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MORBID RISK OF ALCOHOL AND CANNABIS USE DISORDERS AMONG RELATIVES OF PROBANDS IN A NIGERIAN PSYCHIATRIC HOSPITAL

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ABSTRACT

The generation of genetic epidemiological data in Africa to drive public education on the biological basis of substance use disorders (SUDs), which has been popularly misconstrued as a moral failure, has become imperative, in order to encourage access to formal care by patients. This study aimed to determine the morbid risks of SUDs among the first-degree relatives (FDRs) of probands with alcohol use disorder (AUD) and cannabis use disorder (CUD), in comparison with the families of healthy control group. The study elicited information on the morbid risk of SUDs among FDRs of probands with AUD and CUD and relatives of a healthy control group through direct interview or by proxy interview of relatives using the Family Interview for Genetic Studies (FIGS). The best-estimate method was used for the diagnosis in the relatives of the probands and a comparison group. Logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for the differences in proportion of the affected versus unaffected FDRs, while the Weinberger method was used to estimate morbid risks. The morbid risks among FDRs of probands with AUD and CUD were 17.5(95% CI, 17.1-17.9) and 11.6(11.2-12.0), respectively, in comparison with 7.8(95% CI, 7.6-8.0) and 5.7(95% CI, 5.5-5.9), respectively, for the FDRs of the controls. The increased familial risk of SUDs among FDRs of probands with alcohol and cannabis use disorders in an African population is similar to that in the Western population. Therefore, preventive strategies involving the family may be useful.

Keywords: Morbid risk; alcohol; cannabis; first-degree; relatives

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INTRODUCTION

Substance Use Disorders (SUDs) also known as Drug Use Disorders (DUDs), refers to a condition in which the use of one or more substances leads to a clinically significant distress or impairment (Van Den Bree & Pickworth, 2005). The term encompasses acute intoxication, harmful use, dependence syndrome, withdrawal states with or without delirium, psychotic disorders, and amnesic syndrome (World Health Organization, 1994). The health consequences of illicit drug use continue to be a matter of global concern, as a majority of problem drug users continues to have no access to treatment (United Nation Office on Drug and Crime, 2015). The use of psychoactive substances poses a significant threat to the health, social, and economic fabric of families, communities, and nations (United Nation Office on Drug and Crime, 2015). According to the World Health Organization Global Burden of Diseases report, substance use disorders contributed 12.4% of cases of death worldwide in the year 2000. It also accounted for 8.9% of total years lost to disability (World Health Organization, 1994). Understanding its etiology especially in low resource settings will guide the development of evidence-based preventive interventions.

There is increasing evidence that substance use disorders are familial and that genetic factors explain a substantial degree of their familial aggregation (Weissman et al., 1986; Meller et al., 1988; Bierut et al., 1998; Verhulst et al., 2015; Merikangas et al., 2009; Merikangas et al., 1998). Controlled family studies as well as clinical and epidemiological studies have demonstrated the extent to which substance use disorders are familial, with some specificity of familial aggregation found for some drugs (Weissman et al., 1986; Meller et al., 1988). In one controlled family study of SUDs, an eight-fold increased risk of drug use disorders among relatives of affected probands was found compared to those of psychiatric and unaffected controls (Merikangas et al., 1998).

The identified pathways of familial aggregation include shared genetic environments in which, for some substances like alcohol use disorders have been estimated to have 50% heritability (Verhulst et al., 2015). Twin studies have shown that genetic factors explain a portion of the variance in the familial aggregation of substance use disorders (Verhulst et al., 2015; Heath, 1995), while, adoption studies have confirmed the heritability of substance use disorders, they also highlight the importance of the interaction between genetic and environmental factors in the development of substance use disorders (Verhulst et al., 2015; Heath, 1995). Other pathways include, parental and sibling substance abuse (Ouzir & Errami, 2016), and assortative mating, where a high concordance was observed for SUDs between spouses (Homish et al., 2007).

There is dearth of data on the heritability of SUDs in Africa. To the best of the authors' knowledge this was the first report from our continent regarding the familial and morbid risks of SUDs using our methodology. This study addressed this question; what is the morbid risk of alcohol use disorder and cannabis use disorder among the first-degree relatives of probands with alcohol and cannabis use disorders compared to first-degree relatives of a healthy control group?

METHOD

Study design and population

This was a controlled family study using a cross-sectional design. Patients admitted into the drug treatment unit of the Federal Neuropsychiatric Hospital, Enugu, South-Eastern Nigeria were the probands for this family study. The hospital serves the entire South-Eastern states and neighboring geopolitical zones. The hospital offers both acute and long term care for psychiatric in-patients with a comprehensive drug treatment program in collaboration with United Nations Office on Drug and Crime (UNODC). The healthy control group consisted of physically and mentally healthy staff of Enugu North council secretariat.

Probands

Probands with lifetime diagnoses of alcohol and cannabis use disorders that were stable enough to understand and follow the interview process, and gave permission for their relatives to be approached were included in the study. Those with significant organic mental impairment and other major psychiatric disorders (schizophrenia, schizoaffective disorders, bipolar disorders, and major depressive disorders) were excluded based upon review by clinicians with expertise in substance abuse. The sample was composed of a total of 112 probands with diagnosis of SUDs (34 probands of alcohol use disorder and 43 probands of cannabis use disorder), and 35 control from the Local Council secretariat staff. The comparison group was conveniently selected to match similar characteristics of age and sex of the probands. Participants in the comparison group were included if they had no history of substance use disorders and gave permission for the relatives to be approached.

Relatives

There were a total of 940 first-degree relatives, 315 relatives of probands with alcohol use disorder (68 parents, 155 siblings and 92 children), 347 relatives of probands with cannabis use disorders (86 parents, 237 siblings and 24 children), and 278 relatives of the control (70 parents, 172 siblings and 36 children). Fifty nine, 64 and 13 relatives of the probands with alcohol use disorder, cannabis use disorder and the healthy control group, respectively were interviewed directly (in person or via phone call). The rest were interviewed by proxy informants.

Procedure and Measurement

Diagnostic interview

Substance use disorders were established using Mini International Neuropsychiatric Interview (MINI), current and lifetime versions (Sheehan et al., 1998). The MINI differs from other diagnostic instruments in that is semi-structured and administered by experienced clinical interviewers in a much shorter time, as opposed to highly structured Composite International Diagnostic Interview (CIDI) or Diagnostic Interview Schedule (DIS) used by lay interviewers. Two interviewers with experience in clinical psychiatry and substance abuse conducted the diagnostic interviews to establish the diagnosis of substance use disorder using DSM-5 criteria. Kappa derived from joint ratings of individual interviews were good (0.64-0.86) for substance use disorders in the first six training sessions.

The family history information

Family history information was obtained via direct interview of available relatives, or through telephone interviews or via proxy interviews for unavailable relatives using the Family Interview for Genetic Studies (National Institute of Mental Health Genetics Initiative, 1992). The Family Interview for Genetic Studies (FIGS) was developed by principal investigators in the National Institute of Mental Health (NIMH) Schizophrenia and Bipolar Disorder Genetics initiatives and NIMH extramural program staff in 1992, as a guide for systematically collecting information about relatives in family genetic studies of these disorders. It comprises of the general screening questions, the face sheet, and the symptom checklists. The most general information is gathered using the general screening questions about all known relatives in the pedigree, regardless of how distantly related. The face sheet is for each of the informant's first degree relatives, and also for any affected relatives about whom the informant can provide the information. The various symptom checklists (depression, mania, alcohol, and other drug abuses, psychosis, schizoid/paranoid/schizotypal personality disorders) are used to ferret out the diagnostic details that help make possible best estimate diagnosis. Direct interviews and family history are far more concordant for observable disorders such as drug abuse and behavior disorders than for less readily observable disorders such as mood and anxiety disorders.

Diagnostic procedures

Diagnoses of substance use disorders among first-degree relatives and spouses were based upon all available information, including the diagnostic interview, family history reports and medical records, using the best estimate method of diagnosis. Best estimate diagnosis was made by two clinicians with extensive experience in the evaluation and treatment of substance abuse, and who were blind with respect to the diagnostic status of the probands when making the best-estimates of the relatives. In case of doubt a third opinion was sought. Interview status was included as a covariate in the analysis because of the well-established underestimation of diagnoses in the non-interviewed relatives.

Ethical Consideration

Ethical approval was obtained from the Research and Ethics Committee of the Federal Neuropsychiatric Hospital Enugu, Enugu state, Nigeria. International Ethical norms and standards were strictly adhered to at all times.

Data Analysis

The Weinberg method for age correction was used to calculate the lifetimes at risk (morbid risk) for each group of first-degree relatives (Weinberg, 2010). The Weinberg estimator for lifetime morbid risk is given by: $W\text{-}MR = A/A + 0.5U_2 + U_3$. Where, A = the number of affected relatives of a certain class (e.g. first-degree, etc.).U_1 = the number of unaffected subjects who were younger than the minimal risk period of age. U_2 = the number of unaffected subjects who were within the period of risk. U_3 = the number of unaffected subjects who were older than the maximal period age. The corrected denominator, often referred to by the German term Bezugsziffer, or BZ, is meant to approximate the number of lifetime at risk subjects. Limits for age of risk of 15-55 years for substance use disorders were used in this study due to a recent report of age distribution of substance use disorder in Nigeria

(Adamson et al., 2015). Logistic regression analyses were used to estimate odd ratios (OR) and 95% confidence interval (CI) for the differences in the proportion of affected versus unaffected first-degree relatives, controlling for probands sex, interview status (direct versus proxy interview).

RESULTS

A total of 112 participants (34 alcohol use disorder, 43 cannabis use disorder and 35 healthy control group) and their 940 relatives (315 of AUD, 347 of CUD and 278 of the control group) participated in the study. The three groups were similar in age ($p = 0.13$) and gender ($p = 0.57$). Majority (71.4%) of the control group were married ($p < 0.001$) as shown in Table 1. The socio-demographic characteristic of the relatives is shown in Table 2. The table shows that the relatives were similar in the number of FDRs ($p = 0.15$), parents ($p = 1.00$), siblings ($p = 0.20$) and age ($p > 0.05$). They however differ in the number of children ($p < 0.001$). The proportion of the affected first-degree relatives of the probands with alcohol use disorder and the control group were 8.9% vs. 4.7%, parents (35.3% vs. 7.1%) and siblings (15.5% vs. 5.2%), respectively. For relatives of the probands with cannabis use disorder, the proportion of the affected FDRs in comparison with the healthy control group were 5.8% vs. 2.0%, parents (8.1% vs. 5.7%), and siblings (9.7% vs. 3.5%), respectively. The morbid risk (95% confidence interval) of alcohol use disorder among the FDRs of the probands with AUD versus the FDRs of a healthy control group were 17.5(95% CI, 17.1-17.9) vs. 7.8(95%CI, 7.6-8.0) for all FDRs, 39.0(95% CI, 37.4-40.6) vs. 7.1(95% CI, 6.2-8.0) for parents and 27.3(95% CI, 26.3-28.3) vs. 4.4(95% CI, 4.0-4.8) for the siblings. Similarly, the morbid risk (95% confidence interval) of cannabis use disorder among the FDRs of the probands with CUD versus the FDRs of a healthy control group were 11.6(95% CI, 11.2-12.0) vs. 5.7(95% CI, 5.5-5.9) for all FDRs, 8.4(95% CI, 7.8-9.0) vs. 6.3(95% CI, 5.5-7.1) for parents and 24.5(95% CI, 23.5-25.5) and 20.7(95% CI, 18.0-23.4) for the siblings.

Table 1. Socio-demographic and clinical characteristics of the study participants

Variables	Alcohol Probands ($n = 34$)	Cannabis Probands ($n = 43$)	Controls ($n = 35$)	Statistics
Mean Age in years (SD)	34.5(9.7)	30.5(6.8)	33.0(9.0)	$F = 2.1$, $p = 0.13$
Mean Age at First Use (SD)	19.9(6.6)	20.9(7.1)		$t = –0.6$, $p = 0.54$
Mean Duration of Use (years)	7.4(11.0)	6.4(6.1)		$t = 0.5$, $p = 0.63$
Gender				$\chi^2 = 1.1$, $p = 0.57$
Male	30(88.2%)	39(90.7%)	29(82.9%)	
Female	4(11.8%)	4(9.3%)	6(17.1%)	
Marital Status				$\chi^2 = 24.0$, $p < 0.001$
Single	12(35.3%)	31(72.1%)	9(25.7%)	
Married	18(52.9%)	12(27.9%)	25(71.4%)	
Separated/Divorced	4(11.8%)	0(0.0%)	1(2.9%)	
Education				$\chi^2 = 49.1$, $p < 0.001$
Primary	18(52.9%)	4(9.3%)	0(0.0%)	
Secondary	12(35.3%)	19(44.2%)	7(20.0%)	
Tertiary	4(11.8%)	20(46.5%)	28(80.0%)	

NB: SD = Standard Deviation

Table 2. Socio-demographic characteristics of the first-degree relatives of the study participants

Variables	FDRs Alcohol Probands (*n* = 315)	FDRs Cannabis Probands (*n* = 347)	FDRs Controls (*n* = 278)	Statistics
Number of FDRs	315	347	278	F = 1.9, *p* = 0.15
Number of Parents	68	86	70	F = 0.0, *p* = 1.00
Number of Siblings	155	237	172	F = 1.6, *p* = 0.20
Number of Children	92	24	36	F = 12.3, *p* < 0.001
Mean Age of Parents	59.5 ± 7.9	58.0 ± 7.3	59.5 ± 7.9	F = 0.5, *p* = 0.63
Mean Age of Siblings	28.6 ± 10.2	29.4 ± 10.5	30.1 ± 10.3	F = 0.5, *p* = 0.58
Mean Age of Children	7.9 ± 5.6	8.7 ± 5.7	9.4 ± 6.9	F = 0.6, *p* = 0.59
Mean Age of Spouse	25.1 ± 4.6	24.5 ± 4.3	26.7 ± 3.9	F = 0.4, *p* = 0.66
FDRs aged <15years	67	40	35	F = 5.4, *p* = 0.006
FDRs aged 15-55 years	160	228	161	F = 1.2, *p* = 0.31
FDRs aged >55years	88	79	82	F = 4.7, *p* = 0.11

NB: FDRs = First-Degree-Relatives

Table 3. Morbid Risk of substance use disorders among first-degree relatives of probands with alcohol and cannabis use disorders

Variables	Alcohol Use Disorders		Cannabis Use Disorders	
	Probands	Control	Probands	Control
All FDRs				
No of Affected FDRs	28	13	20	7
% Affected FDRs	8.9	4.7	5.8	2.0
BZ (SUD) of FDRs	160	167	172	123.5
% Morbid Risk (FDRs)	17.5	7.8	11.6	5.7
S.E	0.2	0.1	0.2	0.1
95% C.I	17.1-17.9	7.6-8.0	11.2-12.0	5.5-5.9
Parents				
No of Affected Parents	24	5	7	4
% Affected Parents	35.3	7.1	8.1	5.7
BZ (SUD) of parents	61.5	70.5	82	63
% Morbid Risk (FDRs)	39.0	7.1	8.4	6.3
S.E	0.8	0.4	0.3	0.4
95% C.I	37.4-40.6	6.2-8.0	7.8-9.0	5.5-7.1
Siblings				
No of Affected Siblings	24	4	23	6
% Affected Siblings	15.5	2.3	9.7	3.5
BZ (SUD) of Siblings	88	91.5	94	29
% Morbid Risk (FDRs)	27.3	4.4	24.5	20.7
S.E	0.5	0.2	0.5	1.4
95% C.I	26.3-28.3	4.0-4.8	23.5-25.5	18.0-23.4

NB: SUD = Substance Use Disorders, FDRs = First-Degree Relatives, 95%C.I = 95% Confidence Interval, BZ = Bezugsziffer

Table 4. Logistic Regression analyses for the differences in the affected versus unaffected first-degree relatives of probands with alcohol use disorder

AUDs in Relatives	Probands (AUDs)	Control	*p*-value	O.R (95%C.I)
Family History (AUD) in FDRs			<0.001	
Yes	28(82.4%)	13(37.1%)		7.9 (2.6-24.1)
No	6(17.6%)	22(62.9%)		
History of AUD in Parents			<0.001	
Yes	24(70.6%)	5(14.3%)		14.4 (4.3-47.8)
No	10(29.4%)	30(85.7%)		
History of AUD in Siblings			<0.001	
Yes	24(70.6%)	4(14.3%)		18.6 (5.2-66.6)
No	10(29.4%)	31(88.6%)		
History of AUD in Children			1.000	
Yes	0(0.0%)	0(0.0%)		
No	34(100.0%)	35(100.0%)		
History of AUD in Spouse			1.000	
Yes	0(0.0%)	0(0.0%)		
No	34(100.0%)	35(100.0%)		

NB: AUDs = Alcohol Use Disorder; FDRs = First-Degree Relatives; O.R = Odd Ratios; 95%C.I = 95% Confidence Intervals

Table 5. Logistic Regression analyses for the differences in the affected versus unaffected first-degree relatives of probands with cannabis use disorder

CUDs in Relatives	Probands (CUDs)	Control	*p*-value	O.R (95%C.I)
Family History (CUD) in FDRs			0.01	
Yes	20(47.6%)	7(20.0%)		3.6 (1.3-10.4)
No	22(52.4%)	28(80.0%)		
History of CUD in Parents			<0.001	
Yes	7(16.7%)	4(11.4%)		1.2 (0.3-4.2)
No	35(83.3%)	31(88.6%)		
History of CUD in Siblings			<0.001	
Yes	23(54.8%)	6(17.1%)		9.4 (2.8-31.3)
No	19(45.2%)	29(82.9%)		
History of CUD in Children			1.000	
Yes	0(0.0%)	0(0.0%)		
No	42(100.0%)	35(100.0%)		
History of CUD in Spouse			1.000	
Yes	0(0.0%)	0(0.0%)		
No	42(100.0%)	35(100.0%)		

NB: CUDs = Cannabis Use Disorder; FDRs = First-Degree Relatives; O.R = Odd Ratios; 95%C.I = 95% Confidence Intervals

DISCUSSION

The general aim of the current study was to determine the morbid risk of alcohol and cannabis use disorders among FDRs of probands with alcohol and cannabis use disorders, in comparison with a sample of healthy control population. This study to the best of authors' knowledge is the first African study to examine familial transmission of SUDs using this methodology. The highlights of the findings of this genetic epidemiology study are: (1) the proportion of affected FDRs of probands with alcohol use disorder, in comparison with FDRs of the control group were 8.9%

and 4.7%, respectively; (2) the proportion of affected FDRs of probands with cannabis use disorder, in comparison with FDRs of the control group were 5.9% and 2.0%, respectively; (3) the proportion of affected spouse and young children in probands with substance use disorders were not different from those of the control group; (4) the morbid risk of alcohol use disorder among FDRs of probands with alcohol use disorder and FDRs of a healthy control group were 17.5(95% C1, 17.1-17.9) and 7.8(95% CI, 7.6-8.0), respectively; and (5) the morbid risk of cannabis use disorder among FDRs of probands with cannabis use disorder and FDRs of a healthy control group were 11.6(95% C1, 11.2-12.0) and 5.7(95% CI, 5.5-5.9), respectively.

The results of the present study show that alcohol and cannabis use disorders aggregate in the families of probands with alcohol and cannabis use disorders. The morbid risk of AUD and CUD among FDRs of probands with AUD and CUD were 17.5 and 11.6 versus 7.8 and 5.7 of the controls, respectively. The elevation of risk of substance use disorders among FDRs of the probands as shown in the study demonstrates that having a family history of substance use disorder is one of the most potent risk factors for the development of SUDs. The increased risk of SUDs among FDRs of probands with SUDs is consistent with previous family reports (Verhulst et al., 2015; Merikangas et al., 2009; Merikangas et al., 1998). Merikangas et al., (1998) found an 8-fold increased risk of drug use disorders among FDRs of relatives with wide range of SUDs.

The results also show a significant degree of familial clustering of SUDs among parents and siblings of probands with SUDs. This is consistent with reports that show high level of familial transmission of SUDs within sibling pairs relative to control (Merikangas et al., 2009; Merikangas et al., 1998). Familial aggregation was not demonstrated among children of the probands with SUDs in this study. This is contrary to a previous report which found increased risk of SUDs in adult children of probands with SUDs (Merikangas et al., 1998). One plausible explanation of our result is the age of the children involved in our study. The mean age of the children in this study were 7.9 years, 8.7 years and 9.4 years for AUD probands, CUD probands and controls, respectively. These age groups are below the age at maximal risk for SUDs (Adamson et al. 2015). Studies that reported familial aggregation among children were on adult children of the probands (Merikangas et al., 2009; Merikangas et al., 1998). Similarly, the present study did not find any concordance between probands with SUDs and their spouses. Some family studies have reported high concordance rate between probands and their spouses (Merikangas et al., 1998; Homish et al., 2007), a phenomenon they explained using assortative mating (Homish et al., 2007). Our finding could be explained by the small number of married probands (18 for AUD probands and 12 for CUD probands). In addition, cultural factors in some African societies that restrict certain behaviors among females (e.g., smoking and drinking) may have influenced our findings.

Familial aggregation has been described as the occurrence of a trait in more members of a family than can be readily accounted for by chance alone (Mifflin, 2004)]. Though this is not a sufficient proof of genetic transmission, it is a prerequisite for further genetic studies. The pathways to familial clustering of SUDs may be related to either common genetic

or environmental factors (Verhulst et al., 2015; Bailey & Hubbard, 1990). Genetic factors could increase the vulnerability to the development of SUDs through individual differences with respect to the drug effects (e.g., pharmacokinetic or pharmacodynamic differences) (Bailey & Hubbard, 1990). Families may transmit the risk of SUDs through direct mechanisms (e.g., genes, increasing environmental exposure to drugs or facilitating drug availability) or through indirect mechanisms (e.g., impaired parenting behavior, exposure to marital discord, social deprivation etc.) (Robins, 1980; Brown, 1989).

One limitation of this study was the use of family history method predominantly to elicit family history information; although it saved cost and time, the lack of sensitivity for many psychiatric disorders is a major drawback. Direct interview, while having its problems such as selection bias could have made more rigorous diagnosis possible. However, in this study the magnitude of this problem was reduced by controlling for the interview status in the analysis, and the finding that family history methods is more concordant to direct interviews for observable disorders like substance use disorders. In addition, the relatively small sample size in our study is another limitation. The number of female participants was too small to make comparison whether the risk is different between the genders.

CONCLUSION

The findings of this study suggest that alcohol and cannabis use disorders aggregate in the families of the probands with SUDs. This study has enriched the field of genetic epidemiology of SUDs in Africa by providing valuable data to aid clinicians' public education and preventive services of genetic counseling in Africa.

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STATEMENT OF AUTHORSHIP

The first and fourth authors contributed to the study design, analysis and interpretation of data. Drafting of the manuscript was by the first and second authors. Data collection was done by the first and third authors. Supervision of the research project was done by the second and fourth authors. All authors read and approved the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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REFERENCES

Adamson, T.A., Ogunlesi, A.O., Morakinyo, O., Akinhanmi, A.O., Onifade, P.O., Erinosho, O. (2015). Descriptive national survey of substance use in Nigeria. *Journal of Addiction Research and Therapy,* 6, 234. doi: 10.4172/2155-6105.1000234.

Bailey, S.L., Hubbard, R.L. (1990). Developmental variations in the context of Marijuana initiation among adolescents. *Journal of Health and Social Behaviour,* 31, 58-70.

Bierut, L., Dinwiddie, S., Begleiten, H., Crowe, R., Hesselbrock, V., Nurnberger, J, et al. (1998). Familial transmission of substance dependence: alcohol, marijuana, cocaine, and habitual smoking: a report from the collaborative study on the genetics of alcoholism. *Archives of General Psychiatry,* 55, 982-985.

Brown, S.A. (1989). Life events of adolescents in relation to personal and parental substance abuse. *American Journal of Psychiatry,* 146, 484-489.

Heath, A.C. (1995). Genetic influences on alcoholism risk: a review of adoption and twin studies. *Alcohol Health and Research World,* 19, 166–171.

Homish, G.G., Leonard, K.E., Cornelius, J.R. (2007). Predictors of marijuana use among married couples: the influence of one's spouse. *Drug and Alcohol Dependence,* 91, 121-128.

Meller, W.H., Rnehar,t R., Cadoret, R.J., Troughton, E. (1988). Specific familial transmission in substance abuse. *International Journal of Mental Health and Adiction,* 23, 1029-1039.

Merikangas, K.R., Li, J.J., Stipelman, B., Yu, K., Swendsen, J., Zhang, H. (2009). The familial aggregation of cannabis use disorders. *Addiction,* 100, 4, 622-629.

Merikangas, K.R., Stolar, M., Stevens, D.E., Goulet, J., Preisig, M.A., Fenton B. (1998). Familial transmission of substance use disorders. *Archives of General Psychiatry* 55:973-979.

Mifflin, H. (2004). The American Heritage Stedman's Medical Dictionary, 2nd Edition.

National Institute of Mental Health (NIMH) Genetics Initiative, 1992. Family Interview for Genetic Studies (FIGS). Rockville: National Institute of Mental Health.

Ouzir, M., Errami, M. (2016). Etiological theories of addiction: A comprehensive update on neurobiological, genetic and behavioural vulnerability. *Pharmacology, Biochemistry and Behaviour,* 148, 59-68.

Robins, L.N. (1980). The natural history of drug abuse. *Acta Psychiatrica Scandinivica,* 284, 7-20.

Sheehan, D.V., Lecrubier, Y., Harnett-Sheehan, K., Amorim, P., Janavs, J., Weiller, E. et al. (1998). The Mini International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview. *Journal of Clinical Psychiatry,* 20, 22-33.

United Nation Office on Drug and Crime, (2015). *World Drug Report*.

Van Den Bree, M., Pickworth, W.B. (2005). Risk factors predicting changes in marijuana involvement in teenagers. *Archives of General Psychiatry.* 62, 311-319.

Verhulst, B., Neale, M.C., Kender, K.S. (2015). The heritability of Alcohol Use Disorders: a meta-analysis of twin and adoption studies. *Psychol Med.* 45, 5, 1061-1072.

Weinberg, W. (2010). Methoden Und Technik der Statistik mit besonderer beruchksich-tung der Sozialbiology. International *Journal of Data Science,* 8:645-664.

Weissman, M.M., Merikanges, K.R., John, K., Wickramaratre, P., Prusoff, B.A., Kidd, K.K. (1986). Family-genetic studies of psychiatric disorders. Developing technologies. *Archives of General Psychiatry,* 43, 1104-1116.

World Health Organization Global Burden of Diseases. (2004). Disability weights for diseases and conditions: 2004 update.

World Health Organization. (1994). *International Classification of Diseases and Related Health Problems,* 10th edition (ICD-10). Geneva.