

# Prevalence of Substance Use among Psychiatric Patients with Psychosis and Determining its Strongest Predictor

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## Research article

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# Abstract

## Background

Although comorbidity of substance use and psychotic disorders can lead to increase in morbidity and mortality, less is known about the prevalence and predictors. Patients with psychosis tend to be overlooked during clinical assessment, therefore, the possibility of a missed or undertreated condition such as substance use increases. This study aims to measure the prevalence of substance use in patients with psychosis and to assess the strongest predictors.

## Method

In a 1 year observational study (October 2017- November 2018), 311 patients with psychosis who were admitted to Razi Psychiatry Hospital; Tehran; Iran were surveyed through The Structured Interview Based on DSM-5 (SCID) for diagnostic confirmation as well as questions assessing prevalence and possible predictors of substance use.

## Results

Prevalence of Substance Use among Psychiatric Patients with Psychosis was 37.9%. In bivariate analysis, several variables were identified as factors correlated with drug abuse among the participants. These included younger age, male gender, being currently homeless, having family history of drug use, and a history of imprisonment. The most powerful predictor of substance use, however, were male gender, Family history of drug use and being currently homelessness.

## Conclusion

The prevalence of substance use was high among all psychotic disorders, therefore, it is suggested that professionals note the importance of substance use among psychotic patients. The most powerful predictors were male gender, history of imprisonment, and family history of drug use. Active investigation and comprehensive preventive plans are suggested in all patients with psychosis especially among high risk population.

## Background

Substance use is common in psychiatric disorders. Using drugs can complicate the course of the disorder and worsen the outcome. Almost half of the patients with severe mental illness have comorbid substance use disorder (SUD) or have used substance at one stage in their life (1, 2). Substance use is associated with more self-destructive behaviors and attempting more suicide. Using substance cause varied and complex clinical presentations that not only can obscure, but also worsen the symptoms. This is mutually related to all aspects of psychiatric presentations such as mood instability, aggression, psychosis, cognitive deficits and even negative symptoms. Substance use can both predispose and perpetuate any above condition(3–5)

In clinical settings, comorbidity of substance use and psychiatric disorders is a rule rather than an exception. Psychiatric presentations such as psychosis are so enmeshed with using substance that scholars believe even by taking a comprehensive history, in many situations it is not possible to differentiate whether the symptoms precede or caused by the substance of use(6). It has been suggested that both psychosis and addiction share the same genetic etiology (7). Both psychosis and drugs effects has been hypothesized to be related to dopamine dysregulation. Substance can interfere with beneficial effects of many medications such as mood stabilizers and neuroleptics (8). Despite its important prognostic role and its prevalence, the predictors remain poorly understood.

Psychosis, as the loosening of contact with external reality, has several presentations such as delusions, hallucination and thought disturbances (9, 10). In almost all psychiatric conditions, psychosis represents a severe form of the disorder and its presentation should be signified in all diagnostic categories (11). Not only it is functionally disruptive, it also increases the burden of the disease, worsen the outcome and increase mortality (10, 12–14). Most of the previous studies have focused on studying the risk factors of substance use in separate diagnostic categories such as schizophrenia and bipolar mood disorder. In a meta-analysis, Hunt et al, (1) have observed the substance use prevalence of 42 percent in patients with schizophrenia. Substance use was related to an earlier age of onset and the prevalence increased over time for illicit drug use. The latter, further signifies the importance of identifying correlates of substance use in high risk populations. Meta-analysis on bipolar disorder have also shown a high comorbidity of more than 40 percent, specific risk factors has remained controversial (2, 15, 16); however, diagnostic categories tend to be unstable over time and can change to each other. Psychosis is a more etiological phenomena and considering it as a separate clinical syndrome has gained growing interest (9).

Estimating the accurate prevalence of substance use faces complications in Iran as along with stigmatization, the legal and religious constraints make respondents reluctant to reveal information about their substance use status (19). The situation is worse in psychotic patients due to the communication problems. Psychotic patients tend to be neglected, stigmatized, isolated and misunderstood by receiving less attention from their families or health care professionals (10, 13). Unique treatment needs of individuals with psychotic symptoms and comorbid substance use emphasizes the importance of identifying the prevalence as well as correlates in order to map the preventive strategies to reduce the likelihood of developing SUD among in risk patients as well as planning comprehensive treatment plans.

## **Study Aims**

The Objectives of this study were identifying the prevalence of substance use in a clinical population of patients with psychosis and to assess its predicting factors.

## **Methods**

# Design

This was a cross-sectional study during 2017–2018.

## Setting and Participants

The population includes inpatients who presented with psychosis to Razi Psychiatry Hospital -the largest psychiatry hospital- in Tehran, Iran, between October 2017 and November 2018. All adult inpatients experiencing a psychotic disorder were assessed against the inclusion criteria. Inclusion was based on recovering from the psychotic episode to a stage where they could be discharged from the hospital (based on the hospital documents), providing written informed consent and participating in the psychiatry resident's interviews. Exclusion encompassed severe cognitive or negative symptoms as well as medication adverse effects that could interfere with the interview.

## Measures

Structured Interviews based on DSM-5 (SCID-5) for diagnostic confirmation were performed and a demographic questionnaire as well as questions to identify predictors were developed to collect data. Other factors consisted of the duration of psychotic disorder as well as any comorbidities.

The questionnaire content was developed based on a panel opinion consisting of ten experts in the fields of epidemiology and psychiatry. Kappa coefficient and intra-class correlation coefficient (ICC) were used to evaluate the reliability of the questionnaire. ICC was between 0.84-1, and kappa was between 0.9-1 for all variables.

## Data Collection

Data were gathered during face to face interviewer administered survey. Three psychiatry residents were trained to collect the data and perform interviews and monthly sessions were held to discuss the data in order to increase homogeneity of data collection. An interviewer guide for the questionnaire was used to ensure data quality assurance and all interviews were completed in a private and secure unit to protect privacy.

## Ethical Considerations

This study was approved by the Ethic Committee of the University of Social Welfare and Rehabilitation Sciences, Tehran, Iran (IR.USWR.REC.1396.70). Written informed consent was obtained from all participants and participants' anonymity was ensured throughout the study. A supervisor psychiatrist

ruled that all participants were deemed capable of ethically and medically consenting for their participation in this research.

## Data Analysis

The continuous variables were expressed as mean  $\pm$  standard deviation and the categorical variables as numbers and percentages. Logistic regression analysis was used to estimate the association between drug abuse status and its related factors, reported as odds ratio (OR) and 95% confidence interval (CI). We entered variables that P-value  $< 0.2$  into the multiple regression analysis. Also chi-square test was used for data analysis. All data analyses were performed using SPSS software statistical software package version 21 (IBM Corp, Armonk, NY).

## Results

A total of 311 patient with psychosis were recruited. Participants ranged in age from 18 to 77 years, with a mean (SD) of 37.7(12.3) years. The mean (SD) years of education was 8.41 (4.18) years. The majority of the participants (80.1%) were unemployed and a small proportion (4.5%) were homeless. Among the study participants, 34.7% (108 individual) were married, and 29.3% had a history of imprisonment. Table 1 shows the demographic and behavioral characteristics of study participants.

Table 1  
Demographic characteristics of participants

Characteristics		Number	Percent
Gender	Female	106	34.1%
	Male	203	65.3%
Marital status	Single	203	65.3%
	Married	108	34.7%
Literacy	Illiterate	23	7.4%
	literate	288	92.6%
Employment	employed	62	19.9%
	unemployed	249	80.1%
Living with family	Yes	297	95.5
	no	14	4.5
Living status	alone	30	9.6
	With parents	151	48.6
	With partner (or children)	91	29.3
	With friends	2	0.6
	In jail	3	1.0
	With one parent	6	1.9
	With others	26	8.4
Place of residence	Urban	275	88.4
	Rural	36	11.6
Familial history of psychiatric disorder (prescribed medication)	yes	109	35
	no	201	64.6
Familial history of psychiatric admission	yes	61	19.6
	no	249	80.1
Familial history of current SUD	yes	75	24.1
	no	236	75.9

Among the participants 37.9% reported drug use recently (just before admission into the hospital). Table 2 represents the prior history of admission into a psychiatry hospital and Table 3 signifies the diagnostic classifications.

Table 2  
Prior history of admission into a psychiatry hospital.

	Minimum	Maximum	Mean (SD)
Numbers of admission into a psychiatry hospital	0	39	2.91(3.67)
Length of psychiatry hospital admission	0	330	29.31(27.93)
Age at first visit by a psychiatrist (years)	11	65	27.85(10.03)
Age of starting medication (years)	11	65	27.92(10.7)
Numbers of previous abstinence attempts	0	50	2.75(5.92)
Time to relapse (days)	0	2555	508.33(239.24)

Table 3  
Diagnostic classifications of participants based on DSM-5

<b>Diagnostic classifications based on DSM-5</b>		
Diagnosis	Number	%
Bipolar Disorder	85	28
Substance induced psychotic disorder	74	24.3
Schizophrenia	69	22.7
Schizoaffective disorder	25	8.2
Unspecified psychotic disorder	15	4.8
MDD	12	3.9
Multi diagnosis	13	4.3
Dementia	3	1
General Medical condition	3	1
Others	4	1.3

Tables 4 and 5 shows the demographic and behavioral characteristics of study participants in each group and type and time of substances used in participants respectively.

Table 4

Demographic and behavioral characteristics of study participants in each group.

Characteristics		Substance use (n = 118) (37.9%)	No drug use (n = 193) (62.1%)	P-value
Gender	female	16(13.7)	90(46.9)	0.000
	male	101(86.3)	102(53.1)	
Age, group (years)	≤25	25(21.2)	30(15.5)	0.2
	26–49	75(66.1)	111(57.5)	
	≤ 50	15(12.7)	52(26.9)	
Education	≤9	77(65.3)	103(53.4)	0.03
	> 9	41(34.7)	90(46.6)	
Marital status	Single	78(66.1)	125(64.8)	0.9
	Married	40(33.9)	68(35.2)	
Occupation	Employed	30(25.4)	32(16.6)	0.07
	Unemployed	88(74.6)	161(83.4)	
History of imprisonment	Yes	56(47.5)	35(18.1)	0.000
	No	62(52.5)	158(81.9)	
Currently Homelessness	Yes	10(8.5)	4(2.1)	0.011
	No	108(91.5)	189(97.9)	
Chi-square test was used.				
Significant level (P value less than .05).				



Table 5  
Type and time of substances used in participants

	Mean(SD)	min	max	
Age of starting	22.60(8.20)	5	60	
Age of first injection	25.50(8.2)	13	45	
Number of overdoses (lifetime)	1.33(0.16)	0	20	
		number	percent	
Substance use	no	193	62.1	
	yes	118	37.9	
Injection drug use	no	293	94.2	
	yes	17	5.5	
Type of substance used in previous year	Methamphetamines	61	19.6	
	Opiates	Opium (different products available in Iran: teryac, shire, sukhteh)	23	7.4
		Heroin	10	3.2
	Cannabinoids (grass, marijuana)	7	2.3	
	Methadone	4	1.3	
	Tramadole	1	0.3	
	LSD	1	0.3	
	Poly Substance Use Disorder	1	0.3	
	others	1	0.3	
Type of current substance of use (in previous month)	Methamphetamines	98	31.5	
	Opiates	Opium (teryac, shire, sukhteh)	95	30.5
		Heroin	40	12.9
		crack	21	6.8
		norjizak	4	1.3
	Methadone	31	10.0	
	Buprenorphine	6	1.9	
	Opiate syrup	5	1.6	

	<b>Mean(SD)</b>	<b>min</b>	<b>max</b>
	cannabinoids	44	14.5
	Tramadole	32	10.3
	Ecstasies	12	3.9
	alcohol	61	19.6
	Sedative and hypnotics	116	37.3
	others	2	0.6

Table 6

Multiple logistic regression for factors associated with substance use in participants

Characteristics		Unadjusted OR*(95% CI)	P-value for Unadjusted OR	AOR**(95% CI)	P-value for adjusted OR
Age		.97(.95-.99)	.004	.97(.95-.99)	.030
Sex	Female	1		1	
	Male	5.57(3.06–10.13)	.000	7.26(3.34–15.93)	.000
Occupation	Employed	1			
	Unemployed	1.71(.97 – 3.0)	.06	1.14(.58-2.24)	.703
Education	≤ 9	1.64(1.02–2.63)	.40		
	> 9	1			
Homelessness	No	1		1	
	Yes	4.37(1.34–14.28)	.015	5.32(1.17–24.09)	.030
Place of residency	Urban	1			
	rural	.91(.44-1.88)	.81		
Family history of drug use	No	1		1	
	Yes	6.33(3.57–11.24)	.000	6.15(3.08–12.25)	.000
HIV test result	No	1		1	
	Yes	10.28(1.22–86.53)	.032	3.26(.30-34.64)	.326
History of imprisonment	No	1		1	
	Yes	4.07(2.43–6.82)	.000	1.64(.89-3.03)	.108
*Odds Ratio					
**Adjusted Odds Ratio					
Logistic regression was used.					
Significant level (P value less than 0.2 for Univariate and P value less than 0.05 for Multiple).					

In the bivariate analysis, several variables were identified as factors correlated with substance use among the participants. These included younger age (26–49 years), male gender, being currently homeless, having family history of drug use, and a previous history of imprisonment.

Age was the strongest associated risk factor for substance use for participants of this study in final model (OR = 7.26 CI: 3.34–15.93). Adjusted OR for people reporting a family history of drug use were 6.15 times higher than the odds of people who reported no family history of drug use (P-value = 0.000). The odds of substance use among homeless participants was 5.32, but was not significant in final model. The adjusted odds of drug use among those who had a history of imprisonment were 1.64 when compared to people who had not been to prison, however, it was not statistically significant (P-value = 0.108). Both younger age and male gender were also significant in final model.

As in totally, Age, Male gender, Family history of drug use and being currently homeless were the most powerful predictor of substance use among psychosis patients (Table 6).

## Discussion

The current study examined the prevalence and correlations of substance use among patients admitted with psychosis to a psychiatric university hospital. To the best of our knowledge, this study is the first to determine the prevalence, demographic characterization and correlates of substance use among patients with psychotic symptoms independent of their categorical diagnostic classification.

Prevalence of substance use was high among all diagnosed psychotic disorders and this is consistent with previous data, reporting a high prevalence of substance use among patients with variety of diagnosis in clinical or nonclinical psychiatric settings (2, 15, 16). Considering diagnostic categories, most of our studied population consisted of patients with bipolar disorder, substance induced psychotic disorder and schizophrenia, respectively.

Opioids, in all forms, were the most prevalent drugs used in this setting. This is consistent with previous epidemiologic studies in Iran that consider opiates the most prevalent drug used (17). Cultural factors play an important role in initiation and continuing substance use. Opiates are more accessible and are even seen as a cultural norm in some part of the country (17, 18). Although there is more recent research showing an increasing pattern of injecting heroin as well as stimulants use, traditional inhalation of opium remains the leading form of its consumption (17, 19–21)

Although the second most prevalent consumed drug prior to the current hospitalization reported to be hypnotics and sedatives, this might be due to the fact that most of the patients received benzodiazepines in hospital or as a medication along with their other medications by psychiatrists rather than as illicit use. The next most commonly reported drug was methamphetamine compounds (known as crystal or shisheh) in Iran. Amphetamines produce dopaminergic effects in the brain and there is evidence to suggest that it is one of the most important drug that induces or triggers psychosis (8). Although there is limited information about the prevalence of stimulant use among psychiatric patients in Iran, in recent

decades, population surveys suggest increased stimulant consumption (18, 19). The implication of amphetamines in psychiatric populations, necessitates rigorous attention from both policy makers and health care professionals.

The prevalence of alcohol use was much lower than the epidemiological studies worldwide. Globally, 25% of patient with schizophrenia (1) and bipolar disorder (15) will likely have an alcohol use disorder at some stage in their life. The prevalence of alcohol consumption is much lower in Asian countries (22, 23) as well as Iran (17, 24) which is not surprising, because of cultural and religious sanctions. Legal factors play an important role in the availability of certain drugs and spiritual factors can also prevent people from consuming. These data, however, should be interpreted cautiously. Although the anonymity of data collection was emphasized, the aforementioned factors might increase stigma and prevent people from revealing their true levels of alcohol consumption. Some studies in specific clinical settings have found that after opiates, alcohol is the second prevalent substance (25). Further research in this area is required.

Cannabis is the only drug where the link to chronic psychosis and schizophrenia spectrum disorders have been shown in studies (1, 26, 27). Here however, only a few patients reported its application. This is consistent with previous epidemiologic reports of substance use in Iran which do not consider cannabis a prevalent drug of use (17, 18, 25)

The main associated predictors were male gender, younger age, family history of drug use, history of imprisonment and being currently homeless. The link to gender, has been well documented in many studies. Most studies show that males are 2–3 times more susceptible to SUD (2, 16, 17). It has been suggested that susceptibility to perform risky behaviors are higher in men than women. Both biological and societal factors play role in this issue. As men tend to have more freedom and face less stigma than women.

Previous studies support the relationship between substance use in family members and increased risk of current SUD (28, 29). In Iran almost 50 percent of substance users have at least one close family member with substance abuse or dependency (18). Although a cross sectional study cannot reveal the causative relations, both biologic and psychosocial perspective can clarify this relation. Genetic vulnerability to SUD has been documented in twins and adoption studies (7, 29). On the other hands, families are not only the first role model of behaviors, but also provide a structure for shaping behaviors; this structure can consist of nonspecific mechanisms such as distress exposure, separation and other conflicts of marital relationships, and non-adoptive parenting styles (28, 30). Engaging families is a crucial component of treating psychotic disorders. As patients with psychosis may not be able to provide a complete family history during psychiatric assessments, involving family members in comprehensive assessments in order to screen high risk patients and provide preventive and treatment strategies is of important value.

Although controversial, younger age has been suggested to be related to SUD and our data provides evidence in favor of that. Youth is the most at risk age for consuming substances and developing

substance related disorders. Youth might try to show their independence and free will by performing risky behaviors.

Socioeconomic factors are highly associated with increased risk of SUD (17). Being homeless which means lack of social support as well as lower socioeconomic status can be a major risk of developing SUD in patients with psychotic disorders. In this study, however, only a small proportion of the population reported being currently homeless. Therefore the data should be interpreted cautiously. The history of imprisonment, on the other hand, can be related to both risk taking and antisocial behaviors. The mediator remains to be studied more.

## Study Limitations and Strengths

There are some limitations in the present study. Although this is a cross sectional study, the associated factors determined in the analysis, do not interpret as causal factors. The cross sectional design of the study also prevented the precise analysis of sequential association between risky behaviors and substance use disorders. While the study sample is limited to patient who attend to Razi hospital in Tehran, it is not a random sample of this population. Therefore, the results cannot be generalized to all psychiatric patients in Tehran or more broadly in Iran.

As a strength we can mention enough sample size of participants in this study. Unlike previous studies, we have used DSM-5 for diagnostic confirmation. However, the main focus of this study was determining the prevalence and correlates of substance use in patients with psychosis regardless of their diagnostic category.

## Conclusion

The prevalence of substance use was high among all psychotic disorders in the participant population interviewed. The main associated risk factors were younger age, male gender, history of imprisonment, and having a family history of drug use. Active investigation and comprehensive prevention plans are suggested in all patients admitted to hospital with psychosis especially among younger age, male and homeless people with family history of drug use.

## Abbreviations

- DSM-5
- Diagnostic and Statistical Manual of Mental Disorders 5th Edition
- SCID-5
- Structured Clinical Interview for DSM-5
- SUD
- Substance Use Disorder
- ICC

- Intra-class Correlation Coefficient
- OR
- Odds Ratio
- CI
- Confidence Interval

## Declarations

- Ethics approval and consent to participate. This study was approved by the Ethic Committee of the University of Social Welfare and Rehabilitation Sciences, Tehran, Iran (IR.USWR.REC.1396.70). Written informed consent was obtained from all participants and participants' anonymity was ensured throughout the study. An overseeing psychiatrist ruled that all participants were deemed capable of ethically and medically consenting for their participation in this research.
- Consent for publication. Not relevant
- Availability of data and material. All data and material will be available, as the final report of the project will be published in the Social Welfare and Rehabilitation Sciences Website.
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- Authors' contributions. ASH, NP, PH and SBM: the study concept and design. ES, MP, MM and SJF: gathering the data and drafting the manuscript. MN, NP, and ASH: Statistical analysis, AS, SBM, PH: Analysis and interpretation of data. ASH, SBM, PH, NP, and MN Critical revision of the manuscript for important intellectual content.
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## References

1. Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. *Drug and Alcohol Dependence*. 2018;191:234-58.
2. Hunt GE, Malhi GS, Cleary M, Lai HMX, Sitharthan T. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990–2015: Systematic review and meta-analysis. *Journal of Affective Disorders*. 2016;206:331-49.
3. Glasner-Edwards S, Mooney LJ. Methamphetamine psychosis: epidemiology and management. *CNS Drugs*. 2014;28(12):1115-26.
4. Arciniegas DB. Psychosis. *Continuum (Minneapolis, Minn)*. 2015;21(3 Behavioral Neurology and Neuropsychiatry):715-36.

5. McKetin R, Baker AL, Dawe S, Voce A, Lubman DI. Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. *Psychiatry Res.* 2017;251:349-54.
6. Voce A, Calabria B, Burns R, Castle D, McKetin R. A Systematic Review of the Symptom Profile and Course of Methamphetamine-Associated Psychosis: Substance Use and Misuse. *Substance use & misuse.* 2019:1-11.
7. Reginsson GW, Ingason A, Euesden J, Bjornsdottir G, Olafsson S, Sigurdsson E, et al. Polygenic risk scores for schizophrenia and bipolar disorder associate with addiction. *Addiction Biology.* 2018;23(1):485-92.
8. Glasner-Edwards S, Mooney LJ. Methamphetamine psychosis: epidemiology and management. *CNS Drugs.* 2014;28(12):1115-26.
9. Gaebel W, Zielasek J. Focus on psychosis. *Dialogues in clinical neuroscience.* 2015;17(1):9-18.
10. Arciniegas DB. Psychosis. *Continuum (Minneapolis, Minn).* 2015;21(3 Behavioral Neurology and Neuropsychiatry):715-36.
11. Association AP. *Diagnostic and statistical manual of mental disorders (DSM-5®):* American Psychiatric Pub; 2013.
12. Rabinowitz J, Berardo CG, Bugarski-Kirola D, Marder S. Association of prominent positive and prominent negative symptoms and functional health, well-being, healthcare-related quality of life and family burden: a CATIE analysis. *Schizophrenia research.* 2013;150(2-3):339-42.
13. Suetani S, Rosenbaum S, Scott J, Curtis J, Ward P. Bridging the gap: What have we done and what more can we do to reduce the burden of avoidable death in people with psychotic illness? *Epidemiology and psychiatric sciences.* 2016;25(3):205-10.
14. Lally J, Ajnakina O, Stubbs B, Cullinane M, Murphy KC, Gaughran F, et al. Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. *British Journal of Psychiatry.* 2018;211(6):350-8.
15. Hunt GE, Malhi GS, Cleary M, Lai HMX, Sitharthan T. Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990–2015: Systematic review and meta-analysis. *Journal of Affective Disorders.* 2016;206:321-30.
16. Messer T, Lammers G, Müller-Siecheneder F, Schmidt R-F, Latifi S. Substance abuse in patients with bipolar disorder: A systematic review and meta-analysis. *Psychiatry Research.* 2017;253:338-50.
17. Amin-Esmaeili M, Rahimi-Movaghar A, Sharifi V, Hajebi A, Radgoodarzi R, Mojtabai R, et al. Epidemiology of illicit drug use disorders in Iran: prevalence, correlates, comorbidity and service utilization results from the Iranian Mental Health Survey. *Addiction.* 2016;111(10):1836-47.
18. Mokri A. Brief overview of the status of drug abuse in Iran. 2002.
19. Noori R, Daneshmand R, Farhoudian A, Ghaderi S, Aryanfard S, Moradi A. Amphetamine-Type Stimulants in a Group of Adults in Tehran, Iran: A Rapid Situation Assessment in Twenty-Two Districts. *Iran J Psychiatry Behav Sci.* 2016;10(4):e7704.



20. Razzaghi E, Rahimi A, Hosseini M, Chatterjee A. Rapid Situation Assessment (RSA) of drug abuse in Iran. Prevention Department, State Welfare Organization, Ministry of Health, IR of Iran and United Nations International Drug Control Program. 1999.
21. Shadloo B, Amin-Esmaeili M, Haft-Baradaran M, Noroozi A, Ghorban-Jahromi R, Rahimi-Movaghar A. Use of amphetamine-type stimulants in the Islamic Republic of Iran, 2004-2015: a review. *Eastern Mediterranean Health Journal*. 2017;23(3).
22. Cheng HG, Phillips MR, Li X, Zhang J, Shi Q, Xu G, et al. Co-occurrence of DSM-IV mental disorders and alcohol use disorder among adult Chinese males. *Psychological Medicine*. 2017;47(16):2811-22.
23. Chou SP, Lee HK, Cho MJ, Park J-I, Dawson DA, Grant BF. Alcohol use disorders, nicotine dependence, and co-occurring mood and anxiety disorders in the United States and South Korea-a cross-national comparison. *Alcohol Clin Exp Res*. 2012;36(4):654-62.
24. Amirabadizadeh A, Nezami H, Vaughn MG, Nakhaee S, Mehrpour O. Identifying Risk Factors for Drug Use in an Iranian Treatment Sample: A Prediction Approach Using Decision Trees. *Substance Use & Misuse*. 2018;53(6):1030-40.
25. Alavi SS, Mehrdad R, Makarem J. Prevalence of substance abuse/alcohol consumption and their predictors among patients admitted in operating rooms of a General Educational Hospital, Tehran, Iran. *Asian Journal of Pharmaceutical Research and Health Care*. 2016;8.
26. Koskinen J, Löhönen J, Koponen H, Isohanni M, Miettunen J. Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. *Schizophrenia bulletin*. 2009;36(6):1115-30.
27. Kuepper R, van Os J, Lieb R, Wittchen H-U, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *Bmj*. 2011;342:d738.
28. McCutcheon VV, Agrawal A, Kuo SI-C, Su J, Dick DM, Meyers JL, et al. Associations of parental alcohol use disorders and parental separation with offspring initiation of alcohol, cigarette and cannabis use and sexual debut in high-risk families. *Addiction*. 2018;113(2):336-45.
29. Bierut LJ, Dinwiddie SH, Begleiter H, Crowe RR, Hesselbrock V, Nurnberger JI, et al. 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*. 1998;55(11):982-8.
30. Ashery RS, Robertson EB, Kumpfer KL. Drug abuse prevention through family interventions: Diane Publishing; 1998.