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Safety And Efficacy Of Disulfiram In Alcohol Dependent Patients: An Observational Study

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Abstract

Introduction: Alcohol use disorders (AUD) is a chronic disorder in which a person cannot control his or her drinking or craving for alcohol. Disulfiram was the first FDA approved drug used for the treatment of alcohol use disorders. Disulfiram is not an anti-craving drug; it is an alcohol-aversive drug. Our study aims to evaluate the safety and efficacy of disulfiram within the South Indian population.

Materials and Methods: It is a prospective observational study conducted on 83 patients at the Department of Psychiatry at Amrita Institute of Medical Science and Research Centre, Kochi. Adult patients with alcohol dependence on disulfiram and not on treatment with disulfiram both were selected for the study to assess the safety and efficacy.

Results: Relapse was more in control group (46.5%) compared to disulfiram group (17.5%) with a statistically significant p value of 0.05. Complete recovery was more in the disulfiram group (62.5%) compared to the control group (46.5%) and there is a significant difference with p-value of 0.045. The disulfiram group had 16.7% certain ADRs, 50.0% possible ADRs, and 33.3% unlikely ADRs, while the control group had 25% unlikely ADRs and 75.0% possible ADRs.

Conclusion: Our study is to prove that Disulfiram is a safe and effective option for alcohol-dependent patients, as it is better in terms of relapse prevention and recovery over time. Even though there exist safety and compliance issues, it shows an acceptable risk on supervised administration. Relapse prevention and complete recovery were higher in the disulfiram group compared to the control group, and there was a significant difference.

Keywords: Disulfiram, Alcohol use disorders, Adverse drug reactions, Naranjo scale, disulfiram-alcohol interaction, relapse

Introduction

Alcohol use disorders (AUD) constitute a public health concern in India. It is a chronic disorder in which a person cannot control his or her drinking or craving for alcohol. It is also called alcohol use disorder (AUD)[1]. Currently there are three FDA approved drugs which are disulfiram, acamprosate and naltrexone. Disulfiram was the first FDA approved drug used for the treatment of alcohol use disorders[2]. Disulfiram is not an anti-craving drug; it is an alcohol-aversive drug. It irreversibly inhibits the enzyme- acetaldehyde dehydrogenase (ALDH), which is a major enzyme involved in the conversion

of acetaldehyde in alcohol into acetate[3]. This results in acetaldehyde accumulation which can cause hangover symptoms. Hence patient consuming even a small amount of alcohol will experience hangover symptoms if they are on disulfiram. This discourages the patients from consuming alcohol[4]. The other anti-craving drugs, such as acamprosate, baclofen, and naltrexone, show a relatively higher rate of relapse. Patients were still motivated to consume alcohol even during treatment, but the adverse effects were low[5]. Even though disulfiram is associated with acceptable risks, it is still considered as a second-line drug for the treatment of Alcohol Use Disorder (AUD). Our study aims to evaluate the safety and efficacy of disulfiram within the South Indian population.

Methodology

An observational prospective study was done on 83 patients at the department of Psychiatry at Amrita Institute of Medical Science and Research Centre, Kochi from March 2017 to April 2023. Adult patients with alcohol dependence who are on treatment with disulfiram and not on treatment with disulfiram both were selected for the study. Patient details were collected from the Amrita Healthcare Information System (AHIS) and through telephonic conversation after getting the consent from the patients and getting approval from the Ethics Committee (IEC AIMS-2023-PHARM-103A). Patient data was carefully reproduced into the previously made data collection form. The patients were monitored for any disulfiram related adverse drug reaction, whether the patients where motivated to take disulfiram, whether they could refrain from taking alcohol, whether there was any relapse or any of the patients drop off and if the patient took alcohol, then was there any disulfiram-alcohol interaction. Causality of ADR was assessed using Naranjo scale.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables were expressed using frequency and percentage. Numerical variables were presented using mean and standard deviation. Chi square with continuity correction was used to test the statistical significance of the association of all categorical variables between groups. A p value of <0.05 was considered to be statistically significant.

Results

A total of 83 cases were analyzed in which 37.3% patients were in the age group of 41-50 years. The median age of patients in the study was 48 and the mean age was found to be 48.04.[Refer Table 1] [Refer Figure 1].

Table 1: Age distribution of Sample Population

Age (In years)	Test (DSF)		Control		Total		p – value
	N=40	%	N=43	%	N=83	%	
18 - 30	1	2.5	0	0.0	1	1.2	0.386
31 - 40	12	30.0	7	16.3	19	22.9	0.386
41 – 50	14	35.0	17	39.5	31	37.3	0.386
51 - 60	11	27.5	14	32.6	25	30.1	0.386
61 - 70	2	5.0	5	11.6	7	8.4	0.386

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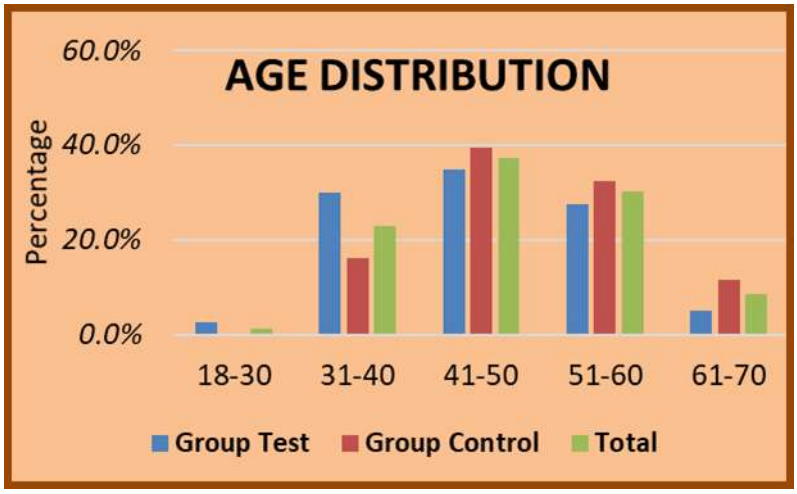
Figure 1: Age distribution of Sample Population

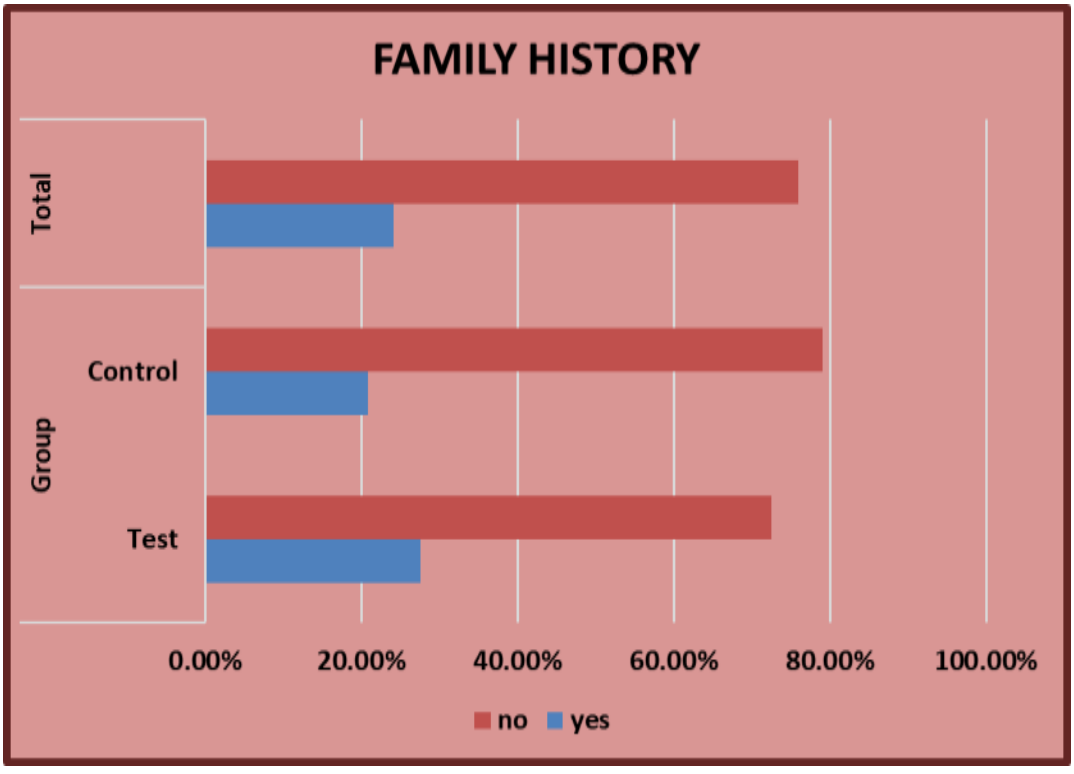


Out of the sample population, 24.1% of the patients had a family history of alcohol dependence. Out of which, 11 (27.8%) patients were from test group and 9 (20.9%) from control group. Refer Table 2 and figure 2.

Table 2: Family History of Alcohol dependence in Sample Population

Family history	Test (DSF)		Control		Total		P – value
	N=40	%	N=43	%	N=83	%	
Present	**11**	**27.5**	**9**	**20.9**	**20**	**24.1**	**0.484**
Absent	**29**	**72.5**	**34**	**79.1**	**63**	**75.9**	**0.484**

Figure 2: Family History of Alcohol dependence in Sample Population



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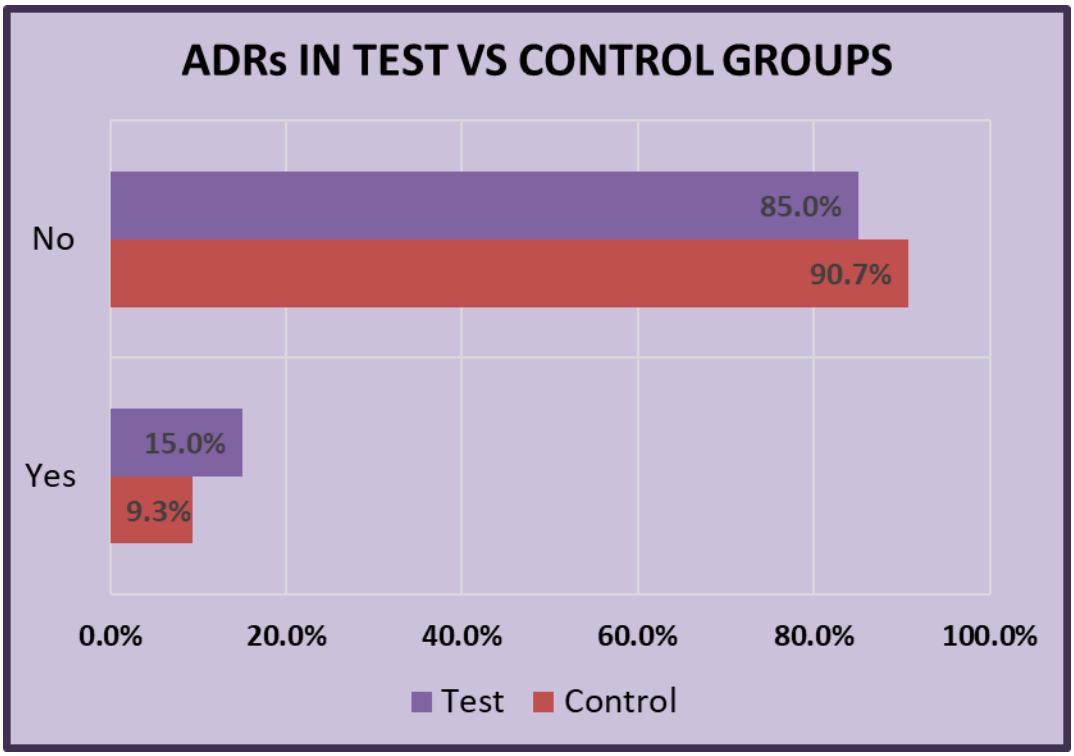
Out of the sample population 10 (12.0%) patients complained of ADRs of which 6 (15%) belonged to the test group and 4 (9.3%) belonged to the control group. ADRs were more in the disulfiram group compared to the control group but the difference was not statistically significant (p-value > 0.05) [Table 3] [Figure 3].

Table 3: Presence of ADRs in Sample Population

ADRs	Test (DSF)		Control		Total		p-value
	N=6	%	N=4	%	N=10	%	
Present	**6**	**15.0**	**4**	**9.3**	**10**	**12.0**	**0.646**
Absent	**34**	**85.0**	**39**	**90.7**	**73**	**88.0**	**0.646**

Figure 3: Presence of ADRs in Test vs Control groups



The most common ADR reported in the test group was decreased appetite (n = 4, 40%), followed by headache (n = 2, 20%), and further followed by gastritis (n = 1, 10%), sedation (n = 1, 10%), skin eruption (n = 1, 10%), lethargy (n = 1, 10%), and irritability (n = 1, 10%). The most common ADR reported in the control group was decreased appetite (n = 3, 75%), followed by headache (n = 2, 50%), and further followed by insomnia (n = 1, 25%), tremors (n = 1, 25%), confusion (n = 1, 25%), and irritability (n = 1, 25%).

According to the Naranjo scale, the disulfiram group had 33.3% definite ADRs, 50.0% probable ADRs, and 16.75% possible ADRs, while the control group had 25% probable ADRs and 75.0% possible ADRs. According to the WHO-UMC causality assessment criteria, the disulfiram group had 16.7% certain ADRs, 50.0% possible ADRs, and 33.3% unlikely ADRs, while the control group had 25% unlikely ADRs and 75.0% possible ADRs.

A total of 40 cases were analyzed in the test group of which 5 (12.5%) of patients were identified with reactions caused by disulfiram-alcohol interaction [Table 4] [Figure 4].

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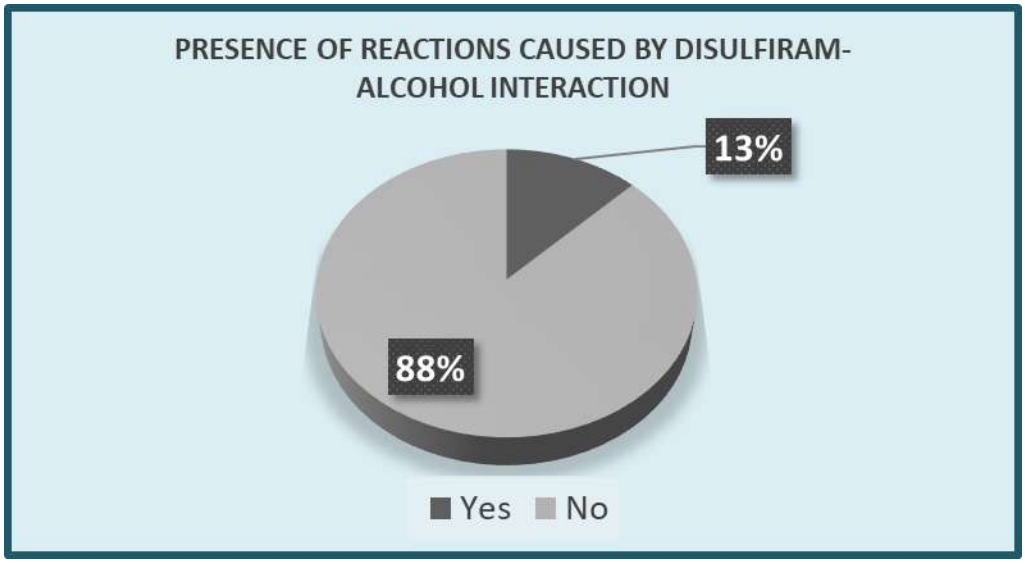
Table 4: Presence of reactions caused by disulfiram-alcohol interaction (if any)

Presence of reactions caused by disulfiram-alcohol interaction (if any)	Test (DSF)	
	N=40	%
Yes	5	12.5
No	35	87.5

Figure 4: Presence of reactions caused by disulfiram-alcohol interaction



Out of the 83 patients, 65 (78.3%) of them were still motivated to take the drug, of which 32 (80%) belonged to the test group and 33 (76.7%) belonged to the control group [Table 5] [Figure 5].

Table 5: Patient motivation to take the drug

Is the patient still motivated to take the drug	Test (DSF)		Control		Total		p – value
	N=40	%	N=43	%	N=83	%	
Yes	32	80.0	33	76.7	65	78.3	0.719
No	8	20.0	10	23.3	18	21.7	0.719

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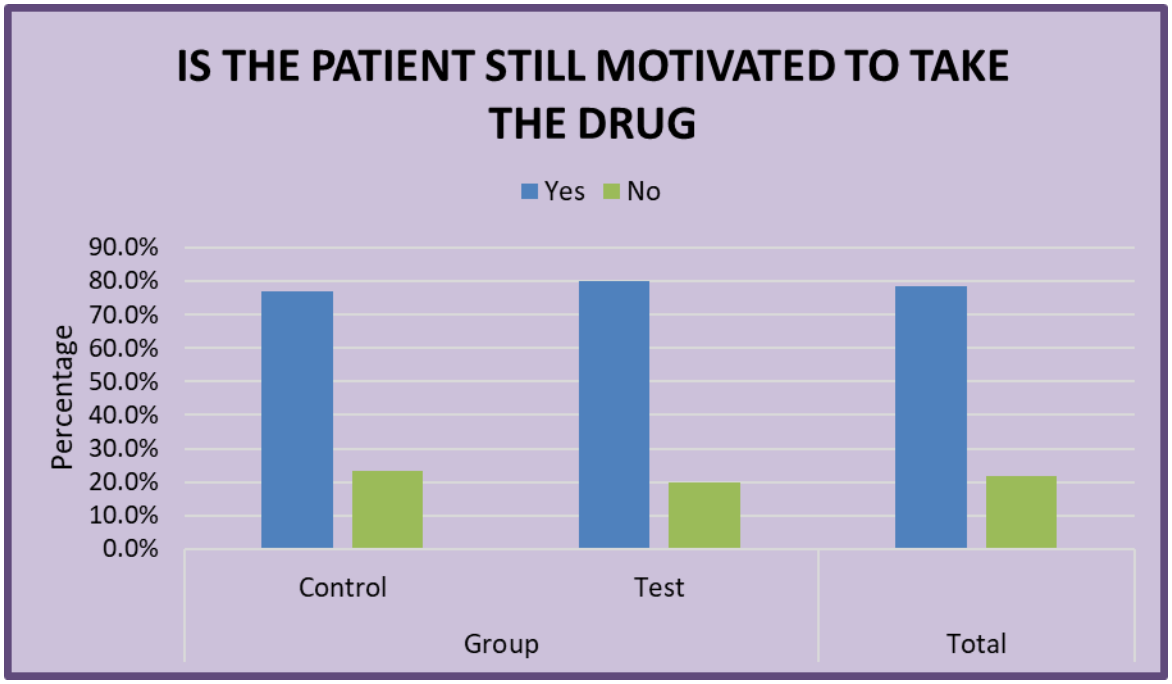
Figure 5: Patient motivation to take the drug



Of the 83 patients analyzed, 65 (78.3%) patients were still motivated to refrain from alcohol, out of which 32 (80%) belonged to the test group and 33 (76.7%) belonged to the control group. The difference in the number of patients motivated to take the drug between the test and control groups was not statistically significant (p-value > 0.05) [Table 6] [Figure 6].

Table 6: Patient motivation to refrain from alcohol

Is the patient still motivated to refrain from alcohol	Test (DSF)		Control		Total		p - value
	N=40	%	N=43	%	N=83	%	
Yes	37	92.5	34	79.1	71	85.5	0.082
No	3	7.5	9	20.9	12	14.5	0.082

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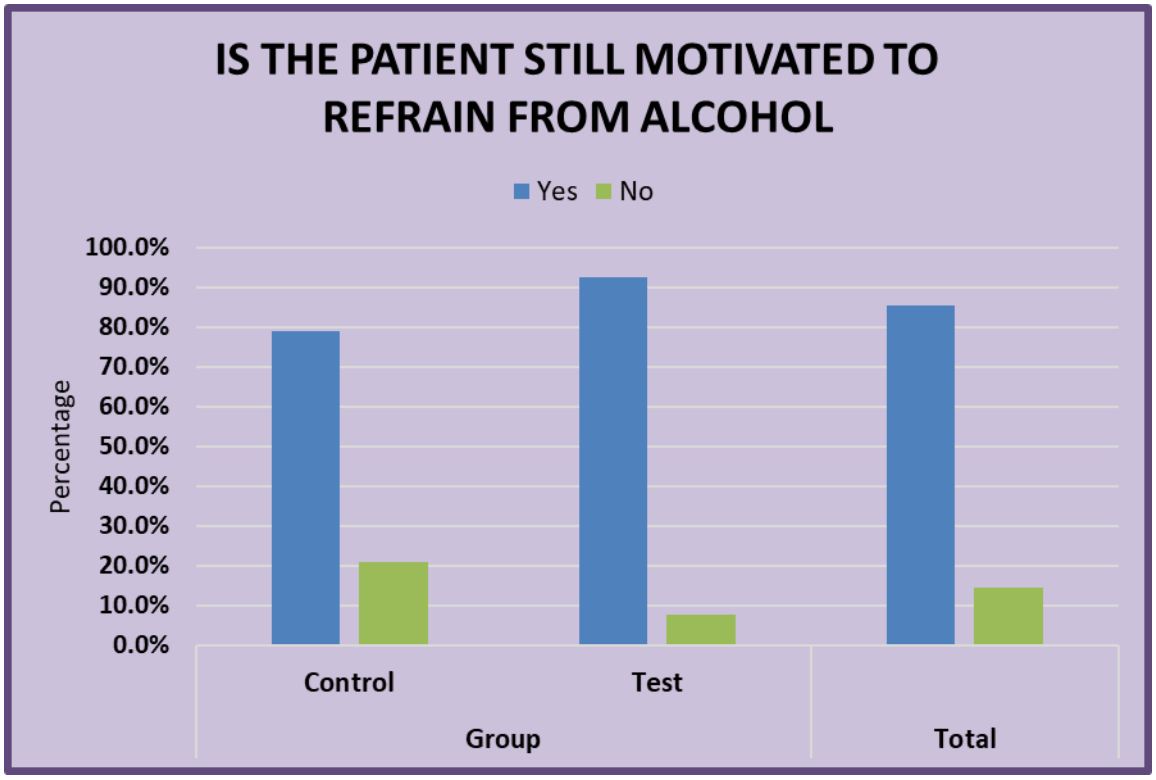
Figure 6: Patient motivation to refrain from alcohol



Out of the 83 patients analysed, 27 (32.5%) patients had relapsed, of which 7 (17.5%) belonged to the test group and 20 (46.5%) belonged to the control group. Relapse was more in the control group compared to the disulfiram group and there is statistical significance (p-value < 0.05) [Table 7] [Figure 7].

Table 7: Relapse in Sample Population

Relapse	Test (DSF)		Control		Total		p - value
	N=40	%	N=43	%	N=83	%	
Yes	7	17.5	20	46.5	27	32.5	0.005
No	33	82.5	23	53.5	56	67.5	0.005

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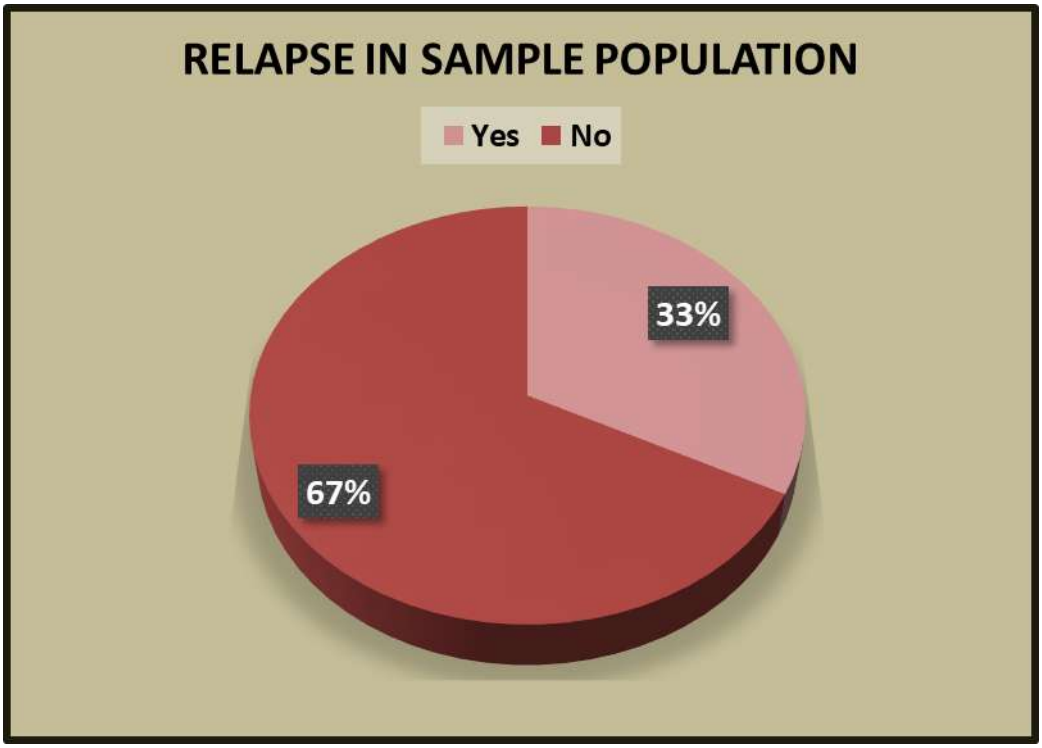
Figure 7: Relapse in Sample Population



A total of 90 cases were analyzed in which 7(7.85%) of patients dropped out, of which 5 (11.1%) belonged to the test group and 2 (4.4%) belonged to the control group. Dropout was more in the disulfiram group compared to the control group. [Table 8] [Figure 8].

Table 8: Dropout in Sample Population

	Test (DSF)		Control		Total	
Dropout	**N=45**	**%**	**N=45**	**%**	**N=90**	**%**
	5	**11.1**	**2**	**4.4**	**7**	**7.85**

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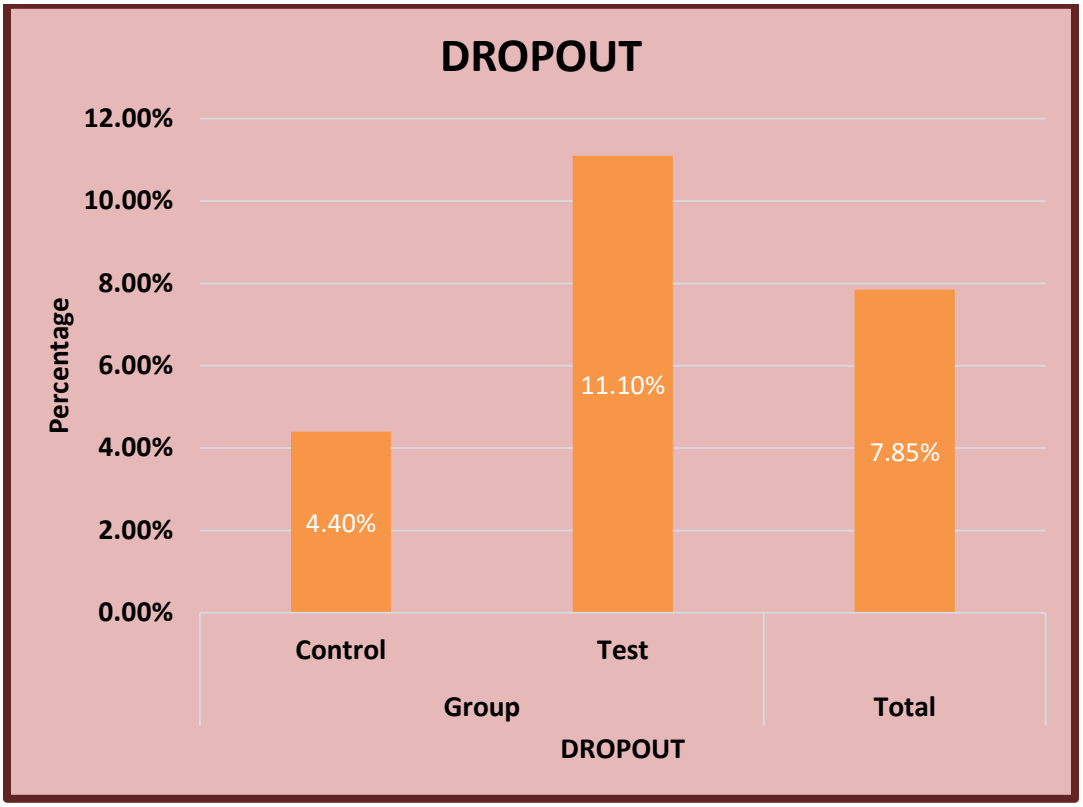
Figure 8: Dropout in sample population



Out of the 83 cases analyzed 7 (9.3%) patients had the drug withdrawn, of which 6 (17.1%) belonged to the test group and 1 (2.5%) belonged to the control group. Withdrawal of the drug was more in the disulfiram group compared to the control group but there is no statistical significance (p-value > 0.05) [Table 9] [Figure 9].

Table 9: Drug dose in Sample Population

Drug dose	Test (DSF)		Control		Total		p - value
	N=40	%	N=43	%	N=83	%	
Withdrawn	6	17.1	1	2.5	7	9.3	0.076
Continued as normal	29	82.9	39	97.5	68	90.7	0.076

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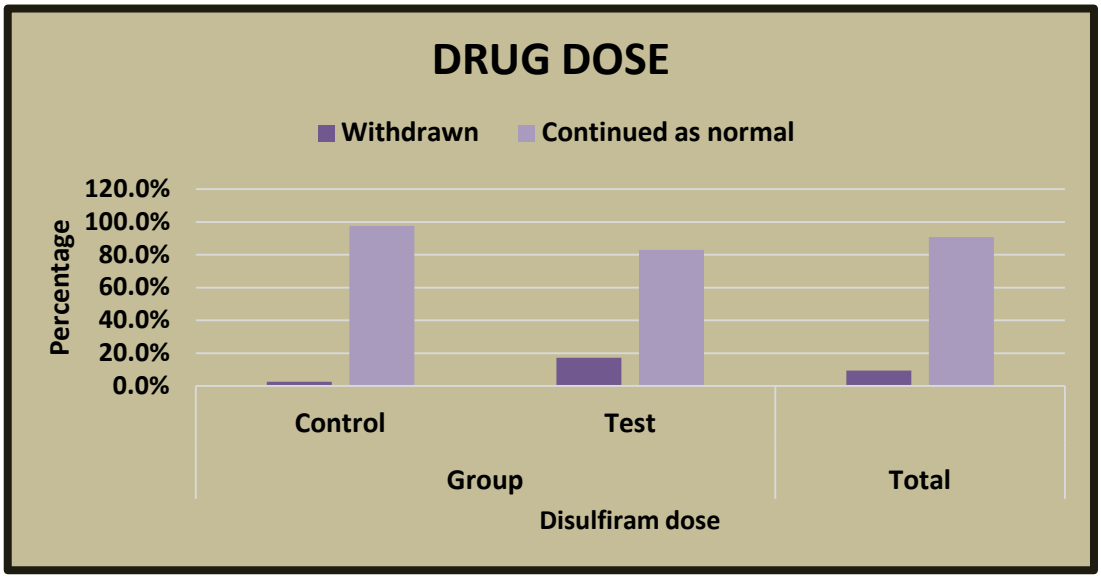
Figure 9: Drug dose in Sample Population

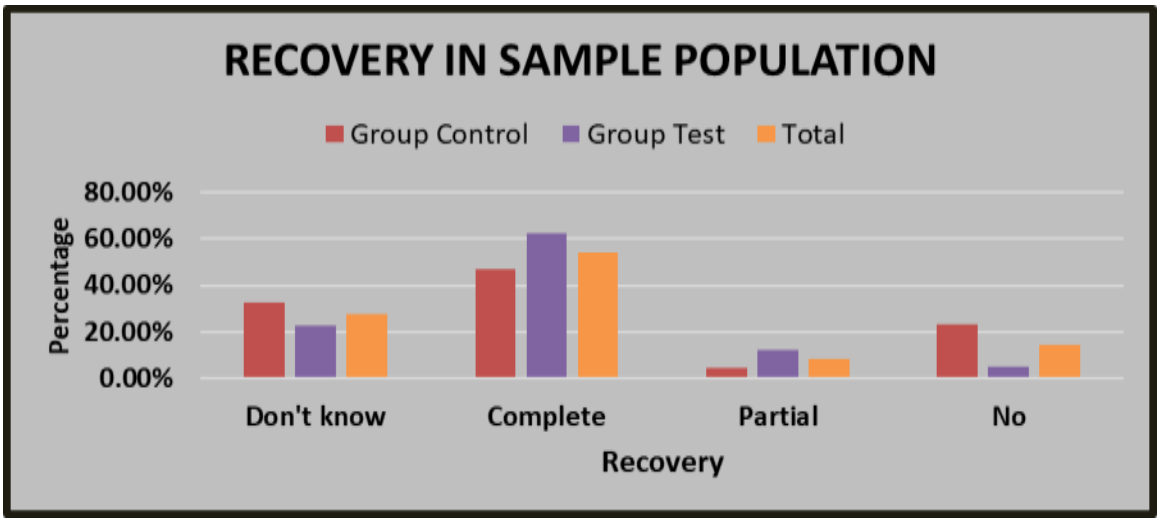


From the sample population, 45 (54.2%) patients had complete recovery, of which 25 (62.5%) belonged to the test group and 20 (46.5%) belonged to the control group. Complete recovery was more in the disulfiram group compared to the control group and there is a significant difference (p-value < 0.05) [Table 10] [Figure 10].

Table 10: Recovery in Sample Population

Recovery	Test (DSF)		Control		Total		p - value
	N=40	%	N=43	%	N=83	%	
Complete	25	62.5	20	46.5	45	54.2	0.045
Partial	5	12.5	2	4.7	7	8.4	0.045
No	2	5.0	10	23.3	12	14.5	0.045
Do not know	9	22.5	14	32.6	23	27.7	0.045

Figure 10: Recovery in Sample Population



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Discussion

This observational study clearly shows significant efficacy and safety of disulfiram by comparing it with placebo. Here we proved our hypothesis which is disulfiram is safe and effective for the treatment of AUD. The effect of disulfiram on maintaining abstinence or preventing relapse is higher than other drugs. The drug effectiveness depends directly upon the patient's cooperation. In our observational study the safety data showed that there was no significant difference between the disulfiram and control groups in studies. Both in control and test group patients were developed with different ADRs. A study conducted in Nepal in comparing disulfiram and naltrexone but the result is that there is no significant difference in between relapse. Disulfiram can prevent dropout[6]. In a study conducted in Australia they reached in conclusion that disulfiram drug has less adherence and toxicity[7]. In study conducted in Pakistan they reached in conclusion that disulfiram showed greater days of abstinence and less relapse rate[8]. Disulfiram, on the other hand, has recently drawn notice as an adjunctive drug to more recent pharmacological treatments, such as an opiate antagonist that particularly lessens alcohol appetite[9]. Theoretically, disulfiram, when combined with an opiate antagonist which directly reduces alcohol appetite, it was observed that patients develop psychological control over their drinking. Disulfiram has been demonstrated to lower cocaine usage in non-alcoholic, cocaine-dependent patients, which is another preliminary evidence that the medication may be a useful treatment for cocaine dependence[10].

In India, family support is generally strong[11]. Almost all of the subjects' wives kept track of their prescriptions. It is also noteworthy that DSF is less expensive than TPM in the Indian context. We designated a single family member to oversee and promote adherence, and that same individual was invited to go with the patient on follow-up visits. The importance of strong family guidance and support in the long-term medical treatment of alcoholism is also emphasized by this study. Even for patients who might not consistently comply, this is beneficial. The limitation of the study was that it was single- centred and had only male subjects.

Future Perspectives

Investigating the role of disulfiram as early intervention strategies for individuals at risk of developing Alcohol Use Disorder (AUD) can be implemented. The identification of at-risk individuals and the implementation of preventive measures could carry substantial implications for public health. The enhancement of treatment adherence through the development of long-acting or extended-release formulations of disulfiram, thereby reducing medication administration frequency, has the potential to improve convenience and efficacy as a treatment option. The incorporation of digital health technologies, such as mobile applications or remote monitoring, presents an opportunity to provide support for individuals undergoing disulfiram treatment. These technological solutions may play a pivotal role in promoting medication adherence, offering real-time support, and overall, augmenting engagement in the treatment process.

Conclusion

Currently, psychiatrists are cautious to prescribe disulfiram in fear that it might induce several unwanted side effects and that the drug has less efficacy. Our study is to prove that Disulfiram is a safe and effective option for alcohol-dependent patients, as it is better in terms of relapse prevention and recovery over time. Even though there exist safety and compliance issues, it shows an acceptable risk on supervised administration. Relapse prevention and complete recovery were higher in the disulfiram group compared to the control group, and there was a significant difference.

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