) on Baclofen experienced a relapse in comparison to 27 participants (77.1%) experienced a relapse. There was no statistically significant difference in relapse rates between the two treatments (p-value = 0.220).



DISCUSSION

The results presented here provide insights into the treatment outcomes of participants who underwent two different treatments, Baclofen and Acamprosate, for managing alcohol use disorder. This discussion aims to analyze the findings, explore their implications, and discuss potential reasons behind the observed differences.

Firstly, the mean age of participants in both groups—Baclofen (37.8 years) and Acamprosate (36.3 years)—did not demonstrate a statistically significant difference (p=0.14). Similarly, the age of onset of alcohol consumption between the groups, with means of 23.4 years for Baclofen and 22.4 years for Acamprosate, showed no substantial variation (p=0.098). These findings suggest that the medications were administered across cohorts of comparable age and with similar ages of alcohol initiation, indicating a balanced distribution of participants in terms of these variables. Kumar A et al., reported that the mean age of patients receiving Baclofen and Acamprosate was 42.73 and 39.67 years, respectively(9). In a different study done in 2010 by Mishra SN et al., reported that the mean age of the patients in the acamprosate and baclofen groups was 42.08 years and 41.28 years, respectively(10). Similar to our findings, other studies also reported that most of the participants in the study were exclusively male(10)(9).

Moreover, the prevalence of a family history of alcoholism among first-degree relatives showed no significant distinction between the two groups (Baclofen: 66.7% vs. Acamprosate: 68.6%; p=0.719). This similarity emphasizes that both sets of participants were subjected to comparable genetic predispositions, potentially influencing their alcohol dependency. Furthermore, examining the average daily alcohol consumption, with means of 14.9 units for Baclofen and 17.3 units for Acamprosate, yielded no statistically significant difference (p=0.182). This finding indicates that both groups engaged in comparable levels of alcohol intake prior to intervention, reinforcing the comparability of baseline alcohol use patterns. Collectively, these observations highlight the substantial similarity between individuals receiving Baclofen and Acamprosate across various parameters related to their history of alcohol use. While certain trends hint at potential nuances between the groups, the absence of statistically significant differences in most variables underlines the adequate comparability of the cohorts, thereby supporting the study's examination of the medications' effects on alcohol dependency.

Furthermore, the analysis of compliance with the prescribed treatment regimen reveals that 82.1% of individuals receiving Baclofen demonstrated compliance compared to 55.9% in the Acamprosate group (p=0.015). This statistically significant difference emphasizes a higher adherence rate among participants treated with Baclofen. Higher compliance with Baclofen suggests that participants found it more manageable and were therefore more likely to adhere to the treatment regimen(11,12). Compliance plays a crucial role in achieving successful treatment outcomes, making this finding particularly relevant. The mean time to the first drink is an important indicator of treatment efficacy and durability(13). Kumar A et al., also reported that dropout rates for the naltrexone, baclofen, and acamprosate groups were 16.66%, 30%, and 16.66%, respectively(9). Acamprosate was therefore linked to the highest number of dropouts. Kumar A et al., reported that patients' attitudes towards the three medications were generally favourable(9). Over the course of the month, attitudes towards the treatment improved in both groups in a statistically meaningful way. They further reported that during 2, 5, and 6 months, Baclofen shown the greatest improvement of

all the groups. In the three and four months, Acamprosate shown greater improvement than the other groups.

Regarding the time taken before the first drink, individuals in the Acamprosate group exhibited a shorter mean time to their initial drink (66 days) compared to those in the Baclofen group (82 days), with a highly significant p-value of less than 0.0001. The distribution across time intervals illustrates a trend wherein a greater proportion of individuals in the Baclofen group abstained for longer durations compared to the Acamprosate group. This could be due to its mechanism of action, which involves reducing cravings and reinforcing effects associated with alcohol consumption(11,12). The statistically highly significant p-value ("<0.0001") reinforces the robustness of this difference. Kumar A et al., also reported a statistically significant decline in the dependence score in both Acamprosate and Baclofen group patients(9). This decline indicated that both drugs decreased the chance of a relapse in people who were alcohol dependent(14). They also reported that acamprosate proved to be better than baclofen.

One significant finding is the difference in adverse effects between the two treatments. Acamprosate demonstrated a higher rate of adverse effects (35.3%) compared to Baclofen (15.4%). This discrepancy might be attributed to the differing mechanisms of action and pharmacological profiles of the two medications. Baclofen, a GABA-B receptor agonist, might have a more favorable side effect profile for certain individuals, leading to better tolerability compared to Acamprosate, which modulates glutamate neurotransmission (14,15). This difference underscores the importance of considering individual patient characteristics when selecting a treatment option. Kumar A et al., reported that side effects were more common among patients who were prescribed acamprosate (26.66%) and baclofen (16.66%)(9). Consequently, baclofen demonstrated the best tolerance and the fewest reported adverse effects. In their study, dizziness was the most commonly reported, occurring in five patients (16.66%), two patients (6.66%) in the baclofen group, and one patient (3.33%) in the acamprosate group.

The assessment of relapse rates between the two treatment cohorts revealed no statistically significant difference (p=0.220), with 64.1% of individuals in the Baclofen group experiencing relapse compared to 77.1% in the Acamprosate group. While the difference is not statistically significant, it does suggest a trend toward lower relapse rates in the Baclofen group, albeit not meeting the threshold for significance(15,16). While Baclofen shows a trend towards lower relapse rates, the lack of statistical significance could be influenced by various factors, including sample size and individual variability in treatment response(17). Further research with larger sample sizes might clarify this aspect. Kumar A et al., report that in the groups receiving baclofen, and acamprosate the corresponding percentages of relapses were 50%, and 40%. The relapse rate among patients prescribed baclofen was reported to be 36% in the Gupta et al. study, which was lower than the results of our investigation(16). The study conducted by Rubio et al. revealed a much greater relapse rate of 55% and 83%, respectively, in patients using naltrexone and acamprosate(18).

CONCLUSION

In conclusion, the findings suggest that Baclofen offers certain advantages over Acamprosate in the context of managing alcohol use disorder. These advantages include lower adverse effects, higher compliance rates, and a significantly longer time to the first drink. These outcomes underscore the potential benefits of Baclofen for some individuals, as

it appears to provide more favorable treatment outcomes and tolerability compared to Acamprosate.

Limitations

This study has several limitations, including its retrospective nature, which may lead to selection bias and incomplete data. The reliance on electronic medical records might result in incomplete documentation of certain variables. Additionally, confounding by indication could impact the observed treatment effects. Additionally, the study was conducted at a single site, which limits its generalizability.

Future directions for research

Future research should focus on conducting larger, randomized controlled trials to compare the efficacy and safety of Baclofen and Acamprosate in the treatment of alcohol dependence. Additionally, research should investigate the mechanisms of action of these two medications to better understand their effects on alcohol dependence. Further research and larger-scale studies could delve deeper into the mechanisms underlying these differences and explore strategies to enhance treatment adherence and mitigate adverse effects, ultimately improving outcomes for individuals combating.

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Conflict of Interest
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