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Association of executive function, craving and precipitants of relapse in alcohol use disorder: A cross-sectional study

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Abstract

Objective: Alcohol use disorder (AUD) is a global health concern. Patients with AUDs often relapse. Various psychosocial factors, as well as cognitive factors, determine relapse. Failure of response inhibition is often associated with relapse. This study aimed to evaluate the association of craving and relapse precipitants with executive function in AUD.

Materials and methods: The study was conducted in the outpatient setting of a tertiary care hospital in North India (between September 2017 to August 2018) on patients with AUD, who presented with a recent relapse.

A total of 46 adult patients with AUD, who relapsed after a quit attempt were enroled in the study. Cross-sectional assessment of relapse precipitants (by using relapse precipitant inventory), craving (by using the obsessive-compulsive drinking scale (OCDS)), and executive function (EF) (by using the Wisconsin Card Sorting Test (WCST)) was done along with various socio-demographic and clinical variables.

Results: The mean age of onset of alcohol use was 21.48±4.25years and the mean duration of alcohol use was 15.13±7.70 years. The average number of relapses in the study population was 3.59±2.06. There is a significant positive correlation between a negative mood state (as a relapse precipitant) and total relapse score with craving. There is a significant association of relapse and craving with deficits of EF (perseverative and non-perseverative errors). Similarly, lessened cognitive vigilance also significantly correlate with EF deficits resulting in a relapse of AUD.

Conclusion: There is a close association of craving, and relapse with deficits of EF, in AUD. Craving and relapse in AUD may be the result of deficits in EF. Future research addressing the cognitive deficits may help in the prevention of craving and relapse.

Keywords

Alcohol use disorder, relapse, craving, executive function, cognition, mood state

INTRODUCTION

Alcohol use disorder (AUD) is a major health problem globally and is responsible for high morbidity and mortality. As per the global status report on alcohol and health 2018, alcohol stands as a major barrier to the sustainable development goals. As per this report, across the globe, 2.3 billion people are currently using alcohol (World Health Organization, 2019).

The National Mental Health Survey 2015-2016 (NMHS) in India had estimated the prevalence of drug usage among the community population. The most commonly used substance was tobacco (20.9%) followed by alcohol (4.64%) and other drugs (0.57%) (Gururaj et al., 2016).

Craving and relapse in substance use disorders including alcoholism: Relapse is very common in substance abuse disorder, unlike other psychiatric diseases. This is very important for treatment evaluation, effectiveness, and outcome in substance use disorder. Relapse prevention is one of the important goals of the management of substance use disorder (Korlakunta et al., 2012). Relapse stands as the biggest obstacle in the path of recovery from substance use disorders. Relapse in drinking falls into three categories: exposure to a small quantity of alcohol, exposure to environmental-related cues and environmental features, and stress (Ferguson et al., 1996).

The main factor which triggers relapse in alcoholics is impaired inhibitory control (Jones et al., 2018). Relapse

after treatment is more likely to occur in patients who consume heavy alcohol (large volumes and more frequent consumption), and have craving as well as higher alcohol-related problems such as financial and relational difficulties (Becker, 2008; Yang et al., 2018). The other factors responsible for relapse are alcohol drinking patterns (e.g. daily drinking, occasional drinking, binge drinking) and early age of onset. Those individuals who drink daily and start drinking before the age of 18 are more likely to relapse (Beck and Heinz, 2013). Craving is the commonest cause of relapse in alcohol-dependent individuals. Craving plays a central role in the maintenance of drug dependence and acquisition. It has two important features, firstly, it tends to be specifically triggered by previous alcohol use; secondly, it can persist even after cessation of alcohol drinking. According to this model, automatic cognitive processes regulate addictive drug use, while craving represents activation of non-automatic processes activated to help either interrupted drug use or block automatic drug use (Thoma et al., 2011; Tiffany and Conklin, 2000). Craving is a subjective phenomenon and it is often measured by applying specific rating scales such as the Obsessive-Compulsive Drinking Scale (OCDS).

Cognitive control of craving and relapse in AUD: The cognitive impairments associated with alcohol use range from little or minimal impairment to serious cognitive deficits (Ryback, 1971). Evidence supports deficits in concept formation and abstract thinking in young- to middle-aged men who were engaged in social drinking (Parker and Noble, 1980). Beatty and colleagues showed that cognitive impairment may be caused by the use of alcohol due to damage in multiple brain areas like prefrontal circuits (Beatty et al., 2000). It has been seen that some of these impairments are reversible when abstinence is achieved (Volkow et al., 1995). By remaining abstinent the brain function is recovered over several months to one year (Sullivan et al., 2000) with improvements in working memory, visuospatial functioning, and attention. This is accompanied by an increase in the volume of the brain when compared with alcohol users who have been treated but have relapsed (Allen et al., 1997). It has been seen in studies that cognitive deficits have resulted in increased craving and vice versa whereas there has been evidence from functional neuroimaging studies showing that cognitive deficits result in ineffective regulation of negative emotions like fear, sadness, and disgust thus involving triggers of affective states, which can lead to craving (Naqvi et al., 2015)or regulate, cue-induced craving using cognitive strategies is a therapeutic goal of cognitive behavioral therapy (CBT).

Craving is considered a compulsive as well as an impulsive phenomenon. Impulsivity largely influences alcohol taking behaviour. Impulsivity is the result of underlying cognitive dysregulation. Individuals, who are having poor response inhibition are likely to have impulsive behaviour (Adinoff et al., 2007; Pattij and De Vries, 2013). Evidence also suggests that in the presence of alcohol-related cues there occurs failure of cognitive control (Thoma et al., 2011). Executive function (EF) refers to higher cognitive functions like planning, organisation, set-shifting and response inhibition. Evidence supports that deficits in executive function may put individuals at a risk for substance use and thus make them likely to have problems related to substance use (Finn et al., 1999). Deficits in set-shifting or information updating can also make it difficult for individuals to use various coping strategies concerning cues related to alcohol use.

In the same way difficulties in response inhibition might also affect how an individual can resist the urge to drink, go to a place to drink, or socialise with a peer group engaged in drinking which may lead to relapse (Thoma et al., 2011).

There is a paucity of literature regarding EF about relapse in AUD. Understanding the association between an EF with craving and relapse in AUD will help in the prevention of relapses. We hypothesise that craving has a positive correlation with relapse. And, also, craving and relapse in alcohol disorders are associated with failure (deficits) in EF. The study aimed to evaluate craving and relapse in inpatients with AUD and to see the association of craving and relapse with EF in AUD.

MATERIALS & METHODS

Design of the study: The study was a cross-sectional, non-intervention study designed to evaluate the association of craving, relapse precipitants with EF in AUD. It was conducted between September 2017 and August 2018, after obtaining approval from the institutional ethics committee vides letter-number 89thECM11B-Thesis/P49.

Study sample: Patients attending the De-addiction Clinic and Adult Psychiatry outpatients of the Department of Psychiatry, a tertiary care hospital in North India and diagnosed with AUD (as per DSM-5) and fulfilling the selection criteria (including the operational definition of relapse and clinical stability) were taken for the study. Informed consent was taken from the patients. Patients aged between 18-60 years, who were able to read and write Hindi and clinically stable (as per the operational definition) were recruited in the study. Patients from this age group were taken because those above 18 are eligible to give informed consent and AUD predominantly affects

young and middle-aged people. The likelihood of medical comorbidities and cognitive disorders are high after the age of 60 years. Hence, we restricted the study population to 18-60 years to avoid any confounding factor in cognitive performance due to advanced age which might have hindered complete assessment (Robbins, 2007). Data shows that the average age of initiation of drinking is about 20 years (Polich et al., 1980). Patients with impaired vision or hearing that makes administration of the tests difficult were excluded. Patients with psychiatric illnesses (except tobacco use disorder and personality disorders) or major medical/surgical illnesses were also excluded. Other psychiatric illnesses are known to affect EF and may influence relapse and craving. Comorbid major medical and/or surgical illnesses may influence the engagement of the patient in the assessment. Hence, these patients were excluded. We also excluded patients who had a family history of severe mental disorders (DSM-5 category: schizophrenia, schizoaffective disorder, bipolar affective disorder) as EF deficits are reported among the first degree relatives of these groups of psychiatric disorders.

Tools: Semi-structured socio-demographic proforma was used to document the socio-demographic details and clinical history. To exclude psychiatric comorbidities, the Mini International Neuropsychiatric Interview was used (M.I.N.I. 7.0.2) (Sheehan, 2016). To evaluate the relapse precipitants, the Relapse Precipitant Inventory (RPI) was used (Mattoo et al., 2003). In addition to the total score, RPI, gives domain scores for "negative mood state", "euphoric state" and "lessened cognitive vigilance". To measure craving, OCDS was used (Anton et al., 1995). The OCDS gives total score as well as scores in subscales (obsessive subscale and compulsive subscale). Similarly, to measure EF the Wisconsin Card Sorting Test (WCST) was used (Heaton et al., 1994). To rule out patients with clinically significant alcohol withdrawal symptoms, the Alcohol Withdrawal Assessment Scoring Guidelines were used (CIWA – Ar) (Sullivan et al., 1989). The tools used in this study were standardised and validated (available in local languages), convenient to use and less time-consuming.

Operational definitions: As no international or national literature has clearly defined the word relapse, relapse and abstinence were operationally defined for this study. The initial transgression of alcohol intake after a quit attempt, defined as lapse which could eventually lead to continued transgression of alcohol intake to a level similar to a pre-quit level, is defined as a relapse (Marlatt and Donovan, 2005; Menon and Kandasamy, 2018) and the minimum period of abstinence should be 30 days (Korlakunta et al., 2012; Mattoo et al., 2009). It was made sure that patients taking part were clinically stable, CIWA – Ar scores less than 10, and were able to read and write Hindi so that they could comprehend the test efficiently. Clinical stability refers to the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA – Ar) score < 10 (Sullivan et al., 1989).

As the phenomenon of relapse happens after a period of sustained abstinence from alcohol, we considered defining the period of abstinence by the above operational definition. This study measured the precipitants of current relapse and severity of craving for the current relapse. Relapse and craving are a dynamic phenomenon and are likely to change from time to time, the factors that attribute to craving and relapse also vary. We attempted to measure the real-time association (cross-sectional) of relapse, craving and EF at a particular point in time. Similarly, clinical stability is required for the assessment of EF; hence, we operationalised the definition for clinical stability. The presence of withdrawal symptoms is likely to hamper the accurate measurement of EF.

Procedure: Patients having a diagnosis of AUD as per DSM-5 were assessed on semi-structured proforma for socio-demographic and clinical variables after informed consent was obtained. Patients were assessed on the selection criteria. The RPI (Hindi version), computerised version of WCST and OCDS were applied to measure the study variables. As ongoing medications (benzodiazepines) may affect cognitive performance, the patients were asked to skip the morning dose of benzodiazepine on the day of cognitive assessment.

Statistical analysis: The data was analysed using computerised software – Statistical Package for the Social Sciences (SPSS) version 16. As the data was normally distributed (as found on Kolmogorov-Smirnov (K-S) test), Pearson's correlation was calculated by correlational analysis (between relapse, craving and EF). As multiple independent tests were applied the corrected p-value (after applying Bonferroni correction) was taken as 0.017 (0.05/3) for statistical significance.

RESULTS

A total of 61 patients were screened, out of which 46 patients met the selection criteria and so included in the study. Another comorbid psychiatric disorder (mood disorder, opioid dependence, depression) was present in five patients, six patients refused to give consent and four patients were excluded as the period of abstinence was less than 30 days. The mean age of the patients' was 36.8±8.75years. Most patients (41.4%) were between 26-35 years of age. All the patients were males and mostly

(86.9%) Hindu. Most of the patients (58.3%) were graduates or above in education level. They were mostly working in semi-skilled or unskilled work (43.4%) and mostly (52.2%) having an income of fewer than 10,000 rupees per month (approx £97). The majority of the study participants were married (71.7%), belong to the urban background (67.4%), and from nuclear families (54.4%) (Table 1). A family history of alcohol use was present in 47.8% of patients. In the patients mean age of onset of alcohol use was 21.5±4.25years and the mean duration of alcohol use was 15.2±7.70 years. The average number of relapses in our study population was 3.59±2.06.

At the time of enrolment in the study, the patients were receiving an average dose of benzodiazepine (chlordiazepoxide equivalent dose) 23.7±4.88 mg/day. There was no statistically significant correlation between the relapse precipitants, craving and EF with the socio-demographic variables like age and clinical variables like duration of illness, number of relapses and severity of withdrawal symptoms.

Table 2 depicts the relation of craving with chances of relapse. The negative mood state domain and total scores of RPI had a significant positive correlation with the obsessive scores, compulsive scores, and total scores of OCDS.

Domains of lessened cognitive vigilance domain of the RPI show a statistically significant positive correlation

Table 1: Socio-demographic characteristics of the participants.

Demographic profile	All patients (n=46)	
	No.	%
Age		
18-25	3	6.3
26-35	19	41.4
36-45	17	37.1
46-60	7	15.2
Sex		
Male	46	100
Religion		
Hindu	40	86.9
Muslim	6	13.1
Education		
<8th Passed	2	4.4
Middle-school (8th passed)	10	21.7
High school (10th passed)	4	8.7
Intermediate (12th passed)	3	6.3
Graduate	16	34.4
Postgraduate & above	11	23.9
Occupation		
Student	1	2.2
Unemployed	6	13.0
Unskilled/semi-skilled workers	20	43.4
Skilled workers	7	15.2
Clerk, shop owner, farmer	11	23.9
Professional/semi-professional	1	2.2
Income of patient/month (In Rs.)		
Upto 10,000	24	52.2
10,001-20,000	10	21.7
>20,000	12	26.1
Marital status		
Married	33	71.7
Unmarried	1	26.1
Separated/divorced	1	2.2
Domicile status		
Rural	31	32.6
Urban	15	67.4
Family structure		
Nuclear	25	54.4
Joint	21	45.6

Table 2: Correlation of relapse precipitants (scores on RPI) with craving (scores on OCDS) in relapsed patients of alcohol use disorder.

Relapse Precipitant Inventory (RPI)	Obsessive-Compulsive Drinking Scale (OCDS)		
	Obsessive subscale	Compulsive subscale	Total
Negative mood state	r=0.554 p=0.000 *	r=0.471 p=0.001*	r=0.526 p=0.000*
Euphoric state	r=-0.160 p=0.289	r=-0.061 p=0.685	r=-0.116 p=0.444
Lessened cognitive vigilance	r=-0.136 p=0.367	r=-0.136 p=0.368	r=-0.139 p=0.357
Total score	r=0.402 p=0.006*	r=0.372 p=0.011*	r=0.396 p=0.006*

*Corrected p-value (after applying Bonferroni correction) for statistical significance is 0.017 (0.05/3).
r= Pearson's correlation co-efficient.

Table 3: Correlation of domains of relapse precipitants (scores on RPI) with EF of cognition (WCST scores) in relapsed patients of alcohol use disorder.

Wisconsin Card Sorting Test (WCST) Domains	Relapse Precipitant Inventory (RPI) domains			
	Negative Mood State	Euphoric State	Lessened Cognitive Vigilance	Total
Percentage (%) of total no of errors	r= 0.147 p=0.331	r= 0.008 p=0.958	r= 0.382 p=0.009 *	r=0.273 p=0.066
Percentage (%) of perseverative responses	r= 0.067 p=0.660	r=0.100 p=0.507	r= 0.297 p=0.045	r=0.215 p=0.151
Percentage (%) of perseverative errors	r=0.089 p= 0.554	r= 0.104 p=0.490	r=0.317 p=0.032	r=0.246 p=0.100
Percentage (%) of non- perseverative errors	r= 0.123 p=0.417	r=-0.089 p=0.558	r= 0.239 p=0.110	r= 0.153 p=0.311
Percentage (%) of conceptual level responses	r= -0.139 p= 0.358	r= -0.057 p=0.706	r=-0.363 p= 0.013 *	r=-0.284 p= 0.055
Categories completed	r= -0.209 p= 0.162	r= -0.049 p= 0.748	r=-0.413 p=0.004 *	r=-0.365 p= 0.013*
Trials to complete 1st category	r= 0.303 p=0.040	r=0.147 p=0.330	r=0.182 p=0.225	r=0.426 p=0.003*

*Corrected p-value (after applying Bonferroni correction) for statistical significance is 0.017 (0.05/3).
r= Pearson's correlation co-efficient.

with percentage of total number of errors (r=0.38, p= 0.01), and statistically significant negative correlation with the percentage of conceptual level responses (r = -0.36, p = 0.01) and categories completed (r = -0.41, p = 0.01) of WCST. The total scores of the RPI shows a statistically significant positive correlation with trials to complete first category (r = 0.43, p = 0.01) of WCST (Table 3).

Obsessive component of OBDS shows a negative correlation with "categories completed" domains of WCST, (r = -0.36, p = 0.01). The compulsive domain of the OCDS shows statistically significant positive correlation with percentage of non-perseverative errors (r = 0.37, p =0.01). Total score of OCDS shows a statistically significant negative correlation with categories completed (r=-0.40, p<0.01) Table 4.

DISCUSSION

The current study was a cross-sectional, non-interventional study on relapsed patients of AUD carried

Table 4: Correlation of domains of WCST with domains of OCDS.

Wisconsin card sorting test domains (WCST)	Obsessive Compulsive Drinking Scale (OCDS)		
	Obsessive subscale#	Compulsive subscale#	Total score
Percentage (%) of total no of errors	r=0.256 p=0.086	r=0.333 p=0.024	r=0.299 p=0.044
Percentage (%) of perseverative responses	r=0.038 p=0.801	r=0.072 p=0.633	R=0.055 p=0.714
Percentage (%) of perseverative errors	r=0.068 p=0.653	r=0.109 p=0.472	r=0.089 p=0.556
Percentage (%) of non- perseverative errors	r=0.297 p=0.045	r=0.368 p=0.012*	r=0.338 p=0.022
Percentage (%) of conceptual level responses	r=-0.236 p=0.114	r=-0.327 p=0.027	r=-0.285 p=0.055
Categories completed	r=-0.356 p=0.015*	r=-0.427 p=0.003*	r=-0.397 p=0.006*
Trials to complete 1st category	r=0.295 p=0.047	r=0.324 p=0.028	r=0.315 p=0.033

*Corrected p-value (after applying Bonferroni correction) for statistical significance is 0.017 (0.05/3).
# OCDS has two subscales (obsessive subscale & compulsive subscale).
r= Pearson's correlation co-efficient.

out over approximately one year, at a tertiary care centre in North India. Patients of other psychiatric illnesses were excluded, as the co-existence of other psychiatric illnesses would have affected the course and outcome of AUD and have led to the biased results of various tools used (Brown et al., 1994).

Clinical characteristics: The mean CIWA score was 1.37±-0.64; it was ensured that the CIWA score of patients at the time of assessment was less than 10, so that that the patient should have the least withdrawal symptoms at the time of taking tests. As withdrawal symptoms affect cognitive performance, patients who were clinically stable and had no withdrawal symptoms to mild withdrawal symptoms were included in the study.

The mean numbers of relapses in our study were 3.59±2.06. Studies show that 50-60% of alcoholics were relapsing within the first three months and 90% within four years after completion of treatment (Hunt et al., 1971)smoking, and alcohol. These curves conform to a negatively accelerated typical extinction curve and are marked by (a. Patients with AUD often experience multiple relapses during their illness. The study participants were on benzodiazepines (chlordiazepoxide equivalent dose of 23.70±4.88 mg/day). As the patients had sleep difficulties for which the benzodiazepine was commonly recommended. To minimise the effect of benzodiazepine on cognitive performance, the patients were asked to skip the dose of benzodiazepine on the day of cognitive assessment.

Association between relapse precipitants and craving: Correlation with scores on RPI and scores on OCDS showed a significant positive correlation between obsessive subscale, compulsive subscale and total OCDS score and negative mood state. This signifies that as the negative mood state increases thoughts regarding alcohol intake also increases, resulting in increased drinking behaviour. It goes in accordance with the hypothesis made in this study. A negative mood state can be a predictor of craving, which might ultimately lead to relapse. Craving behaviour, which is assessed with the OBDS is significantly related to relapse in various studies (Bottlender and Soyka, 2004). The total scores of the RPI also correlated with all parameters of OCDS establishing craving as a significant factor concerning relapse (Evren et al., 2010).

Association between relapse precipitants and EF: Correlation between scores of RPI and WCST indicates that – the more cognitive vigilance is lessened (i.e. score of "lessened cognitive vigilance" increases) there are higher chances of committing an error in the test performance, which is following other studies which have shown impaired cognitive function as the cause of relapse (Kim et al., 2016). An increase in the number of errors signifies the problem in set-shifting thus signifying problems in cognitive flexibility which is responsible for the relapse. There is a negative correlation between a lessened cognitive vigilance and the percentage of conceptual level response; this again signifies that as a score of lessened cognitive vigilance increases the executive performance becomes poorer. As the total score of RPI increased,

fewer categories were completed, which indicates that EF impairment increases the risk of relapse in AUD, which goes with the hypothesis of the study. Failure of response inhibition is the resultant outcome of executive dysfunction, which is associated with relapse.

Association between craving and EF: Correlation of domains of WCST with the domain of OCDS was done to see the association of EF with craving. The significant negative correlation between trials to complete the first category with all subscales of OCDS (obsessive subscale & compulsive subscale) as well as the total score of OCDS indicate that higher craving is associated with poor EF. Similarly, higher craving is associated with more chance of committing non-perseverative errors. The overall picture indicates that the declined performance in EF is associated with increased craving, which goes with the hypothesis of the study.

EF is involved in the planning and regulation of goal-directed behaviour. Poor EF can lead to impulsive and risky behaviour which in turn predisposes to suboptimal decision-making. This deficit in supervisory executive control makes automatic habit responses in response to cues. This deficit can also result in diminished supervisory control of emotional responses thus leading to craving. Studies have shown that various measures of cognitive functioning are affected by measures of clinical severity like craving (Berking et al., 2011; Field et al., 2005)the aim of the study was to investigate whether deficits in adaptive emotion-regulation skills maintain alcohol dependence (AD. This, also, has been replicated in our study thus establishing the role of cognition and craving in relapse and also interrelation between them.

We did not find a significant correlation between all the study variables, which may be due to the small sample size and wide variations in the cognitive performances. Small sample size is a limitation of our study. The cause or effect relationship between relapse, craving and EF could not be established in cross-sectional study design. The attributes of craving and relapse change from time to time and could not be measured through a cross-sectional study design. Medication effects on EF could not be nullified, though an attempt was taken to minimise it. Future research following a prospective-study design in a larger sample may give an insight into the causality.

CONCLUSION

Relapse and craving in AUD have a significant association with executive deficits. Deficits in EF associated with increased craving and more relapses in AUD. There is a need to conduct prospective studies to see the association of cognitive deficits with the outcome of AUD.

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Ethical approval: The study was approved by the institutional ethics committee of King George's Medical University, Lucknow, Uttar Pradesh, India vides letter-number 89thECM11B-Thesis/P49.

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