



A Study of Factors Influencing the Severity of Alcohol Withdrawal State in Patients of Alcohol Dependence Syndrome

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Abstract

Introduction: Beverage alcohol which is a product of fermenting fruit or grape was probably found around before humans walked the earth. It is among the most widely used psychoactive substances in the world. Alcohol Use Disorders is a global problem and is the third leading cause of death throughout the world. Withdrawal symptoms can manifest in an uncomplicated manner like coarse tremors, insomnia, anxiety, increased heart rate while a small but significant number of individuals present in a complicated manner as in delirium tremens which can occur in 5% of the cases. Past history of complicated withdrawal, older age, poor nutritional status and history of high tolerance to alcohol are predictors of increased severity of withdrawal while few more predictors are yet to be established in order to improve the line of management of these individuals.

Materials And Methods: A cross-sectional study was done on 165 individuals who fulfilled the criteria of alcohol dependence syndrome aged between 18-65 years who attended out/ in-patient departments of SSMC and who gave informed consent They were assessed using a semi-structured proforma, Alcohol Use Disorder Identification Test (AUDIT), Clinical Institute of Withdrawal Assessment for alcohol (CIWA-Ar) and individuals who qualified for delirium were assessed using Delirium Rating School (DRS-R98).

Results: Majority of the participants were between 31-50 years (63.6%) with mean age being 41.70 (SD \pm 9.97), males (94.5%) who were mostly educated upto high school (30.9%) and were involved in clerical work or were shop owners or farmers (55.8%). Most of them were married (77.0%). Majority of the study subjects initiated alcohol consumption between 20-30 years of age (81.2%) with mean age being 26.84 (SD \pm 5.36). 60.0% of them

consumed alcohol daily with 39.4% of them consuming 180-270 ml. Majority of them had a family history of alcohol use (66.1%). Most of them did not have a fixed pattern of alcohol use (38.2%). There was no period of abstinence in most of the subjects (53.9%). About 58.8% of them were involved in concomitant use of other substances out of which 57.6% of them used tobacco. CIWA scores of the study subjects done on day 1 had 44.8% of moderate severity, 26.7% being severe, 26.1% being mild while 2.4% had very mild severity. The withdrawal assessment done on day 7 in the same individuals showed 58.2% having mild severity, 32.1% having very mild withdrawal, 7.3% having moderate withdrawal while 2.4% having severe withdrawal.

Conclusion: This study suggests that the severity of alcohol withdrawal decreases where in on day 1 if the severity was moderate became mild or very mild when assessed on days 7. There are various factors which influence the severity of alcohol withdrawal state in patients of alcohol dependence syndrome. While some sociodemographic factors like occupation, income of the individuals, religion play significant role in determining the severity of withdrawal state, others like age, gender, educational status and marital status do not influence withdrawal severity. Few other factors like quantity and frequency of consumption, amount spent, family history and concomitant use of other substances make a major impact in withdrawal. By assessing the severity, we can reduce the morbidity and mortality associated with alcohol and hence also prevent untoward consequences because of them.

Keywords: Alcohol use disorders, withdrawal, delirium, factors, severity

Introduction

Beverage alcohol (ethanol) is a product of fermenting fruit

or grain and was probably found around before humans walked the earth. Evidence of human consumption of these beverages dates back at least 12,000 years, and alcohol was used as part of ceremonies in Babylon, Greece, and the Roman Empire over 5,000 years ago when this drug was also used for pleasure, nutrition and for its medicinal properties (1). Alcohol in beverage form is among the most widely used psychoactive substances in the world (2).

Asian countries such as China, South Korea, and Thailand have experienced steady increases in alcohol consumption since the late 1970s (5). Temporary psychiatry symptoms are common during intoxication and withdrawal of alcohol (6). Taken in large doses, alcohol is considered to have anesthetic or depressive properties. It also has the ability to elicit euphoria, especially when the blood alcohol level is increasing. This phenomenon may be mediated by direct activation by alcohol of the mesolimbic dopaminergic circuit, particularly the ventral tegmental area (VTA) and the nucleus accumbens (NAc). Anxiolysis and relaxation also appear to be part of the spectrum of the rewarding effects of alcohol, although these effects appear to be mediated by activation of the GABAergic neurotransmitter system. (7). Alcohol Use Disorder (AUD) is a complex, multifaceted cluster of behavioural, cognitive, and physiological symptoms (8). According to Diagnostic and Statistical Manual of Mental Disorders, fifth edition, (DSM-5) (American Psychiatric Association, 2013), DSM – 5, different severities of Alcohol Use Disorder and three types of alcohol induced disorders (i.e., Alcohol Intoxication, Alcohol Withdrawal, and Alcohol Induced Mental Disorders) are included (9). Alcoholism or AUD is a global problem and is the third leading cause of death throughout the world. Alcoholism is a state or a condition, where a person is incapable of

resisting his or her desire for alcohol and gets addicted to the same. Drug dependence is again another type of addiction where person becomes dependent on illegal drugs and unable to quit. Compulsive seeking and excessive use of these, despite its harmful consequences converts a habit into addiction. It is a chronic and relapsing brain disorder. The addicted person suffers withdrawal symptoms, while trying to quit or recover from this disease state (10).

The lifetime risk for AUDs is approximately 15 percent for men and 10 percent for women, with 1-year prevalence rates of about 6 percent, figures that are applicable across most socioeconomic and educational levels (11).

If a person has been drinking heavily over prolonged period, a rapid decrease in blood alcohol levels can produce a withdrawal syndrome characterised by symptoms with coarse tremor of the hands, insomnia, anxiety, increased heart rate, blood pressure, body temperature.

Onset of symptoms of uncomplicated alcohol withdrawal usually occurs between 4 and 12 hours following the last drink. Symptom severity tends to peak around the second day, usually subsiding by the fourth or fifth day of abstinence. After this period, less severe anxiety, insomnia, and autonomic symptoms may persist for a few weeks, with some individuals experiencing a protracted alcohol withdrawal syndrome up to 5 – 6 months after cessation of drinking.

A small but significant number of individuals (approximately 10%) with moderate and especially severe alcohol use disorder can experience complicated alcohol withdrawal episodes. Alcohol withdrawal delirium (also known as delirium tremens) can occur in 5% of the cases, usually between 36 and 72 hours following alcohol

cessation. In addition to signs of autonomic hyperactivity, this condition is characterized by illusions, auditory, visual, or tactile hallucinations, psychomotor agitation, fluctuating cloudiness of consciousness, and disorientation. Grand-mal seizures associated with alcohol withdrawal occur in 3 – 5% of the cases, typically within the rest 48 hours following reduction or cessation of drinking. In both instances of complicated alcohol withdrawal, lack or delay in instituting proper treatment is associated with an increased mortality rate.

Prior history of delirium tremens and/or alcohol withdrawal seizures, older age, poor nutritional status, comorbid medical conditions, and history of high tolerance to alcohol are predictors of increased severity of alcohol withdrawal (12).

Alcohol withdrawal is relatively rare in individuals who are not chronic heavy drinkers and is sometimes confused with the sequelae of acute intoxication in younger individuals. (13)

Alcohol withdrawal state presents with varied clinical manifestations which is being assessed in this study and even delirium tremens having a high mortality of about 8%, it becomes important to predict its occurrence by evaluating the various factors contributing for the same

Materials and Methods

The study was conducted in Sri Siddhartha Medical College Hospital & Research Centre, Agalakote, Tumakuru between November 2016 to April 2018. A total of 165 individuals who attended Out-patient or In-patient departments of the hospital, fulfilling the inclusion criteria participated in the study. Informed consent was taken for the study from the participants after explaining the nature of the study.

Inclusion Criteria

Patients attending the outpatient department or admitted in the in-patient department of Sri Siddhartha Medical College with primary diagnosis of alcohol dependence syndrome according to International Classification of Diseases-10 classification Of Mental and Behavioural Disorders/ Diagnostic Criteria for Research (ICD-10/DCR)

Subjects between 18 to 65 years of age.

Exclusion Criteria: All cases of primary psychiatric illness other than alcohol dependence syndrome.

Study Tools Used

- 1. Socio-demographic Proforma:** The questionnaire consists of 11 items that include a number of **demographic variables**.
- 2. Semi-structured Proforma:** This included 13 questions regarding the details of alcohol closed and open-ended responses.
- 3. Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA):** It was developed from the Selected Severity Assessment (SSA) which was published in 1973 by Gross et al. (1973), to enable use at more frequent intervals during the day. This resulted in a 15-item scale, which retained just 7 of the 11 SSA items¹¹. This was later revised as CIWA-Ar which is a validated, standardized 10 item questionnaire developed to assess the signs and symptoms of alcohol withdrawal graded on severity. It has a maximum score of 67. Scores between 0 to 9 indicate very mild withdrawal, 10-15 indicate mild withdrawal; 16-20 indicate moderate and 21-67 indicate severe withdrawal. (27).
- 4. Delirium Rating Scale (DRS):** It is a numerical rating scale that specifically integrates revised Diagnostic and Statistical Manual-3 diagnostic

criteria for delirium. It is a 10-item scale. The shortcomings of DRS were addressed in the revision of DRS in the year 1998 known as DRS-R98 which is a 16-item clinician rated scale with 13 severity items and 3 diagnostic items severity scale, is more valid, reliable and is considered the only validated delirium rating scale in the phenomenology and in the longitudinal studies of delirium patients (28).

5. Alcohol Use Disorder Identification Test (Audit):

The AUDIT was developed by the World Health Organisation (WHO) in 1982 as a simple method of screening for excessive drinking and to assist in brief assessment. It also helps to identify alcohol dependence, harmful or hazardous drinking. There are 10 questions and a maximum score of 40. Total scores between 8 to 19 indicate hazardous drinking and scores >20 indicate dependence level (29).

Sample Size:

165 patients attending the outpatient department or admitted in the in-patient department of Sri Siddhartha Medical College (SSMC), Tumakuru with primary diagnosis of alcohol dependence syndrome according to ICD-10.

Procedure

This was a descriptive cross-sectional study. Individuals who fulfilled the criteria for alcohol dependence syndrome according to ICD-10/DCR and between the age group of 18- 65 who were willing to give a written consent were included in the study. A semi structured Proforma was used to collect the socio demographic details of the patient. As there was an uncertainty about the exact time duration during withdrawal phase at which the patient reported to the OPD or got admitted as inpatient for the treatment for alcohol dependence syndrome, the CIWA-Ar was administered for the first

time as soon as the patient reported to the hospital and was repeated 7 days later to know the variation in the withdrawal symptoms. Only the individuals who qualified for delirium were administered the DRS-R-98 to assess the severity of delirium. Once the patient was free of his withdrawal symptoms he was then administered the AUDIT questionnaire to assess the level of alcohol dependence. The sample size was 165. Data was analysed using SPSS 18.0 and R environment ver.3.2.2 and Microsoft word and Microsoft excel have been used to generate graphs, tables etc. Chi square test and Fisher Exact test have been used to find the significance of the study parameters on categorical scale between two or more groups.

Results

Out of 165 subjects studied, mean age of the sample is 41.70 (SD ±9.97), where 156 (94.5%) were males.

Table 3 shows the educational status of the study subjects. Majority of them were qualified upto high school (30.9%) followed by primary school (25.5%), middle school (17%), illiterates (12.1%), post high-school diploma (11.5%) and graduates or post graduates (3.0%). shows the occupation of the subjects who were included in the study. Majority of them were involved in clerical work or were shop keepers or farmers (55.8%) followed by semi-professionals (16.4%), skilled workers (12.7%), unskilled workers (6.1%), professionals (2.4%) and unemployed (1.8%). income earned by the subjects in a month. Majority of them earned Rs 4810-8009 (44.8%) followed by Rs 1601-4801 (21.2%), Rs 8010-12019 (16.4%), Rs 12020- 16019 (10.3%) and <Rs 1600 (4.2%). Majority of them are married (77.0%) followed by single (16.4%) with least being divorced (1.2%). Mean age of initiation of alcohol consumption in the sample is 26.84 (SD±5.36). Majority of them consumed IMFL (98.8%) followed by

beer (1.2%) and about 99 (60.0%) consumed daily while 33 (20.0%) consumed 2 – 3 times a week. quantity of alcohol consumed by the study subjects. It is seen that most of them consumed 180-270ml (39.4%) followed by 360-540ml (23.6%), 270-360ml and 180-360ml (11.5% each), 90-180ml (10.3%), 270-540ml and >540ml (1.2% each), 90-270ml and 180-540ml (0.6%).

Table 1 shows if the study subjects had a family history of alcohol consumption and it is seen that most of them (66.1%) had a family history while 33.9% did not have.

Table 1: Family History of Patients Studied

Family History	No. of patients (n)	Percentage %
Yes	109	66.1
No	56	33.9
Total	165	100.0

It is seen that majority of them did not have a fixed pattern of consumption (38.2%) followed by use in company (36.4%) and least being alone consumption (25.5%).

Table 2 shows the presence or absence of abstinence in the study subjects. It is observed that majority of them (53.9%) do not have history of abstinence while about 46.1% have history of abstinence.

Table 2: History of Abstinence Of Patients Studied

Abstinence	No. of patients	PERCENTAGE
Yes	76	46.1
No	89	53.9
Total	165	100.0

Table 3 shows concomitant use of any other substance along with alcohol in the study subjects. It is seen that majority of them have tobacco consumption (57.6%) followed by cannabis use (1.2%) while there is no history of any other substance use in 41.2%.

Table 3: Concomitant Use Of Any Other Substance Of Patients Studied:

Other Substance	No. of Patients (N)	Percentage %
None	68	41.2
Tobacco	95	57.6
Cannabis	2	1.2
Heroin	0	0.0
Benzodiazepines	0	0.0
Others	0	0.0
Total	165	100.0

Table 4 shows show the AUDIT scores of the study subjects. It is seen that 46.7% have dependence level of drinking while 53.4% have hazardous pattern of alcohol use.

TABLE 4: Audit Score Distribution of patients studied

Audit	No. of patients (n)	percentage %
8-15	46	27.9
16-19	42	25.5
>20	77	46.7
Total	165	100.0

Table 5 shows CIWA scores of the study subjects done on 1st day and 7th day. It is seen that on 1st day 44.8% belonged to moderate severity followed by severe (26.7%), mild (26.1%) and 2.4% belonged to very mild severity.

On Day 7, majority belonged to mild severity (58.2%) followed by very mild (32.1%), moderate (7.3%) and 2.4% belonged to severe withdrawal.

Table 5: CIWA Score Distribution

CIWA scores	No. of patients (n=165)	Percentage (%)
1 st day		
0-9	4	2.4
10-15	43	26.1
16-20	74	44.8
21-67	44	26.7
7 th day		
0-9	53	32.1
10-15	96	58.2
16-20	12	7.3
21-67	4	2.4

TABLE 6: DRS SCORE DISTRIBUTION

DRS Scores	No. of patients(n)	Percentage (%)
21-25	3	30.0
26-30	5	50.0
>30	2	20.0
Total	10	100.0

Table 6 shows DRS scores of individuals who were diagnosed with delirium amongst the study subjects. It is seen that out of 10 individuals who were in delirium, 50% had a score of 26-30 followed by 30% who scored between 21-25 and 20.0% scored >30.

Correlation of age in relation to the severity of CIWA scores (on both day 1 and day 7). It is seen that age of the study subjects in relation to the CIWA score on day 1 had a 'P' value of 0.104 while that on day 7 is 0.854. Correlation of educational status in relation to the severity of CIWA scores (on both day 1 and day 7). It is seen that educational status of the study subjects in relation to the

CIWA score on day 1 had a 'P' value of 0.725 while that on day 7 is 0.24.

Table 7: Correlation of Occupation In Relation To CIWA Scores

Variables- OCCUPATION	CIWA 1 Scores				Total (n=165)	P value
	0-9 (n=4)	10-15 (n=43)	16-20 (n=74)	21-67 (n=44)		
Professional	0(0%)	1(2.3%)	1(1.4%)	2(4.5%)	4(2.4%)	0.048*
Semi Professional	1(25%)	9(20.9%)	12(16.2%)	5(11.4%)	27(16.4%)	
Clerical/shop owner/ farmer	1(25%)	25(58.1%)	42(56.8%)	24(54.5%)	92(55.8%)	
Skilled worker	0(0%)	2(4.7%)	9(12.2%)	10(22.7%)	21(12.7%)	
Semi skilled worker	0(0%)	2(4.7%)	6(8.1%)	0(0%)	8(4.8%)	
Unskilled worker	2(50%)	3(7%)	2(2.7%)	3(6.8%)	10(6.1%)	
Unemployed	0(0%)	1(2.3%)	2(2.7%)	0(0%)	3(1.8%)	

Variables- OCCUPATION	CIWA 7 Scores				Total (n=165)	P value
	0-9 (n=53)	10-15 (n=96)	16-20 (n=12)	21-67 (n=4)		
Professional	1(1.9%)	2(2.1%)	0(0%)	1(25%)	4(2.4%)	0.041*
Semi Professional	13(24.5%)	13(13.5%)	1(8.3%)	0(0%)	27(16.4%)	
Clerical/ shop owner/ farmer	24(45.3%)	59(61.5%)	7(58.3%)	2(50%)	92(55.8%)	
Skilled worker	3(5.7%)	13(13.5%)	4(33.3%)	1(25%)	21(12.7%)	
Semi skilled worker	4(7.5%)	4(4.2%)	0(0%)	0(0%)	8(4.8%)	
Unskilled worker	7(13.2%)	3(3.1%)	0(0%)	0(0%)	10(6.1%)	
Unemployed	1(1.9%)	2(2.1%)	0(0%)	0(0%)	3(1.8%)	

Table 7 shows correlation of occupation in relation to the severity of CIWA scores (on both day 1 and day 7). It is seen that occupation of the study subjects in relation to the CIWA score on day 1 had a significant 'P' value of 0.048 while that on day 7 is also significant with a 'P' value of 0.041

Table 8: Correlation of Income In Relation To CIWA Scores:

Variables	CIWA 1 Scores				Total (n=165)	P value
	0-9 (n=4)	10-15 (n=43)	16-20 (n=74)	21-67 (n=44)		

Income in Rupees						
≥ 32050	0(0%)	0(0%)	1(1.4%)	1(2.3%)	2(1.2%)	0.757
16020-32049	0(0%)	1(2.3%)	0(0%)	2(4.5%)	3(1.8%)	
12020-16019	0(0%)	8(18.6%)	7(9.5%)	2(4.5%)	17(10.3%)	
8010-12019	1(25%)	6(14%)	12(16.2%)	8(18.2%)	27(16.4%)	
4810-8009	2(50%)	15(34.9%)	38(51.4%)	19(43.2%)	74(44.8%)	
1601-4801	1(25%)	11(25.6%)	12(16.2%)	11(25%)	35(21.2%)	
≤ 1600	0(0%)	2(4.7%)	4(5.4%)	1(2.3%)	7(4.2%)	
Variables	CIWA 7 Scores				Total (n=165)	P value
	0-9 (n=53)	10-15 (n=96)	16-20 (n=12)	21-67 (n=4)		
Income in Rupees						
≥ 32050	1(1.9%)	0(0%)	0(0%)	1(25%)	2(1.2%)	0.015*
16020-32049	0(0%)	3(3.1%)	0(0%)	0(0%)	3(1.8%)	
12020-16019	5(9.4%)	10(10.4%)	2(16.7%)	0(0%)	17(10.3%)	
8010-12019	9(17%)	17(17.7%)	1(8.3%)	0(0%)	27(16.4%)	
4810-8009	20(37.7%)	47(49%)	6(50%)	1(25%)	74(44.8%)	
1601-4801	13(24.5%)	17(17.7%)	3(25%)	2(50%)	35(21.2%)	
≤ 1600	5(9.4%)	2(2.1%)	0(0%)	0(0%)	7(4.2%)	

Table 8 shows correlation of income in relation to the severity of CIWA scores (on both day 1 and day 7). It is seen that income of the study subjects in relation to the CIWA score on day 1 had a ‘P’ value of 0.757 while that on day 7 is 0.015 which is statistically significant.

It was observed that the correlation of age of initiation of alcohol consumption in relation to the severity of CIWA scores on day 1 and day 7 had a ‘P’ value of 0.567 on day 1 while on day 7 it was 0.706.

Table 9: Correlation Of Type Of Alcohol Consumed In Relation To The Severity Of CIWA Scores:

Variables	CIWA 1 Scores				Total (n=165)	P value
	0-9 (n=4)	10-15 (n=43)	16-20 (n=74)	21-67 (n=44)		
Type						
IMFL	4(100%)	43(100%)	73(98.6%)	43(97.7%)	163(98.8%)	0.025*
Beer	0(0%)	0(0%)	1(1.4%)	1(2.3%)	2(1.2%)	

Variables	CIWA 7				Total (n=165)	P value
	0-9 (n=53)	10-15 (n=96)	16-20 (n=12)	21-67 (n=4)		
IMFL	52(98.1%)	95(99%)	12(100%)	4(100%)	163(98.8%)	0.527
Beer	1(1.9%)	1(1%)	0(0%)	0(0%)	2(1.2%)	

Table 9 shows the correlation of type of alcohol consumed in relation to the severity of CIWA scores on day 1 and day 7. It is seen that type of alcohol consumed had a ‘p’ value of 0.025 on day 1 which is statistically significant while on day 7 it was 0.527

Table 10: Correlation of Amount Spent On Alcohol Consumption In Relation To the Severity of CIWA Scores

Variables	CIWA 1 Scores				Total (n=165)	P value
	0-9 (n=4)	10-15 (n=43)	16-20 (n=74)	21-67 (n=44)		
Amount Spent in Rupees						
<200	2(50%)	24(55.8%)	22(29.7%)	4(9.1%)	52(31.5%)	<0.001**
200-400	2(50%)	17(39.5%)	51(68.9%)	39(88.6%)	109(66.1%)	
>400	0(0%)	2(4.7%)	1(1.4%)	1(2.3%)	4(2.4%)	

Variables	CIWA 7 Scores				Total(n=165)	P value
	0-9 (n=53)	10-15 (n=96)	16-20 (n=12)	21-67 (n=4)		
Amount spent in Rupees						
<200	27(50.9%)	25(26%)	0(0%)	0(0%)	52(31.5%)	<0.001**
200-400	24(45.3%)	70(72.9%)	12(100%)	3(75%)	109(66.1%)	
>400	2(3.8%)	1(1%)	0(0%)	1(25%)	4(2.4%)	

Table 10 shows the correlation of type of amount spent on alcohol consumption in relation to the severity of CIWA scores on day 1 and day 7. It is seen that the amount spent on alcohol of alcohol consumed had a ‘p’ value of <0.001 both the days which was statistically significant.

Table 11: Correlation of Quantity of Alcohol Consumption In Relation To the Severity of CIWA Scores

Variables	CIWA 1 Scores				Total (n=165)	P value
	1-9 (n=4)	10-15 (n=43)	16-20 (n=74)	21-67 (n=44)		
Quantity (ml)						
90-180	1(25%)	15(34.9%)	8(10.8%)	0(0%)	24(14.5%)	0.001**
90-270	0(0%)	1(2.3%)	0(0%)	0(0%)	1(0.6%)	
180-270	3(75%)	14(32.6%)	28(37.8%)	9(20.5%)	54(32.7%)	
180-360	0(0%)	4(9.3%)	11(14.9%)	4(9.1%)	19(11.5%)	
180-540	0(0%)	1(2.3%)	0(0%)	0(0%)	1(0.6%)	
270-360	0(0%)	4(9.3%)	11(14.9%)	8(18.2%)	23(13.9%)	
270-540	0(0%)	0(0%)	1(1.4%)	1(2.3%)	2(1.2%)	
360-540	0(0%)	3(7%)	15(20.3%)	21(47.7%)	39(23.6%)	
>540	0(0%)	1(2.3%)	0(0%)	1(2.3%)	2(1.2%)	

Variables	CIWA 7 Scores				Total(n=165)	P value
	0-9 (n=53)	10-15 (n=96)	16-20 (n=12)	21-67 (n=4)		
Quantity (ml)						
90-180	18(34%)	6(6.3%)	0(0%)	0(0%)	24(14.5%)	<0.001**
90-270	1(1.9%)	0(0%)	0(0%)	0(0%)	1(0.6%)	
180-270	19(35.8%)	32(33.3%)	3(25%)	0(0%)	54(32.7%)	
180-360	4(7.5%)	12(12.5%)	3(25%)	0(0%)	19(11.5%)	
180-540	0(0%)	1(1%)	0(0%)	0(0%)	1(0.6%)	
270-360	2(3.8%)	19(19.8%)	2(16.7%)	0(0%)	23(13.9%)	
270-540	0(0%)	2(2.1%)	0(0%)	0(0%)	2(1.2%)	
360-540	7(13.2%)	24(25%)	4(33.3%)	4(100%)	39(23.6%)	
>540	2(3.8%)	0(0%)	0(0%)	0(0%)	2(1.2%)	

Table 11 shows the correlation of quantity of alcohol consumed in relation to the severity of CIWA scores on day 1 and day 7. It is seen that the quantity of alcohol consumed had a 'P' value of 0.001 on day 1 and <0.001 on day 7 which were both statistically significant.

Table 12: Correlation of Frequency of Alcohol Consumption In Relation To the Severity Of CIWA Scores:

Variables	CIWA 1 Scores				Total (n=165)	P value
	1-9 (n=4)	10-15 (n=43)	16-20 (n=74)	21-67 (n=44)		
Frequency						
Daily	2(50%)	17(39.5%)	42(56.8%)	38(86.4%)	99(60%)	<0.001**
Twice or more a week	2(50%)	25(58.1%)	29(39.2%)	6(13.6%)	62(37.6%)	
Once a week/weekly	0(0%)	1(2.3%)	1(1.4%)	0(0%)	2(1.2%)	
Twice a month	0(0%)	0(0%)	1(1.4%)	0(0%)	1(0.6%)	
Monthly	0(0%)	1(2.3%)	0(0%)	0(0%)	1(0.6%)	

Variables	CIWA 7 Scores				Total (n=165)	P value
	0-9 (n=53)	10-15 (n=96)	16-20 (n=12)	21-67 (n=4)		
Frequency						
Daily	26(49.1%)	59(61.5%)	10(83.3%)	4(100%)	99(60%)	0.154
Twice or more a week	25(47.2%)	35(36.5%)	2(16.7%)	0(0%)	62(37.6%)	
Once a week/weekly	1(1.9%)	1(1%)	0(0%)	0(0%)	2(1.2%)	
Twice a month	1(1.9%)	0(0%)	0(0%)	0(0%)	1(0.6%)	
Monthly	1(1.9%)	0(0%)	0(0%)	0(0%)	1(0.6%)	

Table 12 shows the correlation of frequency of alcohol consumed in relation to the severity of CIWA scores on day 1 and day 7. It is seen that the frequency of alcohol consumed has a 'P' value of <0.001 on day 1 which is statistically significant while it was 0.154 on day 7.

The correlation of family history in relation to the severity of CIWA scores on day 1 and day 7. It is seen that family history has a 'P' value of 0.084 on day 1 which is suggestive of being statistically significant while it was 0.646 on day 7.

The correlation of abstinence in relation to the severity of CIWA scores on day 1 and day 7 has a 'P' value of 0.644 on day 1 while it was 0.481 on day 7.

Table 14: Correlation of Concomitant Other Substance Use In Relation To the Severity of CIWA Scores

Other substance	CIWA 1 Scores				Total
	1-9	10-15	16-20	21-67	
None	2(50%)	19(44.2%)	37(50%)	10(22.7%)	68(41.2%)
Tobacco	2(50%)	24(55.8%)	37(50%)	32(72.7%)	95(57.6%)
Cannabis	0(0%)	0(0%)	0(0%)	2(4.5%)	2(1.2%)
Heroin	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Benzodiazepines	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Others	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Total	4(100%)	43(100%)	74(100%)	44(100%)	165(100%)

P=0.021*, Significant, Fisher Exact Test

Other substance	CIWA 7 Scores				Total
	1-9	10-15	16-20	21-67	
None	21(39.6%)	41(42.7%)	5(41.7%)	1(25%)	68(41.2%)
Tobacco	32(60.4%)	53(55.2%)	7(58.3%)	3(75%)	95(57.6%)
Cannabis	0(0%)	2(2.1%)	0(0%)	0(0%)	2(1.2%)
Heroin	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Benzodiazepines	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Others	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Total	53(100%)	96(100%)	12(100%)	4(100%)	165(100%)

P=0.911, Not Significant, Fisher Exact Test

Table 14 shows the correlation of concomitant other substance use in relation to the severity of CIWA scores on day 1 and day 7. It is seen that other associated substance use has a 'P' value of 0.021 on day 1 which is statistically significant and 0.911 on day 7.

Discussion

Complications related to alcohol withdrawal account for a significant demand in healthcare resources and are associated with an increase of morbidity and mortality. The reported numbers of patients who undergo a complicated course of alcohol withdrawal vary widely

between 5 and 20% and are dependent on several factors such as the clinical setting of withdrawal, the applied therapeutic approach for alcohol withdrawal syndrome (AWS) and individual characteristics of patients.

The present study consists of 165 study subjects who attended out-patient or in-patient departments of Sri

Siddhartha Medical College, Tumakuru and who fulfilled the criteria for alcohol dependence syndrome between November 2016 to April 2018.

In the current study most of the study subjects were between the age group of 30-50 years (63.6%) with Mean \pm SD: 41.70 \pm 9.97 and were predominantly males (94.5%). These findings were similar to the studies done earlier where majority of them had a mean (SD) age of 42.2 (15.5) years and were males (54.4%) (44-48). In this study when correlation of age and gender were done in relation to the CIWA scores on Day 1 and Day 7, 'P' values were found to be 0.104 and 0.854 and 0.862 and 0.188 respectively which were not statistically significant. These findings were similar to those observed by Ghulam et.al (48).

Other socio demographic characteristics in the current study like education and occupation, it was observed that majority of the participants were educated upto high school (30.9%) followed by primary school (25.5%). The subjects mostly were involved in clerical work or were farmers or shop owners (55.8%) followed by semi-professionals (16.4%). About 77.0% of the individuals were married while 16.4% were single. They had a contradictory result in education domain where they found that most of them were illiterates (37.67%). This could probably be due to the lower levels of education in that region (49). In the current study it was also observed that educational status of the subjects was not a contributory factor for the severity of withdrawal state ('P' values on day 1 and day 7 being 0.725 and 0.241). This finding was similar to that of a study done by John Abraham and R. Chandrashekharan where education as a variable does not have any association with the severity of withdrawal 9 ('P' value – 0.517) (50).

Occupation had an impact on the severity of withdrawal state which was statistically significant ('P' values being 0.048 and 0.041 on days 1 and 7). The income of the subjects showed statistical significance only on day 7 ('P' value being 0.015). While marital history had no influence on the severity of withdrawal state, religion showed statistical significance for religion when correlated with CIWA scores on day 1 ('P' value was 0.003) but being 0.803 on day 7 which was not statistically significant.

In the present study, age of initiation of alcohol consumption predominantly seen in the age group of 20-30 years (81.2%) followed by 31-40 years (13.3%) with Mean \pm SD: 26.84 \pm 5.36. This finding was similar to that of the study done by John A et al. where the median age at the first drink was 27.9 [9.0] (47). Age of initiation of alcohol use even though was not statistically significant ('P' value being 0.567 on day 1 and 0.706 on day 7) seemed to be an influence on the severity of withdrawal state. Another study done by Bonomo YA, Bowes G also found that about 90% of the participants consumed alcohol by age 20 years and teenage drinking patterns and other health risk behaviours in adolescence predicted alcohol dependence in adulthood (50).

It was observed in this study that daily drinking (60.0%) was found in majority of the study subjects followed by twice or more a week (8.5%) and it had a significant impact on the severity of withdrawal with 'P' value being <0.001 on day 1 which is statistically significant and 0.154 on day 7. About 180-270ml of consumption was seen in a greater group of subjects (39.4%) followed by 360-540ml (23.6%). It was a major factor which influenced the severity of withdrawal with 'P' value being 0.001 on both day 1 and 7. These findings were similar to those in a study done previously by John Abraham and R.Chandrashekaran wherein they found concluded that

amount of alcohol consumed was associated with severity of withdrawal ('P' value- 0.001) [66]. However another study found that there was no correlation between the average amount of alcohol intake/drinking day (mean: 216 g/day, range: 40–840) and the number of drinking days (mean: 24 ± 8) in the last month and the severity of AWS (Spearman's $r = -0.005$ or $r = -0.0147$, respectively) which was done by Tilman Wetterling and Martin Driessen (52). Most of them consumed IMFL (98.8%) followed by beer (1.2%). The prevalence of IMFL use was statistically significant ('P' value-0.025). The amount spent on alcohol use in most subjects was between Rs 200-400 (66.1%) followed by < Rs200 (31.5%). It played a vital role in the severity of withdrawal with 'P' values being < 0.01 and < 0.001 on day 1 and day 7. The circumstance of use was not fixed in majority of the subjects (38.2%) followed by use in a company (36.4%) and alone consumption was seen in 25.5% of the subjects

In the present study, we found that majority of the study subjects had no history of head injury (92.1%) while the rest had history of head injury (7.9%) mostly due to fall from the bike (69.3%) which was similar to that found by doing the correlation between head injury and withdrawal severity which had a 'P' value of 0.240 on day 1 which was not statistically significant while it was 0.075 on day 7 which is suggestive of statistical significance. This is similar to that found in a study by Sharp B and Schermer CR where they concluded that AWS has a low incidence rate among intoxicated trauma patients (27).

It was also found that majority of the subjects had a family history of alcohol consumption (66.1%) while 33.9% did not have. The consequences of alcohol consumption in their family members were either continued usage (61.1%) followed by death of these members (24.1%). Their role in influencing the severity of

withdrawal was established with 'P' value being 0.084 suggestive of statistical significance on day 1 while it was 0.646 on day 7. This was similar to that found by Grob C, Mick I who in their study family history was strongly associated with the severity of withdrawal ('P' value- 0.02) (36).

In this study, majority of the patients did not have a history of prior hospitalisation (85.5%) while 14.5% was not previously hospitalised. Majority of them who were hospitalised were diagnosed with alcohol induced gastritis (26.1%) followed by head injury (13.0%) and uncontrolled hypertension (13.0). There was no association between prior hospitalisation and the severity of withdrawal observed in this study ('P' values being 0.212 and 0.117 on day 1 and 7 respectively).

A majority of the subjects did not have any chronic medical condition (84.2%) while it was seen in 15.8% of them and were predominantly having hypertension and diabetes (12.7%). There was no strong association found between presence of a chronic medical condition with the severity of withdrawal as the 'P' value was found to be 0.896.

Another finding in this study was that majority of the subjects did not have any period of abstinence (53.9%) while the rest (46.1%) had and it was also found that the reasons of quitting alcohol consumption were mainly family pressure (32.9%) and ill health (32.9%). They restarted alcohol use mainly due to craving (36.8%) and peer pressure (28.9%). In this study, association between periods of abstinence and withdrawal severity was not present ('P' values being 0.644 and 0.481 respectively on day 1 and 7). This study had a contradictory finding done by Sabine Loeber and Theodora Duka provides first evidence, that repeated withdrawal from alcohol might be associated with reduced brain plasticity as indicated by a

delay of recovery from impairment of attention/executive function (53).

In the current study, majority of the individuals had history of other substance use (68.8%) where tobacco consumption was predominant (57.6%) followed by cannabis (1.2%). It was also noted that there was an association between other substance use and severity of withdrawal ('P' value – 0.021) on day 1 which was statistically significant and on day 7 ('P' value-0.911) which was not statistically significant. Kelly P. Cosgrove, Reese McKay found in their study that continued tobacco smoking during withdrawal interfered with the subsequent normalization of the GABA_A receptors and was associated with higher levels of craving, which may increase relapse risk (54-56).

Relation between AUDIT Scores and Withdrawal severity:

Majority of the subjects were categorised to have hazardous pattern of alcohol use (53.4%) while dependence pattern was seen in 46.6% of the study subjects.

There was a strong relationship between AUDIT scores and severity of withdrawal assessment done on day 1 and day 7 ('P' value- < 0.001) which is statistically significant.

Severity Assessment of Withdrawal State:

When CIWA scores were computed on day 1, most of them belonged to moderate (44.8%) followed by severe (26.7%), then mild (26.1%) and very mild (2.4%). When the same individuals were assessed on day 7, majority of them belonged to mild (58.2%) followed by very mild (32.1%), moderate (7.3%) and then severe (2.4%). There was also a strong association between CIWA -1 and CIWA-7 scores which was statistically significant ('P' value - < 0.001). There was a strong relationship between

CIWA Scores and AUDIT scores with 'P' values being < 0.001 on both day 1 and day 7 which were statistically significant.

Delirium Rating Scale (DRS):

In this study, out of the 10 patients in delirium whose severity was assessed, majority of them scored between 26-30 (50.0%) followed by 21-25 (30.0%) and then > 30 (20.0%). Relationship between DRS scores and CIWA on 1st day had statistically not significant ('P' value- 1.000) while on day 7 it was statistically significant ('P' value- 0.357).

Some of the limitations of the study observed were that as the sample size included predominantly males, gender difference and its role in influencing the severity could not be assessed. There were very few cases of delirium and so a clear-cut conclusion regarding its severity and its precipitating factors could not be analyzed and future research needs to be done in this regard.

Conclusion

This study suggests that the severity of alcohol withdrawal decreases where in on day 1 if the severity was moderate became mild or very mild when assessed on days 7. There are various factors which influence the severity of alcohol withdrawal state in patients of alcohol dependence syndrome. While some sociodemographic factors like occupation, income of the individuals, religion play significant role in determining the severity of withdrawal state, others like age, gender, educational status and marital status do not influence withdrawal severity. Few other factors like quantity and frequency of consumption, amount spent, family history and concomitant use of other substances make a major impact in withdrawal. By assessing the severity, we can reduce the morbidity and mortality associated with alcohol and hence also prevent untoward consequences because of them. This would also

pave way for a new approach in motivational enhancement therapy which would address the issue in various other dimensions and hence would help in decreasing the overall prevalence of alcohol use.

References

1. Kaplan HI, Sadock VA. Kaplan and Sadock's Comprehensive Textbook of Psychiatry. 10th ed. Maryland, USA: Wolters Kluwer; 2017.
2. Allan Tasman, Jerald Kay, Jeffrey A. Lieberman, Michael B. First, Michelle B. Riba. Psychiatry. 4th ed. Wiley Blackwell; 2015
3. Rizeanu S. Editor note. J Alcohol Drug Depend 2017, 5 (5)
4. Phillips R. Alcohol – A history; 2014
5. Hansen DJ. Historical evolution of Alcohol consumption in Society. Alcohol: Science, Policy and Public Health 1993, 10
6. Report by WHO SEARO region; Prevalence of Harm from alcohol use get high on life without alcohol 2003
7. Silva et al. The Prevalence and correlates of hazardous drinking in industrial workers: A study from Goa, India. Alcohol and Alcoholism; 38: 78 -83
8. Lal R. Substance use disorders: A manual for physicians, New Delhi: National Drug Dependence Treatment Centre, National Drug Dependence Centre, All India Institute of Medical Sciences; 2005
9. Prabhu S, Patterson Silver Wolf, David A, Catherine N, Kumar R. Prevalence, Nature, Context and Impact of Alcohol use in India: Recommendations for Practice and Research; 2010.
10. Srivastava S, Bhatia MS. Quality of life as an outcome measure in the treatment of alcohol dependence. Ind Psychiatry J. 2013; 22: 41-6
11. Gilpin NW, Koob GF. Neurobiology of Alcohol Dependence - Focus on Motivational mechanisms. Alcohol Research and Health, 2008: 31 (3)
12. Stolerman IP. Encyclopedia of Psychopharmacology; 2015:Pg 379
13. Trzepaez PT, Mittal D, Torres R, Canary K, Norton J, Jimerson N. Validation of the delirium rating scale – revised 98: Comparison with the delirium rating scale and cognitive test for delirium. The Journal of Neuropsychiatry and Clinical Neurosciences. 2001; 13 (2): 229-42.
14. Babor TF, Higgins- Biddle JC, Saunders JB, Monteiro MG. The Alcohol use disorder identification test – Guidelines for use in primary care. 2nd ed..Geneva. WHO 2001: 1- 38
15. Somers JM, Goldner EM, Waraich P. Prevalence studies of substance related disorders: A systematic review of literature. Can J Psychiatry 2004; 49:373-84
16. World Health Organisation. Global Status Report on Alcohol 2004; WHO, 2004.
17. Hiroch U, Kapur N, Webb R, Dunn G. Deaths from natural causes in people with mental illness, A cohort study. J. Psychosom Res 2008; 64: 275-83
18. Louro RP, Anton EO, Zuniga VL. Epidemiology of Alcohol Withdrawal syndrome, Mortality and factors of poor Prognostic. Anales de medicina interna (Madrid, Spain: 1984), 23(7): 307-9: 2006
19. Monte R, Rabunel R, Casariego E, Lopez H, Matios A, Pertega S. Analysis of the Factors determining Survival of Alcohol withdrawal syndrome patients in a General Hospital. Alcohol and Alcoholism 2010;45:151-58
20. Monte R, Rabunel R, Casariego E, Sonia. Risk factors for Delirium Tremens in Patients with alcohol withdrawal syndrome in a hospital setting. European Journal of Internal Medicine 2009;20(7): 690-
21. Cloninger CR, Bohman M, Sigvardsson S. Inheritance

- of alcohol abuse: Cross-fostering analysis of adopted men. *Arch Gen Psychiatry* 1981; 38:861-8.
22. Penick EC, Powell BJ, Bingham SF, Liskow BI, Miller NS, Read MR. A comparative study of Familial Alcoholism. *J Stud Alcohol* 1987;48:136-4
 23. Worobec TG, Turner WM, O'Farrell TJ, Cutter HS, Bayog RD, Tsuang MT. Alcohol use by alcoholics with and without a history of parental alcoholism. *Alcohol Clin Exp Res* 1990 ;14:887-92.
 24. Varma VK, Basu D, Malhotra A, Sharma A, Mattoo SK. Correlates of early and late-onset alcohol dependence. *Addict Behav.* 1994 ;19:609-19.
 25. Manjunatha N, Saddichha S, Sinha BN, Khess CR, Isaac MK. Chronology of alcohol dependence: Implications in prevention. *Indian J Community Med* 2008; 33:233-7.
 26. Johnson PR, Banu S, Ashok MV. Severity of alcoholism in Indian males: Correlation with age of onset and family history of alcoholism. *Indian J Psychiatry* 2010;52: 243-49.
 27. Lukan JK, Reed DN Jr, Looney SW, Spain DA, Blondell RD : Risk factors for delirium tremens in trauma patients. *J Trauma* 2002;53: 901-906.
 28. Field CA, Claassen CA, O'Keefe G: Association of alcohol use and other high-risk behaviours among trauma patients. *J Trauma* 2001; 50: 13-1
 29. Committee on Practice Guidelines, Working Group on Pharmacological Management of Alcohol Withdrawal: *Alcohol Withdrawal*. Bethesda MD: American Society of Addiction Medicine; 2001
 30. Sharp B, Schermer CR, Esposito TJ, Omi EC, Ton-That H, et al (2012) Alcohol Withdrawal Syndrome in Trauma Patients: A Prospective Cohort Study. *J Trauma Treat* 1:128.
 31. Bouthoorn SH, van der Ploeg T, van Erkel NE, van der Lely N (2011) Alcohol intoxication among Dutch adolescents: acute medical complications in the years 2000-2010. *Clin Pediatr (Phila)* 50: 244-251.
 32. Bitunjac K, Saraga M (2009) Alcohol intoxication in pediatric age: ten- year retrospective study. *Croat Med J* 50: 151-156.
 33. Kuzelová M, Harárová A, Ondriasová E, Wawruch M, Riedel R, et al. (2009) Alcohol intoxication requiring hospital admission in children and adolescents: retrospective analysis at the University Children's Hospital in the Slovak Republic. *Clin Toxicol* 47: 556-561.
 34. Beck KH, Boyle JR, Boekeloo BO (2004) Parental monitoring and adolescent drinking: results of a 12-month follow-up. *Am J Health Behav* 28: 272-279.
 35. Kristjansson AL, Sigfusdottir ID, James JE, Allegrante JP, Helgason AR (2010) Perceived parental reactions and peer respect as predictors of adolescent cigarette smoking and alcohol use. *Addict Behav* 35: 256-259.
 36. Ryan SM, Jorm AF, Lubman DI (2010) Parenting factors associated with reduced adolescent alcohol use: a systematic review of longitudinal studies. *Aust N Z J Psychiatry* 44: 774-783.
 37. Prescott CA, Kendler KS (1999) Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. *Am J Psychiatry* 156: 34-40.
 38. Morean ME, Corbin WR (2010) Subjective response to alcohol: a critical review of the literature. *Alcohol Clin Exp Res* 34: 385-395.
 39. Groß C, Mick I, Reichert J, Zimmermann US (2016) Adolescents Admitted to In-Patient Treatment with Alcohol Intoxication: Risk and Resilience Factors

- Associated with Problematic Alcohol Use. *J Alcohol Drug Depend* 4: 231.
40. Conger JJ [1956] Alcoholism: theory, problem and challenge II Reinforcement theory and the dynamics of alcoholism. *Q J Stud Alcohol* 17:296-305
41. Young EH [1987] Relationship of Residents emotional problems, coping behaviours and gender. *J Med Educ* 62: 642-650
42. Greeley J, Oei T (1999) Alcohol and tension reduction. *Psychological Theories of Drinking and Alcoholism*. (2nd edn), New York: Guilford Press, 14-53.
43. Breslin FC, O'Keeffe MK, Burrell L, Ratliff-Crain J, Baum A (1995) The effects of stress and coping on daily alcohol use in women. *Addict Behav* 20: 141-147.
44. Chaplin TM, Hong K, Bergquist K, Sinha R (2008) Gender differences in response to emotional stress: an assessment across subjective, behavioral, and physiological domains and relations to alcohol craving. *Alcohol Clin Exp Res* 32: 1242-1250.
45. Wang J, Keown LA, Patten SB, Williams JA, Currie SR, et al. (2009) A population-based study on ways of dealing with daily stress: comparisons among individuals with mental disorders, with long-term general medical conditions and healthy people. *Soc Psychiatry Psychiatr Epidemiol* 44: 666-674.
46. Esper LH, Furtado EF (2013) Gender Differences and Association between Psychological Stress and Alcohol Consumption: A Systematic Review. *J Alcoholism Drug Depend* 1: 116. doi:10.4172/2329-6488.1000116
47. Prevalence of alcohol and drug dependence in rural and slum population of Chandigarh: A community survey; B. S. Chavan, Priti Arun, Rachna Bhargava, and Gurvinder Pal Singh: *Indian J Psychiatry*. 2007 Jan-Mar; 49(1): 44-48. doi: [10.4103/0019-5545.31517] Deb PC, Jindal BR. Drinking in rural areas. Study in selected villages of Punjab, Ludhiana, India, Monograph, Punjab.Ludhiana: Agricultural University; 1975
48. Dube KC, Kumar N, Kumar A, Gupta SP. Prevalence and pattern of Drug use amongst college students. *Acta Psychiatr Scand* 1978; 57:336-46
49. John A, Barman A, Bal D, Chandy G, Samuel J, Thokchom M, et al. Hazardous alcohol use in rural southern India: Nature, prevalence and risk factors. *Natl Med J India* 2009; 22:123-5.
50. Ghulam R, Rahman I, Naqi S, Gupta SR. An epidemiological study of drug abuse in urban population of Madhya Pradesh. *Indian J Psychiatry*. 1996;38:160-5
51. Chavan BS, Arun P, Bhargava R, Singh GP. Prevalence of alcohol and drug dependence in rural slum population of Chandigarh: A community survey. *Indian J Psychiatry* 2007; 49:44-8
52. Bonomo YA, Bowes G, Coffey C, Carlin JB, Patton GC (2004) Teenage drinking and the onset of alcohol dependence: A cohort study over seven years. *Addiction* 99: 1520- 1528.
53. Abraham J, Chandrashekar R (1997). The Severity of Alcohol Dependence Data Questionnaire: Modification and Validation: *Indian J Psychiat*,39 (1) 8-12.
54. Wetterling T, Driessen, Dieter R, Junghanns KK. (2001). The severity of alcohol withdrawal is not age dependent: *Alcohol and Alcoholism*, Volume 36, Issue 1, Pages 75-78.
55. Loeber S, Duka Theodora (2010). Effects of Repeated Withdrawal from Alcohol on Recovery of Cognitive Impairment under Abstinence and Rate of Relapse:

Alcohol and Alcoholism;45 (6), 541-7

56. Cosgrove KP et al. (2014). Tobacco smoking interferes with GABA-A receptor neuroadaptations

during prolonged alcohol withdrawal: PNAS; 111 (50), 18031–36