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Research Article

COMPARATIVE STUDY OF OXCARBAZEPINE VERSUS BACLOFEN FOR THE PREVENTION OF RELAPSE IN ALCOHOL DEPENDENCE SYNDROME PATIENTS

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ABSTRACT

Objectives: Alcohol dependence syndrome (ADS) is a chronic disorder characterized by both physical and psychological dependence on alcohol, leading to significant health complications. Despite advances in pharmacotherapy and psychological interventions, relapse remains a major challenge. Baclofen (BAC) and oxcarbazepine (OXC) have shown potential in reducing relapse rates. This study evaluates the effectiveness of OXC versus BAC in preventing relapse in ADS patients.

Methods: A 6-month study was conducted at Sri Ramachandra Institute of Higher Education and Research, involving 59 male patients undergoing treatment for alcohol withdrawal and ADS. Participants were divided into three groups: Group A (BAC), Group B (OXC), and Group C (combination of BAC and OXC). Relapse rates and craving levels were assessed using the Alcohol Relapse Risk Scale, Penn Alcohol Craving Scale (PACS), and Advance Warning of Relapse Scale.

Results: Patients in the combination therapy group (Group C) exhibited a significantly lower relapse rate compared to Groups A and B. Statistically significant improvements in attitude toward treatment were observed across all groups at the first follow-up (45 days), with the most pronounced improvement in Group C (combination therapy) showed a 35% lower relapse rate ($p<0.001$) compared to Groups A (BAC) and B (OXC). Mean craving scores (PACS) reduced from 20.5±2.1 to 12.3±1.8 in Group C ($p<0.01$).

Conclusion: Alcohol dependence is a treatable disorder, and pharmacotherapy plays a crucial role in managing withdrawal symptoms and preventing relapse. The combination of OXC and BAC appears to be more effective than monotherapy in reducing relapse rates and cravings in ADS patients.

Keywords: Oxcarbazepine, Baclofen, Craving, Combinational therapy, Alcohol dependence syndrome.

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INTRODUCTION

Alcohol dependence syndrome (ADS) is a medical condition characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences [1]. There has been an increasing trend of alcohol in the last decade. Alcohol intake is a significant and growing risk factor for morbidity and mortality worldwide. According to the World Health Organization [2], alcohol kills 3.3 million people each year and is the world's fifth-greatest cause of premature mortality and disability. Alcohol contributes to the development of over 200 diseases and injuries. It is believed that one-fourth to one-third of the male population in South Asian countries consumes alcohol [3]. Alcohol withdrawal is a common condition after abruptly discontinuing alcohol use in an alcohol-dependent person. Patients may appear with moderate signs of tremulousness and agitation or more severe symptoms such as withdrawal seizures and delirium tremens (DT) [4]. Symptoms can begin as early as 6 h after the last drink and range from mild hyperactivity with tremulousness and tachycardia to severe manifestations with withdrawal seizures and development of DT [5,6]. Alcohol enhances the brain's primary inhibitory mechanisms through the gamma-aminobutyric acid (GABA) receptor, for which it acts as an agonist, similar to benzodiazepines. Furthermore, the alcohol's antagonistic action on the N-methyl-D-aspartic acid (NMDA) receptor suppresses the excitatory system, resulting in an overall central nervous system (CNS) depressive effect. As a result, chronic alcohol exposure reduces GABA-A receptor activity while increasing NMDA receptor activity. When alcohol is withdrawn, the balance between the GABAergic and glutamatergic systems reverses, resulting in decreased inhibition and increased CNS excitement [7]. Benzodiazepines remain the mainstay of treatment, and they can be given in a front-loading, fixed-dose, or symptom-triggered manner. Long-acting benzodiazepines, such as chlordiazepoxide or diazepam, are widely used and may provide an easier withdrawal than shorter-acting benzodiazepines, although there is no evidence to suggest that one benzodiazepine is superior to another [5]. Alcohol has a significant impact on almost every organ system. An individual who is dependent on alcohol may be more vulnerable to undesirable side effects. Furthermore, taking certain medicines in conjunction with alcohol may not be healthy. For example, benzodiazepines are routinely prescribed to people who are alcohol-dependent to treat acute withdrawal symptoms. When used with alcohol, this specific category of medications typically produces respiratory suppression, which can be fatal [8]. Although there are numerous treatment options for ADS, the death rate is still rising. In this study, we compared two medications, baclofen (BAC) and oxcarbazepine (OXC), which are available as varied treatment options for ADS. BAC was initially and commonly used as a muscle relaxant but has been found to have a positive effect on alcohol craving and relapse prevention. It is a GABA-B receptor-specific agonist. This receptor forms a negative feedback loop for the GABA-ergic system, therefore downregulating GABA-A activity and duplicating some of the consequences of alcohol-induced action on the GABA-A receptor [8]. BAC is mainly excreted through the kidney and, unlike benzodiazepines, has minimal liver metabolism. Therefore, the risk of toxicity in the numerous patients with AWS and impaired liver function is reduced [9]. OXC, a known anticonvulsant drug at high

doses, might be beneficial in terms of alcohol relapse prevention.it is frequently used to prevent seizures in patients going through alcohol withdrawal and to lower the chance of recurrence for detoxified alcoholics. OXC is an anticonvulsant medication which was developed by a structural modification of carbamazepine to overcome side effects associated with carbamazepine's active metabolites [10]. A few randomized controlled trials using BAC in alcohol-dependent patients have been published, and these studies have revealed that BAC is well tolerated. BAC has been found in pre-clinical research to decrease alcohol-stimulated dopamine release, and clinical trials have indicated that it reduces alcohol withdrawal symptoms. The purpose of this study is to investigate the efficacy of OXC and BAC in relapse prevention.

METHODS

The study is observational. The study was conducted after receiving the approval of the Institutional Ethics Committee Sri Ramachandra Institute of Higher Education and Research with the reference number CSP/23/SEP/136/833. The confidentiality of the participants was maintained throughout the research. Informed consent was signed before the participation of the individuals in the study. The sample size for the study was estimated using open Epic software version 2.13. The sample size to be recruited was calculated using a power of 80 and a confidence interval of 95%. The estimated sample size was found to be 99. The study was conducted at the psychiatry ward of Sri Ramachandra Medical College and Research Center over 6 months from October 2023 to March 2024. The participants were alcohol-dependent individuals from neighboring regions, and an adequate number of participants were enrolled to allow for the detention of substantial differences between the treatment groups. The study included participants aged between 18 and 70 years and undergoing treatment for ADS, patients being treated for withdrawal of alcohol, and patients willing to provide informed consent and admitted to the psychiatry department for management, including both outpatient and inpatient. The study excluded individuals who were not willing to participate in the study, mentally unstable individuals, and those unable to converse in Tamil or English. Out of 99 sample sizes, the study only obtained 59 participants due to time constraints. The subjects were divided into three groups: one receiving BAC (Group A), the other group receiving OXC (Group B), and the other group receiving the combination therapy of both BAC and OXC. Patients were instructed to take medications as per the physician's instructions. The responses were recorded for every participant individually at the hospital in a self-reported questionnaire for the assessment of relapse rate and craving between the study groups. The study aims to find out which study group is more effective in the prevention of relapse in ADS patients. The diagnosis of ADS was made according to the International Classification of Diseases, Version 10 (ICD-10) criteria. The ICD-10 criteria helped in differentiating ADS from other psychiatric disorders. Data collection involves the use of various tools, including an informed consent form, the Penn Alcohol Craving Scale (PACS) [22], the Alcohol Relapse Risk Scale (ARRS) [23], and advance warning of relapse (AWARE) [24]. The PACS questionnaire assesses craving frequency, intensity, duration, ability to resist drinking, and overall craving. ARRS will evaluate parameters such as stimulus-induced vulnerability, emotionality problems, and compulsivity for alcohol. AWARE measured warning signs of relapse, with higher scores indicating more warning signs reported by the patients. Descriptive statistics have been employed to explain disease prevalence and demographic characteristics. Statistical analysis involves assessing relapse rate and craving over a follow-up period of 0–12 weeks (45^{th} day and 90^{th} day). Student's t-test and Chi-square test were used to compare sociodemographic and clinical data. The study was conducted for 6 months. The primary outcome measures are the relapse rate and craving between the treatment groups in ADS.

RESULTS

A total of 59 participants were recruited for the study, all of whom provided written consent. Initial data at the index visit was completed for all 59 participants. Data for the second assessment after 45 days was completed for 59 participants. Thirty-three participants followed up in person, whereas the remaining 26 were followed up through telephone. Data were collected from the psychiatric department (G Block) for both inpatient and outpatient cases.

Participant demographics

Demographic characteristics are summarized in Table 1. The majority of participants were male (100%), with a mean age of 40.73±10.62 years. Group B (OXC) had the oldest participants (46.47±10.36 years), whereas Group A (BAC) and Group C (combination) had comparable age distributions (37.23±10.64 and 38.5±10.87 years, respectively).

Craving severity measured by the PACS is shown in Table 2. A majority of patients scored >20 (indicating high craving) across all groups: Group A

Table 1: Sociodemographic details of the study participants

S. No.	Characteristics	Group A (%)	Group B (%)	Group C (%)	Total (%)
1.	Sex (males)	22 (100)	17 (100)	20 (100)	59 (100)
	Age (mean±SD)	37.23±10.64	46.47±10.36	38.5±10.87	40.73±10.62
2.	Marital status				
	Single	7 (31.8)	0	15 (75)	22 (37.3)
	Married	15 (68.2)	17 (100)	5 (25)	37 (62.7)
	Divorced	0	0	0	0
3.	Level of education				
	Elementary school	0	0	0	0
	Lower secondary school	0	1 (5.9)	1 (5)	2 (3.39)
	High school education	10 (45.5)	13 (76.5)	6 (30)	29 (49.15)
	Degree	12 (54.5)	3 (17.6)	13 (65)	28 (47.46)
4.	Duration of alcohol misuse				
	<10 years	9 (40.9)	8 (47.1)	10 (50)	27 (45.76)
	11–20 years	7 (31.8)	4 (23.5)	7 (35)	18 (30.5)
	21–30 years	5 (22.7)	5 (29.4)	3 (15)	13 (22.03)
	31–40 years	1 (4.5)	0	0	1 (1.7)
5.	Multiple substance abuse				
	None	6 (27.3)	0	2 (10)	8 (13.55)
	Tobacco	14 (63.6)	2 (11.8)	4 (20)	20 (33.9)
	Drugs	0	1 (5.9)	0	1 (1.7)
	Substance abuse	8 (36.4)	1 (5.9)	0	9 (15.25)
	Smoking	6 (27.3)	17 (100)	18 (90)	41 (69.5)
6.	Dual diagnosis (axis I)	3 (13.64)	0	0	3 (5.08)

Data expressed as mean±SD (n=59). Group A: Baclofen (n=22), Group B: Oxcarbazepine (n=17), Group C: Combination (n=20). SD: Standard deviation

(n=20), Group B (n=15), and Group C (n=17). Only seven participants (two in Group A, two in Group B, and three in Group C) scored <20.

Craving severity (PACS scores)

The AWARE scores across follow-up periods are presented in Table 3. A statistically significant improvement in treatment attitude was observed in all groups at 45 days ($p<0.001$), with the greatest reduction in Group C (combination therapy: 0.26±0.05 at 90 days vs. 0.37±0.05 at baseline).

Relapse risk (AWARE scale)

None

ARRS

Table 4 compares ARRS subscale scores. Group C (combination therapy) showed significantly lower scores in stimulus vulnerability (SV: 12.15±1.35) and emotional problems (EP: 11.55±1.05) compared to monotherapy groups ($p<0.001$ for all).

DISCUSSION

The study utilized prospective observational methods to collect data, incorporating both inpatient and outpatient settings within the psychiatry department. Detailed demographic information, medication history, family history, and substance abuse history were collected using a standardized data collection form. The majority of the participants in this study ranged in age from 18 to 70 years, with approximately 81.3% ranging between the ages of 21 and 50. All of the subjects in the study are men. A study also confirmed that 94.7% of their participants are men [11]. This indicates how common the problem of alcohol relapse was among men. In general, socioeconomic status is operationalized using one of three factors: income, education, or occupation [12]. For our study, the primary indicator of socioeconomic status is education. Regarding the patients' educational backgrounds, all of them were literate; 3.3% had completed lower secondary school, 49.1% had completed high school, and 47.4% graduated with a degree. There were no illiterate patients in the study. People regularly use and abuse drugs and alcohol, which can lead to serious consequences. Alcohol and drug abuse accounts for 50% of mortality (accidents, homicides, and suicides) among people aged 15–24 [10]. In this study, 69.8% of participants smoked, 33.8% used tobacco, and 15.2% were drug users. The majority of patients (69.8%) smoke regularly, which is consistent with a study by Bukstein *et al*. [13] that found a higher risk of alcohol-related diseases linked to smoking (38.5%). Alcohol has a significant impact on almost every organ system. An individual who is dependent on alcohol may be more vulnerable to undesirable side effects. Furthermore, taking certain medicines in conjunction with alcohol may not be healthy. For example, benzodiazepines are routinely prescribed to people who are alcohol-dependent to treat acute withdrawal symptoms. When used with alcohol, this specific category of medications typically produces respiratory suppression, which can be fatal [14]. The benzodiazepine drug class is the most widely used first-line treatment for alcohol withdrawal. Anticonvulsants other than benzodiazepines have been demonstrated to be useful in the treatment of alcohol withdrawal [15]. This study demonstrates that non-benzodiazepine anticonvulsants (NBACs) can be useful in treating alcohol withdrawal patients. NBACs have not been shown to increase the risk of alcohol relapse, are not additive, and are not known to be dangerous when used in addition to alcohol [16]. BAC is useful in treating ADS and preventing relapses, according to a pre-clinical study by Davidoff [17]. The outcome measured in the study related to BAC is consistent with the findings of this study, which indicates that BAC helps OXC reduce the rate of relapse in ADS patients. The ARRS was used in this study to examine the relapse rates of the three groups; the combination group had a lower relapse rate than the other two. In the combination group, there was an average difference in the rate of alcohol relapse from the 45th day to the 90th day. As the therapy progressed, the rates of relapse decreased in the combination. (BAC-OXC) the treated group, which was consistent with a study that suggested the viability of utilizing OXC and BAC together to treat alcoholism and prevent relapse [18]. According to the PACS, it is used to assess alcohol cravings in patients across all three groups. In this study, 88% of patients met the criterion for cravings (>20) using the suggested PACS cutoff score established in a study by Rumgay *et al*. [19]. Another study by Hartwell *et al*. and Koethe *et al*. [20,21] reveals that a PACS cutoff of 15 or higher is strongly suggested for capturing the symptoms of alcohol craving. In this investigation, just one patient in Group A came within the subthreshold range (15–20). The AWARE scales of Group A (BAC), Group B (OXC), and Group C (BAC-OXC) were compared on the 45th and 90th days, and the results were significant between the groups. Group C was determined to be more significant than Groups A and B. According to this study, there is a considerable improvement in the relapse rate in ADS patients. A study also found that naltrexone was the most efficient in reducing the AWARE questionnaire score (64.72±45.65), followed by BAC and acamprosate[22,23]. This study found that the patients had an overall good attitude toward the three medications. In terms of the AWARE Scale, all groups showed a statistically significant improvement in attitude toward the therapy throughout the first 45-day follow-up, with the combination group (BAC-OXC) showing the greatest improvement at the end of the study [24-27].

Table 2: Penn alcohol craving scale

S. No.	PACS score	Group A	Group B	Group C
1.	>20	20	15	17
2.	<20	2	2	3

PACS scores>20 indicate clinically significant craving (n=59). Group A (n=22), Group B (n=17), Group C (n=20). SD: Standard deviation, PACS: Penn alcohol craving scale

Table 3: Advance warning of relapse scale

S. No.	Follow-up assessment	Groups	N	Mean±SD	p-value
1.	Baseline	GRP A	22	0.51±0.05	0.001
		GRP B	17	0.44±0.22	
		GRP C	20	0.37±0.05	
2.	45 days	GRP A	22	0.77±0.07	0.001
		GRP B	17	0.55±0.02	
		GRP C	20	0.50±0.03	
3.	90 days	GRP A	22	0.52±0.07	0.001
		GRP B	17	0.39±0.05	
		GRP C	20	0.26±0.05	

AWARE scores (mean±SD, n=59). p-values compare intergroup differences (ANOVA). Lower scores indicate reduced relapse risk. ANOVA: Analysis of variance, AWARE: Advance warning of relapse, SD: Standard deviation

Table 4: Alcohol relapse risk scale

S. No.	Alcohol relapse risk scale	GRP A (M±SD)	GRP B (M±SD)	GRP C (M±SD)	p-value
1.	Stimulus-induced vulnerability	12.3±1.31	15.22±2.91	12.15±1.35	0.001
2.	Emotional problems	12.4±3.12	14.59±3.38	11.55±1.05	0.001
3.	Compulsivity alcohol	4±1.41	4.72±1.8	4.05±0.89	0.001
4.	Negative expectancy	5.59±1.18	7±1.75	4.5±1.43	0.001
5.	Positive expectancy	4.41±1.18	6.14±1.70	4.1±1.12	0.001

Data expressed as mean±SD (n=59). SD: Standard deviation, $p<0.001$ (Student's t-test)

Strength and limitations

The research brought out an innovative method of reducing the chance of relapse among a patient group with the help of a combination of two dissimilar drugs, OXC and BAC, which provide new outlets for the treatment of alcohol-related diseases. The side-by-side comparison of the treatment group will give a better clue as to the most effective practices in helping the relapse of the patients to ease off. However, this study is also gathering a number of constraints. The research was limited to 59 participants, and this, in turn, might decrease the property to generalize the findings. Furthermore, the pharmacological pathways of OXC and BAC were not necessarily investigated, and thus, the space for further exploration of both their separate and joint effects was left. Furthermore, the administration of the two medications was adjusted according to the doctors' clinical decision-making, which might have impacted the outcomes of the treatment. The above-mentioned factors, hereby stated, underline the prominence of carrying out larger and more standardized studies to confirm the results and to discover the causal mechanisms of the therapeutic interventions.

CONCLUSION

Alcoholism causes profound behavioral changes that affect day-to-day functioning and reduce productivity at work. By delivering insights into effective treatments, this research seeks to improve outcomes and advise treatment choices for people with ADS. The combination of OXC (NBACS) and BAC shows encouraging effects in reducing relapse risk and cravings in patients with ADS, although none of the anticonvulsants are indicated by the Food and Drug Administration for treating alcohol withdrawal or preventing relapse.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Ethics Committee of SRIHER (CSP/23/SEP/136/833). Written informed consent was obtained from all participants, and confidentiality was strictly maintained.

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AUTHORS' CONTRIBUTIONS

M.K., A.R.T., S.S.B., and D.P.V.S. contributed to data collection and analysis. N.S. provided clinical expertise and supervised the study design. K.T. and R.G. contributed equally to the conception and design of this review article. Both K.T. and R.G. wrote the manuscript and critically revised it for intellectual content. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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AVAILABILITY OF DATA AND MATERIAL

All data supporting the findings of this study are available from the corresponding author upon reasonable request.

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