

The effect of the severity of nicotine dependence on psychopathology, insight and illness severity in schizophrenia

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Abstract

Aim: Compared to the general healthy population, and other psychiatric disorders the prevalence of smoking is found to be much higher among people with schizophrenia. Our study aims to determine the prevalence of nicotine dependence and investigate the effects of the severity of nicotine dependence on psychopathology, illness severity and insight in a population of people with schizophrenia.

Material and Methods: A cross-sectional study was carried out in a psychotic disorders outpatient clinic at Bakirkoy Training and Research Hospital. Four hundred and ten schizophrenia patients were administered by the Positive and Negative Symptom Scale (PANSS), Schedule for Assessment of Insight (SAI), Clinical Global Impression Severity of Illness (CGI-S) and the Turkish version of Fagerstrom Test for Nicotine Dependence (FTND).

Results: The prevalence of nicotine dependence among the patients was 49.0%. The one-way analysis of variance revealed that subjects with severe nicotine dependence scored more in the positive subscale of PANSS and CGI-S compared with patients with mild-moderate nicotine dependence. Those with severe nicotine dependence were also prescribed higher doses of antipsychotic.

Conclusions: Our findings indicate an association between nicotine dependence, positive symptoms and severity of illness. Identifying this relationship can be helpful in the management of smoking cessation treatment in patients with schizophrenia.

Keywords: Dependency; Nicotine; Psychopathology; Schizophrenia.

INTRODUCTION

Nicotine dependence is a very common clinical condition in patients with schizophrenia when compared with both the general population (1) and other psychiatric disorders (2). In a meta-analysis, the prevalence of nicotine dependence was found to be approximately three times higher among people with schizophrenia than the general population, with a smoking prevalence rate of 62% (3). It has been determined that schizophrenia patients are more likely to have heavy cigarette smoking (3). For this reason, it is not surprising that smoking-related morbidity and mortality are more common in patients with schizophrenia (4).

The reason for the increased rate of cigarette smoking in patients with schizophrenia is uncertain. The "self-medication" theory suggests that schizophrenic patients smoke cigarettes to reduce the severity of their positive and negative symptoms and to improve their cognitive functions. It is thought that nicotine reduces negative symptoms and improve cognitive functions by causing a temporary increase in the activity of the mesocortical

dopamine system (5). It is also suggested that schizophrenia patients smoke cigarettes to reduce side effects of antipsychotic drugs (6). It has been determined that schizophrenia and nicotine dependence might share a common genetic vulnerability (7). It has been found that nicotinic receptor expression is reduced in many brain regions in schizophrenia (8).

In addition, it has been reported that schizophrenia patients who smoke cigarettes have more positive symptoms and receive higher doses of antipsychotic drugs (9). Thus, it is suggested that nicotine exacerbates psychosis and may weaken beneficial effects on cognitive functions.

In studies evaluating psychopathology and nicotine dependence in schizophrenia patients, different results have been obtained. While some studies have reported that schizophrenia patients who smoke cigarettes have more positive and negative symptoms (10), other studies did not reveal any differences (11). It has been found that while schizophrenic patients with severe nicotine dependence exhibit more positive symptoms (9,10),

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patients with mild nicotine dependence have less positive symptoms (12).

There have been studies on cigarette smoking in schizophrenia in Turkey (13-16). However, to our knowledge, there have been no studies investigating the severity of nicotine dependence in schizophrenia. The Fagerstrom Test for Nicotine Dependence (FTND) is often used as a measure of physical dependence on nicotine (17). Statements on cigarette smoking by individuals reflect only smoking status. However, nicotine dependence is independent of the number of cigarettes smoked, the level of nicotine in cigarettes, and the duration of smoking. The FTND has been reported to have a strong association with the diagnosis of nicotine dependence in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (18, 19).

In this study, patients with schizophrenia who smoked cigarettes were divided into groups according to the severity of nicotine dependence. The aim of our study was to compare schizophrenic patients who smoked cigarettes with schizophrenia patients who did not smoke cigarettes in terms of sociodemographic characteristics, psychopathology, insight, and illness severity. Consistent with previous studies, it is assumed that schizophrenia patients who are heavy smokers have more positive symptoms and higher disease severity than other groups.

MATERIAL and METHODS

Patient Samples

The sample group of this cross-sectional study comprised patients who were followed and monitored at the Bakirkoy Training and Research Hospital as outpatients with schizophrenia diagnosis in accordance with the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (20). A total of 557 participants were recruited consecutively from this outpatient clinic during the 6-month period of time between January 1, 2017 and July 1, 2017. Of the 557 patients, 147 patients were excluded due to exclusion criteria. Patients who had an acute psychotic episode, who had chronic systemic and neurological disorders, who had mental retardation, who used illicit substances and alcohol in the last 1 year, and who refused to participate in the study were excluded from the study. These disorders and clinical conditions were selected as exclusion criteria due to their possible effects on psychopathology, insight, and severity of illness. Nicotine dependence were diagnosed according to the DSM-IV-TR (20). The study was approved by the Ethics Committee of Bakirkoy Training and Research Hospital (Confirmation number: 24.11.2016-7150). Informed consent form was obtained from the patients.

Sociodemographic data form

It is a semi-structured data form prepared by the researchers. This form contained questions about the identity information, age, gender, duration of education, duration of disease, antipsychotic drugs, smoking history, mean number of cigarettes smoked per day, duration of smoking, alcohol, and other substance use, additional medical illnesses, and other psychiatric medications.

Positive and Negative Syndrome Scale (PANSS)

The PANSS is a 30-item semi-structured instrument to perform psychopathological measurements related to

positive, negative, and general symptoms of schizophrenia (21). This scale included 30 items, 18 items for the Brief Psychiatric Rating Scale (BPRS) and 12 items from the Psychopathology Rating Schedule (PRS). The 30 items are arranged as seven positive symptom subscale items (P1 - P7), seven negative symptom subscale items (N1 - N7), and 16 general psychopathology symptom items (G1 - G16). All 30 items are rated on a 7-point scale (1 = absent; 7 = extreme). It consists of four measures including PANSS total score, PANSS positive subscale score, PANSS negative subscale score, and PANSS general psychopathology subscale score. The validity and reliability study of the Turkish version of this scale was performed by Kostakoğlu et al. (22).

Schedule for the Assessment of Insight (SAI)

It is a semi-structured clinician-administered instrument developed for assessment of insight in schizophrenia by David in 1990 (23). The validity and reliability study of the Turkish version of this scale was performed by Arslan et al. (2001) (24). It is composed of four components including awareness of mental illness, ability to re-label psychotic experience as abnormal, adherence to treatment, and awareness of previous mental disorders. The items are rated on 3-point scales ranging from 0 to 2 points. Higher scores indicate higher levels of insight.

Clinical Global Impression-Severity of Illness (CGI-S)

It was developed by Guy et al. (1976) to assess the clinical course of all mental disorders at all ages for clinical research purposes (25). It is filled out during a semi-structured interview conducted by the physician to assess the treatment response of individuals with psychiatric disorders. This scale yields three different measures: Severity of illness, overall improvement, and therapeutic index. The CGI-Severity (CGI-S), which is the first component of the scale, was assessed in our study. The CGI-S asks the clinician one question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

Fagerstrom Test for Nicotine Dependence (FTND)

It is a 6-item scale designed to measure nicotine dependence in cigarette smokers (17). It was used because it is often preferred in treatment efficacy studies. The factor analysis and reliability study of the Turkish version of this scale was performed by Uysal et al. (26). In parallel with previous studies, all the nicotine-dependent patients were classified as mild-moderate dependence (FTND-M ≤ 6) or severe dependence (FTND-M > 6) (3,9,17).

Procedure

After the patients who agreed to participate in the study read and signed the informed consent form, they were assessed by the sociodemographic data form. They filled out the Fagerstrom Test for Nicotine Dependence if they smoked cigarettes. The Positive and Negative Syndrome Scale, the Schedule for the Assessment of Insight, and the Clinical Global Impression Scale were filled out by the author. The description of the study, the collection of sociodemographic information, and the assessment of the scales were completed within approximately 30-

45 minutes on the day of recruitment. The antipsychotic drugs and their doses which they were taking at the time of the recruitment were recorded. For antipsychotic drugs chlorpromazine equivalent doses were calculated for each patient as described by others (27,28). Participants who were taking long-acting injectable antipsychotics, the dose of injectable form was converted to the equivalent dose of oral form, and then converted to the chlorpromazine equivalent dose. For cases who were taking more than one antipsychotic drugs, chlorpromazine equivalent doses were calculated for each drug separately.

Statistical Methods

The distributional properties of the variables were examined by the Kolmogorov-Smirnov test. Since the parameters were normally distributed, the Student's t-test was used to compare quantitative data of the two groups (smokers and non-smokers). The Chi-square test was used to compare qualitative data. The patients who smoked cigarettes were further divided into the two groups as mild/moderate smokers and heavy smokers according to the FTND. Then, these two groups were compared with the non-smoking group. The One-Way ANOVA test was used to compare quantitative data of the three groups. The results were assessed at a 95% confidence interval, at a significance level of p<0.05, and at high significance levels of p<0.01 and p<0.001. The Statistical Package for the Social Sciences 18.0 (SPSS, SPSS Inc., Chicago, IL, USA) was used to analyze data.

RESULTS

Of the 557 patients who were monitored at our center, 410 were included in the study due to exclusion criteria. Of the 410 schizophrenia patients participating in the study, 201 (49.0%) smoked cigarettes. The mean age of the patients who did not smoke cigarettes was significantly higher than that of the patients who smoked cigarettes (42.70 (± 11.14) years vs. 42.43±8.9 years, p<0.05). The ratio of men to women was significantly higher in the smoking group (83.5% vs. 16.5%, p<0.001). The duration of education was significantly shorter in the smoking group than in the non-smoking group (8.63±3.40 years vs. 9.73 (± 4.05) years,

p<0.05). There was no significant difference between the smoking group and the non-smoking group in terms of duration of illness, chlorpromazine equivalent dose, and scale scores (Table 1). The DSM-IV-TR diagnosis among patients with schizophrenia were obsessive-compulsive disorder (8.78%), mood disorders (6.58%), and others (4.63%). The schizophrenic patients with alcohol and substance dependence are generally followed up other than this outpatient clinic, so there was no schizophrenic patients with other substance or alcohol dependence comorbidity. The comorbid medical illnesses and conditions were hypothyroidism (6.1%), Type 2 diabetes mellitus (12.92%), essential hypertension (8.29%), and epilepsy that under control with treatment (5.12%).

The patients were divided into the three groups as non-smokers, smokers with mild/moderate dependence and severe dependence according to the FTND. These three groups were compared in terms of age, duration of education, duration of illness, chlorpromazine equivalent dose, and PANSS, SAI, CGI-S scores (Tables 2 and 3). There was a significant difference in chlorpromazine equivalent doses of antipsychotic drugs between the three groups (F (2.407)=11.775, p<0.001). According to post-hoc comparisons, severely dependent smokers (mean= 1194.95, SD=584.01) received significantly higher doses of antipsychotic medication than smokers with mild/moderate dependence (mean=981.6, SD=546.18) and non-smokers (mean=875.22, SD=532.21). This comparison revealed that there was a significant difference between the three groups in terms of PANSS positive subscale score (F(2, 407)=3.20, p=0.042) and CGI-S score (F (2.407)=3.33, p=0.037).

According to Tukey HSD post-hoc test, severely dependent smokers (mean= 9.94, SD=3.38) had significantly higher PANSS positive subscale score than smokers with mild/moderate dependence (mean=8.81, SD=2.76) (p<0.05). severely dependent smokers (mean=2.26, SD=0.93), had significantly higher CGI-S score than smokers with mild/moderate dependence (mean=1.92, SD=0.89) (p<0.05) (Table 3).

Table 1. Demographic and clinical characteristics of schizophrenic patients with and without nicotine dependence

	Patients without nicotine dependence (n=209)	Patients with nicotine dependence (n=201)	t	x ²	p
Age (years±SD)	42.70(± 11.14)	42.43(±8.9)	0.297		0.003*
Gender				24.358	0.000**
Male	61.6%	83.5%			
Female	38.4%	16.5%			
Duration of education (years±SD)	9.73 (± 4.05)	8.63(±3.40)	2.832		0.012*
Duration of illness (years±SD)	19.44 (± 8.82)	19.20(8.40)	0.472		0.623
Chlorpromazine equivalents	875.22 (± 532.21)	1089.66(±572.05)	-3.743		0.472
PANSS-positive symptom subscale(±SD)	9.66 (± 3.53)	9,35(±3.11)	1.010		0.940
PANSS-negative symptom subscale	13.31 (± 4.89)	12,81(±4.37)	1.060		0.616
PANSS-general psychopathology subscale	24.91 (± 6.85)	24,24(±7.37)	0.945		0.720
PANSS- Total	47.85 (± 12.87)	46.31(±12.81)	1.184		0.833
SAI	13.30 (± 5.56)	16.38(±31.46)	-1.430		0.479
CGI-S	2.07 (± 0.96)	2.07(±0.92)	0.366		0.156

PANSS: The Positive and Negative Syndrome Scale, SAI: Schedule for Assessment of Insight, CGI-S: Clinical Global Impression Severity of Illness SD: Standard deviation, *p<0.05 **p<0.001

Table 2. Demographic characteristics of patient groups according to the severity of nicotine dependence

		N	Mean	SD	F	P value	NS-M Mean dif.	NS-S Mean dif.	M-S Mean dif.
Age (years)	Non-smoker	209	42.70	11.14	0.164	0.849	0.62	-0.11	-0.74
	Mild/moderate	97	42.08	8.93			P=0.871	P=0.995	P=0.862
	Severe	104	42.82	9.06					
	Total	410	42.59	10.13					
Duration of education (years)	Non-smoker	209	9.73	4.05	5.238	0.006	0.80	1.40	0.60
	Mild/moderate	97	8.92	3.49	P=0.188	P=0.005*	P=0.485		
	Severe	104	8.32	3.25					
	Total	410	9.18	3.77					
Duration of illness (years)	Non-smoker	209	19.44	8.82	0.118	0.889	0.35	-0.23	55.00
	Mild/moderate	97	19.08	8.85	P=0.940	P=0.973	P=0.880		
	Severe	104	19.67	8.26					
	Total	410	19.41	8.67					
Chlorpromazine equivalents	Non-smoker	209	875.22	532.21	11.775	0.000	-106.42	-319.72	213.30
	Mild/moderate	97	981.64	546.18	P=0.256	P=0.000**	P=0.017*		
	Severe	104	1194.95	584.01					
	Total	410	981.50	563.31					

NS: non-smoker, M : Patients with Mild/moderate nicotine dependence, S: Patients with severe nicotine dependence, Mean dif.: Mean difference, SD: Standard deviation

Table 3. Clinical characteristics of patient groups according to the severity of nicotine dependence

		N	Mean	SD	F	P value	NS-M Mean dif.	NS-S Mean dif.	M-S Mean dif.
PANSS-positive symptom subscale	Non-smoker	209	9.66	3.53	3.201	0.042*	0.84	-0.28	1.12*
	Mild/moderate	97	8.81	2.76	p=0.098	p=0.760	p=0.044*		
	Severe	104	9.94	3.38					
	Total	410	9.53	3.34					
PANSS-negative symptom subscale	Non-smoker	209	13.31	4.89	1.012	0.364	0.80	0.17	-0.62
	Mild/moderate	97	12.50	4.11	p=0.334	p=0.946	p=0.601		
	Severe	104	13.13	4.54					
	Total	410	13.07	4.63					
PANSS-general psychopathology subscale	Non-smoker	209	24.91	6.85	1.799	0.167	1.51	-0.12	-1.64
	Mild/moderate	97	23.40	7.04	p=0.192	p=0.987	p=0.229		
	Severe	104	25.04	7.59					
	Total	410	24.59	7.11					
PANSS total	Non-smoker	209	47.85	12.87	2.173	0.115	3.10	0.01	-3.09
	Mild/moderate	97	44.74	11.91	p=0.120	p=1.00	p=0.202		
	Severe	104	47.83	13.48					
	Total	410	47.11	12.85					
SAI	Non-smoker	209	13.30	5.56	2.566	0.078	-5.85	-0.23	5.61
	Mild/moderate	97	19.15	44.20	p=0.078	p=0.996	p=0.167		
	Severe	104	13.53	4.48					
	Total	410	14.74	22.03					
CGI-S	Non-smoker	209	2.07	0.96	3.336	0.037*	0.14	-0.19	-0.34*
	Mild/moderate	97	1.92	0.89	p=0.405	p=0.205	p=0.029*		
	Severe	104	2.26	0.93					
	Total	410	2.09	0.94					

PANNS: The Positive and Negative Syndrome Scale, SAI: Schedule for Assessment of Insight, CGI-S: Clinical Global Impression Severity of Illness
NS: non-smoker, M : Patients with Mild/moderate nicotine dependence, S: Patients with severe nicotine dependence
Mean dif.: Mean difference, SD: Standard deviation *p<0.05

DISCUSSION

This study found that 49.0% of the 410 schizophrenia patients smoked cigarettes and that 51.7% of these smokers met the criterion for severe nicotine dependence. The prevalence of tobacco smoking among adults 15 years and older in Turkey was determined as 27.1% (29). Smoking has been shown to be more prevalent in schizophrenia patients than in the general population (3). Studies conducted in Turkey have revealed that the prevalence of nicotine use in schizophrenia patients varies between 45% and 72% (13-16). Moreover, the smoking rates in schizophrenia patients were found 53.4-70% (9, 30) in European countries, 70-90% in USA (31), and 38.1%-65% in Asian countries (10,32). In one study conducted in Brazilian patients with schizophrenia examining nicotine dependence, the rate of smoking was found higher than our study (57.8%) (33). A meta-analysis of worldwide studies reported that smoking prevalence range is 58 to 88% in schizophrenia patients (3). These differences in the studies may be related to different diagnostic criteria, sample size, different sociocultural and ethnic structures, and types of antipsychotic medication.

In our study, the duration of education was longer in non-smokers than in smokers with mild/moderate dependence and severely dependent smokers. In individuals with severe mental illnesses, low education levels have a major impact on the initiation of cigarette smoking (34). In parallel with other studies, the majority of smokers were male (9, 35). The rate of smoking dependence in the general population of our country has been found to be 3 times higher in men than in women (29).

In our study, chlorpromazine equivalent dose was higher in severely dependent smokers than in non-smokers and mild/moderate group. Similarly, Krishnadas et al. (2012) found that heavy smokers received high-dose antipsychotics (9). The use of high-dose antipsychotics in patients with severe nicotine dependence may indicate the induction of antipsychotic metabolism caused by nicotine and/or the need for more aggressive treatment for positive symptoms. In parallel to this, heavy smokers had higher PANSS positive subscale score than mild/moderate smokers while there is no difference in negative symptoms between groups. These results are different from the results of previous studies showing the relationship between nicotine dependence and negative psychopathology (32). According to this study, participants with severe nicotine dependence has less score in the negative symptomatology (32). Patkar et al (19) reported that negative symptoms were the strongest contributor to predicting smoking behavior. These two studies suggested that these results supported the self-medication hypothesis which indicates that nicotine could be an attempt to alleviate negative and cognitive symptoms by schizophrenic patients.

Nicotinic receptors are located in dopaminergic cell bodies in the ventral tegmental area. Nicotine stimulates dopamine release in this region. Nicotine-dependent

dopamine release in the mesocortical dopamine system increases cognitive functions and reduces negative symptoms (36). Neuroimaging has shown that nicotine increases dopamine release in the dorsal and ventral striatum in humans (37). The fact that our study found that severely dependent smokers had higher PANSS positive subscale score than mild/moderate group may be related to nicotine-induced enhancement of dopamine release in the mesolimbic dopamine system. Exacerbation of psychosis by nicotine may prevent the positive effects of nicotine on negative symptoms and cognitive functions. Another finding supporting this is the fact that the severity of disease was higher in heavy smokers than in mild/moderate smokers. It has been shown that substance abuse itself is associated with an increase in the severity of disease when deterioration caused by the disease process is excluded (38).

Study limitations

Our study has some limitations. The cross-sectional nature of our study makes it difficult to establish a clear cause-effect relationship for nicotine dependence, psychopathology, and clinical status of the disease (such as severity of illness). The lack of comparison with a control group is another limitation of our study. In addition, the fact that the study was conducted only in non-hospitalized schizophrenic patients and did not involve hospitalized schizophrenia patients prevents generalization of results. However, to our knowledge, our study is the first study investigating the severity of nicotine dependence and its association with the psychopathology and clinical features of the illness in schizophrenia patients in Turkey. Thus, we think that our study will contribute to medical literature.

CONCLUSION

As a result, our study found that patients with schizophrenia who were severely dependent smokers had more positive symptoms and higher disease severity than those with mild/moderate dependence. It was also determined that severely dependent smokers received higher doses of antipsychotic medication than mild/moderate group and non-smokers. Although our study have not established a causal relationship, diagnosing and treating nicotine dependence may be beneficial in reducing morbidity and mortality rates in schizophrenia. Taking the severity of nicotine dependence and the severity of schizophrenia symptoms into consideration together will increase the success of smoking cessation treatment.

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REFERENCES

1. Kelly C, McCreddie R. Cigarette smoking and schizophrenia. *Adv Psychiatr Treat* 2000;6:327-33.
2. Uçok, A, Polat A, Bozkurk O, Meteris H. Cigarette smoking among patients with schizophrenia and bipolar disorders.

- Psychiatry Clin Neurosci 2004;58(4):434-7.
3. de Leon J, Diaz FC. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* 2005;76(2):135-57.
 4. Kelly DL, McMahon RP, Wehring HJ, Liu F, Mackowick KM, Boggs DL, Cigarette smoking and mortality risk in people with schizophrenia. *Schizophr Bull* 2011;37(4):832-8.
 5. Kumari V, Postma P. Nicotine use in schizophrenia: the self medication hypotheses. *Neurosci Biobehav Rev* 2005;29(6):1021-34.
 6. Lyon ER. A review of the effects of nicotine on schizophrenia and antipsychotic medications. *Psychiatr Serv* 1999;50(10):1346-50.
 7. Yoshimasu K, Kiyohara C. Genetic influences on smoking behavior and nicotine dependence: a review. *J Epidemiol* 2003;13(4):183-92.
 8. Wing VC, Wass CE, Soh DW, George TP. A review of neurobiological vulnerability factors and treatment implications for comorbid tobacco dependence in schizophrenia. *Ann N Y Acad Sci* 2011;1248: 89-106.
 9. Krishnadas R, Jauhar S, Telfer S, Shivashankar S, McCreadie RG. Nicotine dependence and illness severity in schizophrenia. *Br J Psychiatry* 2012;201(4):306-12.
 10. Kao YC, Liu YP, Cheng TH, Chou MK. Cigarette smoking in outpatients with chronic schizophrenia in Taiwan: relationships to socio-demographic and clinical characteristics. *Psychiatr Res* 2011;190(2-3):193-9.
 11. Kotov R, Guey LT, Bromet EJ, Schwartz JE. Smoking in schizophrenia: diagnostic specificity, symptom correlates, and illness severity. *Schizophr Bull* 2010;36(1):173-81.
 12. Aguilar MC, Gurpegui M, Diaz FJ, De Leon J. Nicotine dependence and symptoms in schizophrenia: Naturalistic study of complex interactions. *Br J Psychiatry* 2005;186:215-21.
 13. Ekinçi O, Ekinçi A. Cigarette smoking in patients with schizophrenia in Turkey: relationships to psychopathology, socio-demographic and clinical characteristics. *Dusunen Adam The Journal of Psychiatry and Neurological Sciences* 2012;25:321-9.
 14. Uzun Ö, Cansever A, Basoğlu C, Ozsahin A. Smoking and substance abuse in outpatients with schizophrenia: A 2-year follow-up study in Turkey. *Drug Alcohol Depend* 2003;70(2):187-92.
 15. Karşıdağ C, Alpay N, Kocabıyık A. Schizophrenia and Cigarette Dependence. *Dusunen Adam The Journal of Psychiatry and Neurological Sciences* 2005;18:13-20.
 16. Uludağ YT, Güleç G. Prevalence of Substance Use in Patients Diagnosed with Schizophrenia. *Arch Neuropsychiatr* 2016;53:4-11.
 17. Fagerström KO, Kunze M, Schoberberger R, Breslau N, Hughes JR, Hurt RD, Nicotine dependence versus smoking prevalence: comparisons among countries and categories of smokers. *Tob Control* 1996;5(1):52-6.
 18. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, Washington, DC: Author; 1994.
 19. Patkar AA, Gopalakrishnan R, Lundy A, Leone FT, Certa KM, Weinstein SP. Relationship between tobacco smoking and positive and negative symptoms in schizophrenia. *J Nerv Ment Dis* 2005;190(9):604-10.
 20. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, text rev. DC: Author; 2000. Washington.
 21. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-76.
 22. Kostakoğlu AE, Batur S, Tiryaki A. Pozitif ve Negatif Sendrom Ölçeğinin (PANSS) Türkçe Uyarlamasının Geçerlik ve Güvenilirliği [Validity and Reliability of Turkish Adaptation of Positive and Negative Syndrome Scale (PANSS)]. *Türk Psikoloji Dergisi* 1999;14(44):23-32.
 23. David AS. Insight and psychosis. *Br J Psychiatry* 1990;156:798-808.
 24. Arslan S, Günay Kılıç B, Karakılıç H. İçgörünün Üç Bileşenini Değerlendirme ölçeği güvenilirlik ve geçerlik çalışması [Three Components of Insight Assessment Scale reliability and validity study]. *Türkiye'de Psikiyatri*. 2000;3:17-24.
 25. Guy W. ECDEU Assessment manual for psychopharmacology. revised US dept health, education and welfare publication (ADM), Rockville, Md: National Institute of Mental Health 1976;76-338.
 26. Uysal MA, Kadakal F, Karşıdağ Ç, Bayram NG, Uysal Ö, Yılmaz V. Fagerstrom nikotin bağımlılık testinin Türkçe versiyonunun güvenilirliği ve faktör analizi. *Tuberk Toraks* 2004;52(2):115-21.
 27. Atkins M, Burgess A, Bottomley C. Chlorpromazine equivalents: a consensus of opinion for both clinical and research applications. *Psychiatric Bulletin* 1997;21:224-6.
 28. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* 2003;64(6):663-7.
 29. Küresel Yetişkin Tütün Araştırması Türkiye 2012. www.halksagligiens.hacettepe.edu.tr/KYTA_TR.pdf.
 30. LLerena A, de la Rubia A, Peñas-Lledó EM, Diaz FJ, de Leon J. Schizophrenia and tobacco smoking in a Spanish psychiatric hospital. *Schizophr Res* 2003;60(2-3):313-7.
 31. Centers for Disease Control and Prevention Cigarette smoking among adults--United States, 2004. *MMWR Morb Mortal Wkly Rep* 2005;54(44):1121-24.
 32. Yee A, Bt Nek Mohamed NN, Binti Hashim AH, Loh HS, Harbajan Singh MK, Ng CG, et al. The effect of nicotine dependence on psychopathology in patients with schizophrenia. *Biomed Res Int* 2015;2015:730291.
 33. Chaves L, Shirakawa I. Nicotine use in patients with schizophrenia evaluated by the Fagerström Tolerance Questionnaire: a descriptive analysis from a Brazilian sample. *Rev Bras Psiquiatr* 2008;30(4):350-2.
 34. De Leon J, Gurpegui M, Diaz FJ. Epidemiology of comorbid tobacco use and schizophrenia: Thinking about risks and protective factors. *Journal of Dual Diagnosis* 2007;3:9-25.
 35. Zhang XY, Li CB, Li M, Zheng YL, Zhang CX, Yan QZ, et al. Smoking initiation and schizophrenia: a replication study in a Chinese Han population. *Schizophr Res* 2010;119(1-3):110-4.
 36. George Y. Neurobiological links between nicotine addiction and schizophrenia. *J Dual Diagn* 2007;3:27-42.
 37. Brody AL, Olmstead RE, London ED, Farahi J, Meyer JH, Grossman P, et al. Smoking induced ventral striatum dopamine release. *Am J Psychiatry* 2004;161(7):1211-8.
 38. Gut-Fayand A, Dervaux A, Olié JP, Lôo H, Poirier MF, Krebs MO. Substance abuse and suicidality in schizophrenia: a common risk factor linked to impulsivity. *Psychiatry Res* 2001;102(1): 65-72.