Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2019; 11(Suppl 1):136-146
doi: 10.18863/pgy.598097

RESEARCH

The Relationship Between Antipsychotic Drug Use and Electrocardiography Parameters

Antipsikotik İlaç Kullanımının Elektrokardiyografi Parametreleri ile İlişkisi

Mehmet Emin Demirkol [1], Lut Tamam [1], Soner Çakmak [1], Caner Yeşiloğlu [1]

Abstract

Antipsychotic drugs have many known metabolic and cardiac effects. The aim of this study was to evaluate the relationship between electrocardiographic parameters and antipsychotic drug use in inpatients with psychotic disorder. For this purpose, electrocardiograms (ECG) of 200 psychotic patients who were hospitalized in our clinic were examined and the relationship between QTc interval, R-R distance and PR interval, the number of antipsychotic drugs used and the effect of antipsychotics on QTc were investigated. According to the data obtained, QTc intervals of the patients using multiple antipsychotic drugs were found to be significantly longer than those using monotherapy. When antipsychotic drugs were classified according to their potency on QTc, QTc intervals were found to be significantly longer in those receiving moderately effective drugs compared to lower effective drugs. In conclusion, considering the frequency of cardiovascular side effects in the follow-up and treatment of patients with psychotic disorder, multiple antipsychotic drugs use should be avoided as much as possible and drug selection should be given importance.

Keywords*:* Antipsychotic drug, arrhythmia, electrocardiography (ECG), psychosis, QT interval.

Öz

Antipsikotik ilaçların bilinen birçok metabolik ve kardiyak etkisi bulunmaktadır. Bu çalışmanın amacı yatarak tedavi görmüş psikotik bozukluk tanılı hastaların elektrokardiyografik parametreleri ile antipsikotik ilaç kullanımı arasındaki ilişkiyi değerlendirmektir. Bu amaçla kliniğimizde yatmış olan 200 psikotik bozukluk hastasının elektokardiyografileri (EKG) incelenerek, QTc aralığı, R-R mesafesi ve PR aralığı ile kullanılan antipsikotik ilaç sayısı ve antipsikotiklerin QTc üzerine etkisinin gücünün ilişkisi araştırılmıştır. Elde edilen verilere göre çoklu antipsikotik ilaç kullananların QTc aralıklarının monoterapi kullananlara göre anlamlı olarak daha uzun olduğu saptanmıştır. Antipsikotik ilaçlar QTc üzerine etki güçlerine göre sınıflandırıldığında, orta şiddette etkili ilaç alanların düşük etkili ilaç alanlara göre QTc aralıklarının anlamlı olarak daha uzun olduğu saptanmıştır. Sonuç olarak psikotik bozukluk tanılı hastaların takibi ve tedavisinde kardiyovasküler yan etki sıklığı dikkate alındığında, çoklu antipsikotik ilaç kullanımından mümkün oldukça kaçınılmalı ve ilaç seçimine önem verilmelidir.

Anahtar sözcükler: Antipsikotik ilaç, aritmi, elektrokardiyografi (EKG), psikoz, QT aralığı.

[1] Cukurova University Faculty of Medicine Department of Psychiatry, Adana, Turkey

✉ Mehmet Emin Demirkol, Cukurova University Faculty of Medicine Department of Psychiatry, Adana, Turkey
emindemirkol@gmail.com

Submission date: 01.06.2019 | Accepted: 07.08.2019 | Online published: 10.08.2019

SCHIZOPHRENIA spectrum and other psychotic disorders have been shown to weaken the ability to assess reality as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Delusions, hallucinations, disorganized thinking, disorganized behavior and negative symptoms are diagnostic criteria for schizophrenia. Schizophrenia, schizoaffective disorder, delusional disorder, schizotypal disorder are chronic disorders with exacerbations and remission periods (American Psychiatric Association 2013). Although the use of multiple drugs in the treatment of these disorders is not a preferred method, physicians are increasingly choosing combination therapies based on their clinical experience (Clark et al. 2002). Chronic course, inadequate response to treatment, and side effects after dose increase lead physicians to combination therapy (Kumsar and Dilbaz 2012). Özalmete et al. (2009) found the rate of multiple antipsychotic drug use as 38-64% in inpatient psychiatry clinics and 54% in outpatient clinics. Multiple antipsychotic use is associated with increased side effects, increased mortality and increased incidence of metabolic syndrome.

Cardiovascular effects of antipsychotics in general could be listed as prolongation of ventricular repolarization, tachycardia, myocarditis, changes in sinoatrial nod, cardiomyopathy, myocarditis, and arrhythmia (Passman ve Kadish 2001). The QT interval is the distance from the beginning of the QRS complex to the end of the T wave on the electrocardiogram (ECG) and indicates the duration of ventricular repolarization (Czekalla et al. 2001). Prolongation of the QT interval increases the risk of ventricular tachycardia and sudden cardiac death (Passman ve Kadish 2001). Factors causing prolongation of the QT interval include drug use, gender, age, bradycardia, hypokalemia, hypomagnesemia, and congenital long QT syndrome (Takeuchi et al. 2015). There is no definite cut-off QT value that increases the risk (Moss 1993). Antipsychotic drugs show a combination of both arrhythmogenic and antiarrhythmic properties. They can suppress the sympathetic nervous system effect in the hypothalamus and show local anesthetic effect. With these effects, they can show antiarrhythmic effect by stabilizing the cell membrane. In addition to prolongation in QT interval in ECG due to antipsychotics, flattening in T wave, ST segment collapse, prolongation in PR interval, emergence of U wave and increase in heart rate (shortening at R-R distance) can also be detected. Prolongation of the PR interval is observed due to delayed electrical conduction from the atrium to the ventricle and poses a risk for atrial fibrillation (Balcıoğlu 1999).Since the QT interval is affected by heart rate changes, it is recommended to consider the corrected QT (QTc) interval. When calculating QTc, Bazzet formula is frequently used in clinical practice and literature (Chong and Mahendran 2011). The QTc interval is also affected by the antipsychotics used. A study in Turkey found that the QTc values of patients using haloperidol and thioridazine (typical antipsychotics) were longer than those using risperidone and zuclopenthixol monotherapy and the control group (Ilhan et al. 1999).

Endocrinological problems as well as cardiovascular problems in psychotic patients cause shortening of life. One of such endocrinological problems is metabolic syndrome. Diagnostic criteria for metabolic syndrome include abdominal obesity, deterioration of lipid profile, elevated blood pressure, elevated fasting blood glucose level, elevated body mass index. In addition to the disorder features, metabolic side effects of antipsychotics are also known. Adverse effects of atypical antipsychotic drugs, which are more effective

in negative symptoms than typical antipsychotics, are associated with deterioration of glucose tolerance, weight gain, and changes in the lipid profile (Akdemir et al. 2006).

In this study, we investigated the relationship between several ECG parameters (i.e. QTc interval, R-R distance, PR interval) and antipsychotic drug use in patients with psychotic disorders. The aim of this study was to determine whether multiple drug use increases the risk of cardiovascular side effects which is one of the important causes of death in patients with psychotic disorders.

Method

In this retrospective study, files of 200 patients who have been followed up with a diagnosis schizophrenia for at least 1 year in the Department of Psychiatry of Çukurova University Faculty of Medicine (CUFM) according to DSM-5 criteria between 2013 and 2019, were evaluated. One patient with hypomagnesemia, 4 with hypokalsemia, 3 with hyponatremia, 3 with hyperpotasemia, 3 with hypothyroidism, and 5 patients with branch blocks were excluded as the QTc interval may be affected by these factors. In addition, 6 patient files with no clinical scales were also excluded. As a a part of routine procedures in our inpatient clinic, all patients had an ECG during their hospitalization. A derived 12-lead ECG with a standard paper velocity of 25 mm / sec was examined. QTc intervals were calculated by Bazett Formula by a single physician. Ethical approval for this study was obtained from the CUFM Non-Interventional Clinical Trials Ethics Committee.

On the first day of hospitalization, the body mass index (BMI) is calculated with the formula kg/m2 in the Inpatient Clinics of Department of Psychiatry of CUFM. Waist circumference is recorded in cm. Blood triglycerides, HDL, glucose, LDL levels are measured after 12 hours fasting by enzymatic methods at 07:00. LDL, HDL, triglyceride, glucose levels are studied in mg/dl. Arterial blood pressure is measured by experienced service nurses with sphygmomanometer and stethoscope. The pressure value when phase 1 korotkoff sound is heard is recorded as systolic and the pressure value when phase 5 korotkoff sound is heard as diastolic blood pressure in mm/hg. In addition, as a routine procedure in our clinic, ECG of each hospitalized patient is taken at the time the patient is admitted to the clinic.

Symptom severity of schizophrenia and psychotic disorders were evaluated with the Positive and Negative Syndrome Scale (PANSS) which has already been present in patient files. Sociodemographic information was obtained by examining the recorded data in patient files.

Cardiological Evaluation

On the morning of hospitalization, 12-lead ECGs were obtained from all patients after a period of at least 12 hours of no caffeine or smoking. In our study, the QTc interval was calculated with the most commonly used method, Bazett formula (QTc => QT/rr) (Bazett 1930). QT interval is measured as the distance from the beginning of the Q wave to the end of the T wave. QT was calculated in all leads due to the variability of the QT interval between the leads (Funck ve Jaillon 1993).

The QT interval includes repolarization and depolarization of the ventricles in the ECG. Ventricular depolarization begins with the Q wave on the ECG, and QT interval ends with the T wave corresponding to repolarization. Since the QT distance is

affected by the heart rate, corrected QT (QTc) is calculated to ensure normalization of the QT interval to 60 beats/min (Moss 1996).

Psychiatric Measure

Positive and Negative Syndrome Scale (PANSS)

This scale was developed to evaluate the general psychopathology and determine the severity of positive and negative symptoms in patients with schizophrenia and other psychotic spectrum disorders. It is a 30-item scale filled by the interviewer. Each item is scored between 1-7. Higher scores indicate increased symptom severity (Kay et al. 1987). In the Turkish validation study, Cronbach's alpha values were 0.71 for the general psychopathology subscale, 0.75 for the positive symptoms, and 0.77 for the negative (Kostakoğlu et al. 1999).

The results of previous studies have been examined to classify the effects of antipsychotic drugs on QTc. After this evaluation, antipsychotic drugs that did not show any effect on QTc when used at therapeutic doses were grouped as ineffective drugs. Those whose effect is less than 10 milliseconds (ms) are classified as 'low effect' (aripiprazole, olanzapine, clozapine, paliperidone, risperidone, sulpiride, flupentixol), those with an effect between 10-20 ms were grouped as 'moderate-effect' (amisulpride, chlorpromazine, haloperidol, quetiapine, ziprasidone) drugs. Those whose effect is longer than 20 ms are classified as highly-effective (pimozide), whereas antipsychotics (zuclopenthixol) with insufficient studies and ECG changes are classified as unknown. (Glassman and Bigger 2001, Haddad and Anderson 2002, Taylor 2003, Meyer et al. 2009). If patient use only one drug they were classified in monotherapy group, otherwise they were listed in multiple drug use group.

Statistical Analysis

Descriptive statistics are given as mean ± standard deviation or median-quartile width according to the distribution of continuous variables. Categorical variables are shown as percentage and number. The participants were divided into two groups as monotherapy and combined therapy of antipsychotics. The normality distribution of the parameters was evaluated by Shapiro Wilks test. When the distribution of data was normal, t-test was used to compare the groups. When distribution was not normal, independent groups were compared using Man Whitney U test. Categorical variables were analyzed by chi-square test. Pearson correlation coefficient was used when non-categorical sociodemographic data and scale scores of patients were normally distributed and the Spearman Rho correlation coefficient for those with no normal distribution. In addition, the significance level and logistic regression analysis results are presented based on approximate relative odds ratio (OR) and 95% confidence interval, Wald, beta values. In simple linear regression analysis, the number of antipsychotics, age, gender were considered as independent variables and they were analyzed by logistic regression method. Critical value p=0.05 was used in the analysis of statistical significance.

Results

The differences between the QTc interval and marital status, place of residence, family history of psychiatric disorder, occupation, suicide attempt, smoking, alcohol and substance misuse were not statistically significant. When the QTc interval and gender

relationship were analyzed, it was found that the QTc interval was significantly longer in women. Table 1 compares the sociodemographic and clinical data of the patients with the QTc interval in ms.

Table 1. Comparison of QTc interval and sociodemographic and clinical data

	QTc interval (Mean± standard deviation) (N)	**p**
Gender		
Female	398.5±25 (81)	<0.001
Male	378.7±35 (94)	
Marital Status		
Single	387.8±31 (127)	0.942
Married	387.4±38 (48)	
Occupation		
Unemployed	389.3±34 (136)	0.272
Employed	382.7±24 (39)	
Location		
City Center	386.1±33 (134)	0.194
Rural	393.7±30 (41)	
Psychiatric disorder in family		
Absent	388.3±31 (72)	
Present	387.6±33 (103)	
Suicide attempt		
Absent	386.9±31 (156)	0.276
Present	395.6±40 (19)	
Cigarette use		
Absent	389±33 (117)	0.513
Present	385.5±31 (58)	
Alcohol use		
Absent	388.1±28 (168)	0.588
Present	381.2±90 (7)	
Drug use		
Absent	389.7±31 (163)	0.067
Present	362.9±45 (12)	

Table 2. Association between QTc interval, R-R distance, PR interval with the potency of antipsychotics on QTc

(ms+sd)	**Group 1 No antipsychotic (N=31)**	**Group 2 Low effective (N=115)**	**Grup 3 Moderate to severe (N=29)**	**F**	**p**	**Comparison between the groups**
QTc	373.7±37.1	387.6±28.8	404.2±36.8	6.8	<0.001	3>2*, 3>1*
RR	809±128.1	781±117.5	774±116.3	0.819	0.88	
PR	158.7 ±31.6	146.7±15.0	158.9±19.3	7.6	0.72	

We compare the potency of the antipsychotics with the QTc interval, the R-R distance and the PR interval (Table 2). The QTc intervals of those using moderate to severe antipsychotic drugs was significantly higher than those using low-effect antipsychotic drugs. There was no statistically significant difference in QTc intervals between those using low-effect antipsychotics and those who are not using antipsychotics. There were no significant difference between the effect of antipsychotics on RR distance and PR interval.

Table 3 compares the number of antipsychotics used with QTc interval, R-R distance, and PR interval. The difference between the QTc interval of those using two or

more antipsychotics and those using monotherapy and those who do not use antipsychotics is statistically significant. There were no statistically significant differences between those using monotherapy and those who do not use antipsychotics. There was no statistically significant difference between the R-R distance and the PR interval and the number of antipsychotics used. Table 4 compares the QTc interval, PR interval, R-R distance with age, duration of disorder, level of education, number of hospitalizations, PANSS total value and subscales. There was a positive correlation between QTc interval and age, PANSS negative, PANSS general psychopathology subscales, and PANSS total score.

Table 3. Comparison of the number of antipsychotics used with QTc interval, R-R distance, and PR interval

(ms+sd)	Group 1 No antipsychotic (N=31)	Group 2 Monotherapy (N=74)	Grup 3 Multiple drug (N=70)	F	p	Comparison between the groups
QTc	373.7±37.1	379.5±23.1	403±34	14.6	<0.001	3>2*, 3>1*
RR	809±128.1	782.5±122.5	776.5±111.3	0.824	0.90	
PR	158.7±31.6	146.2±14.2	152.2±18.5	4.6	0.63	

Table 4. Correlation between QTc interval, R-R distance, PR interval and some clinical and sociodemographic data

	Age	Duration disorder	Level of education	Number of hospitalizations	PANSS Neg	PANSS Pos	PANSS General	PANSS total
QTc interval	**.231***	.061	-.020	-.061	**.192***	.110	**.162***	**.208***
RR distance	-.110	.145	-.099	.015	-.077	-.003	-.128	-.101
PR interval	.092	.107	-.055	.169	-.050	.078	-.114	-.061

Neg: Negative, Pos: Positive, General: General Psychopathology; Statistically significant values are written in bold and indicated with * (p<0.05).

In Table 5, the relationship between QTc interval and age, gender, number of antipsychotics and PANSS total scores were analyzed by linear regression method. The effect of each value on the QTc interval is statistically significant. In our study, hypertension was found in 21 (12%), increased fasting blood glucose levels in 27 (15.4%), increased triglyceride levels in 61 (34.8%), decreased HDL levels in 103 (58.8%), and increased body mass index 61 (34.8%) of 175 patients. Of the 175 patients, 58 (32.6%) were smokers.

Table 5. Linear regression analysis of QTc interval and age, sex, antipsychotic number, PANSS total score

Model	Non-standardized coefficient		Standardized coefficient	t	p
	Beta	SD	Beta		
Constant	356.129	10.981		32.431	<0.001
Age	.858	.166	.326	5.157	<0.001
Gender	-18.922	4.176	-.288	-4.532	<0.001
Number of antipsychotics	13.495	2.896	.299	4.659	<0.001
PANSS Total	.170	.059	.187	2.871	<0.05

Discussion

The most important outcome of this study was that the use of multiple antipsychotics significantly extended the QTc interval. These results suggest that the use of multiple antipsychotics should be avoided in patients with psychotic disorders at risk for cardiac

diseases. Schizophrenia is one of the most common causes of loss of functionality in all diseases. Cross-cultural or cross-country findings show similarity. In addition to mental problems, metabolic diseases, cardiac and pulmonary problems significantly disrupt the daily functioning of patients. Schizophrenia is also a chronic disorder that shortens expected life duration despite increased treatment opportunities (Harvey et al. 2012). Expected life duration in patients with schizophrenia is 20% shorter than in general population. Cardiovascular problems are one of the most common causes of death in schizophrenia patients. Patients with schizophrenia are thought to be 2 times more affected by these problems than the general population (Hennekens et al. 2005). Smoking, deteroiation in lipid profile, hypertension, obesity, diabetes which are risk factors for cardiovascular diseases, are also higher in patients with schizophrenia than in the general population (Doll and Peto 1981). We found hypertension in 11.8% of patients, increased triglyceride levels in 34.3%, decreased HDL levels in 57.9%, increased fasting blood glucose levels in 15.2%, and increased waist circumference in 34.3% consistent with previous studies.

Typical antipsychotics are effective on positive symptoms and cause serious side effects such as extrapyramidal syndrome and tardive dyskinesia. Atypical antipsychotics have less extrapyramidal side effects, they are more effective than typicals on negative symptoms. The vast majority of atypical antipsychotic drugs, which include clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, cause weight gain and metabolic abnormalities that pose a risk on the cardiovascular system (Hennekens et al. 2005).

QTc elongation caused by antipsychotics has been the focus of interest of researchers for many years. Synergistic and additive effects of multiple uses of antipsychotics on QTc have been reported in the literature. QT interval begins with fast sodium channels in ventricular depolarization phase. Potassium, sodium and calcium ions play a role in the repolarization phase (DeBuske 1999). Antipsychotics block hERG (also known as KCNH2) Ik potassium channels, causing prolongation of QT interval. Prolongation of the QTc interval increases the risk of fatal Polymorphic Ventricular Tachycardia, known as Torsades de pointes. Prolonged QTc is associated with increased risk of cardiovascular problems, coronary artery diseases, and sudden cardiac death (Takeuchi et al. 2015).

Previous studies have reported that the addition of aripiprazole or risperidone to clozapine does not significantly extend the QTc interval, but that the addition of sertindol or ziprasidone extends the QTc interval. Publications reporting that the use of multiple antipsychotics extends the QTc interval are also available (Takeuchi et al. 2015). In our study, we grouped antipsychotics as low-effect, moderate-effect, severe-effect and unknown concerning their effects on the QTc interval. Compared to the QTc intervals, antipsychotics with moderate and severe effects on the QTc interval were found to have a longer QTc interval than the group treated with low-effect or unknown antipsychotics. The difference between the groups is significant and consistent with the literature. Although the QTc interval of those using low-effect or unknown antipsychotics is longer than those that do not useantipsychotics, the difference is not statistically significant.

Schizophrenia goes on with recurrent episodes despite treatment and has residual symptoms. Although its superiority is not proven, combined antipsychotic use is prefer-

red by clinicians by 12.9-35% (Van Noord et al. 2011). 40% of patients in our study use combined antipsychotic treatment.

Stölbellger et al. (2005) compiled studies about adults without cardiovascular disease and showed that the QTc interval can be extended by exacerbation of psychosis regardless of drug use. In a study comparing psychotic patients in remission and acute psychotic episodes, the QTc interval of patients in remission was calculated as 403 ms while the QTc interval of patients experiencing acute psychotic episodes was calculated as 453 ms. Many studies have shown that the elongation in the QTc interval correlates with increased drug dose. Male gender and being older than 65 years of age were found to be risk factors for sudden cardiac death. Although QTc elongation with sulpiride has been shown to occur, QTc elongation has not been associated with the use of amisulpride or zuclopenthixol (Stollberger et al. 2005). Harrigan et al. (2004) found that the average QTc interval was prolonged by 1.7 ms with olanzapine, 3.6-3.8 ms with risperidone, 7 ms with haloperidol, 6 ms with quetiapine, and 17 ms with ziprasidone. Di Sciascio et al (2011) showed that the QTc interval increased significantly after a second antipsychotic was added to antipsychotic treatment, but there was no significant difference in patients using monotherapy by exchanging antipsychotics.

In our study, the mean QTc interval of two or more drug groups was shown to be significantly longer than the mean of those using monotherapy and those who do not use antipsychotics. The mean QTc interval of patients using monotherapy was 5.8 ms longer than those who did not use antipsychotics, but the difference was not statistically significant. The difference between the mean of the QTc intervals is higher than the sum of the expected QTc elongation with any two antipsychotics, suggesting that they act synergistically.

Antipsychotics can cause tachycardia (shortening of distance between R-R waves in ECG), sudden death, orthostatic hypotension as a result of anticholinergic and Alpha 1 antagonistic effects. (Michelsen and Meyer 2007). 2.7% of patients with antipsychotic use were found to have elongation in the PR interval (Kinagi et al. 2014). We compared the number of antipsychotics used and the RR distance and PR interval. There were no statistically significant differences between the groups. The cause of this condition may be that patients with tachycardia used additional medications and therefore excluded from the study.

The upper limits of the accepted QTc interval are different in men and women. This value is 440 ms for men and 470 ms for women (Taylor 2003). QTc interval greater than 500 ms is a definite risk factor for arrhythmia (Botstein 1993). After puberty, women have longer QTc intervals than men. There is an increase in QTc intervals for both genders during the post-puberty youth years. This increase lasts until the age of 60 and then the QTc interval is shortened (Vink et al. 2017). In our study, the mean QTc interval was 398.5 ms in women and 378.7 ms in men. A statistically significant and positive relationship was observed between the QTc interval and the age. No significant correlation was found between ECG parameters (R-R distance and PR interval) and sociodemographic data and PANSS scores. This may be the result of patients with tachycardia were excluded from the study because of using antiarrhythmic drugs.

Akbarzadeh et al (2013) evaluated smoking and non-smoking cases in terms of pulse, QTc interval dispersion, and QT dispersion. Although there were studies in the

literature in the opposite direction, there was no significant difference between smoking and the parameters. In both groups, it was determined that the parameters changed significantly after 10 minutes of smoking a single cigarette. In our study, 32.6% of the patients were smoking, which is an important risk factor for cardiovascular diseases, but no significant effect on QTc was found. Conflicting results have been found in the literature, leading to uncertainty in interpreting the effect of smoking on QTc. Extensive studies are needed to clarify this issue.

We did not find any significant effect of gender, age, level of education, occupation, place of residence and number of hospitalizations on the QTc interval. These results suggest that the effects of antipsychotics on QTc interval and the use of combined antipsychotics play an important role in cardiovascular diseases and arrhythmia, which are the most common causes of death in schizophrenia. In our study, the prolongation of the QTc interval with the use of combined antipsychotics was found to be greater than the sum of the expected average QTc interval prolongation of each drug in monotherapy. This data suggests that combined antipsychotic use may have a synergistic effect on QTc rather than additive effect.

Retrospective design, selection of all patients from inpatients in a tertiary healthcare facility, inability to monitor blood levels of antipsychotic drugs, absence of ECGs taken before hospitalization, and the mechanism of action of different antipsychotic drugs on QT interval could not be clarified are limitations of our study. Drugs have been given by nurses to ensure no additional drugs are used. In future studies, the addition of dispersion to QTc measurements, observation of autonomic nervous system effects such as heart rate variability, investigation of the effects of antipsychotics on the cardiovascular system will provide support to the literature.

References

Akbarzadeh MA, Yazdani S, Ghaidari ME, Asadpour PM, Bahrololoumi BN, Golabchi A (2014) Acute effects of smoking on QT dispersion in healthy males. ARYA Atheroscler, 10:89-93.

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, Fifth edition. Arlington, VA, American Psychiatric Association.

Akdemir A, Örsel S, Karaoğlan A (2006) Antipsikotiklere bağlı metabolik yan etkiler. Klinik Psikiyatri Dergisi, 9:5-16.

Balcıoğlu İ (1999) Antipsikotiklerin yan etkileri. In Depresyon, Somatizasyon ve Psikiyatrik Aciller Sempozyumu Kitabı (Ed E Eker):157-168. İstanbul, Cerrahpaşa Tıp Fakültesi Yayınları.

Bazett HC (1930) An analysis of time relations of electrocardiograms. Heart, 7:353–367.

Botstein P (1993) Is QT interval prolongation harmful? A regulatory perspective. Am J Cardiol, 72:50–52.

Clark RE, Bartels SJ, Mellman TA, Peacock WJ (2002) Recent trends in antipsychotic combination therapy of schizophrenia and schizoaffective disorder: Implications for state mental health policy. Schizophr Bull, 28:76-84.

Chong SA, Mahendran R (2001) Cardiac effects of psychotropic drugs. Ann Acad Med, 30:625-631.

Czekalla J, Beasley CM, DeIlva MA, Berg PH, Grundy S (2001) Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis. J Clin Psychiatry, 62:191-198.

Di Sciascio G, Calo S, Amodio G, D'onofrio S, Pollice R (2011) The use of first generation versus second generation antipsychotics as add-on or as switch treatment and its effect on QTC interval: The Italian experience in a real-world setting. Int J Immunopathol Pharmacol, 24:225–230.

Doll R, Peto R (1981) The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. J Natl

Cancer Inst, 66:1191-1308.

DuBuske LM (1999) Second-generation antihistamines: The risk of ventricular arrhythmias. Clin Ther, 21:281–295.

Funck-Brentano C, Jaillon P (1993) Rate-corrected QT interval: Techniques and limitations. Am J Cardiol, 72(6):17B-22B.

Glassman AH, Bigger JT Jr. (2001) Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry, 158:1774–1782.

Haddad PM, Anderson IM (2002) Antipsychotic - related QTc prolongation, torsade de pointes and sudden death. Drugs, 62:1649–1671.

Harrigan E, Miceli J, Anziano R, Watsky E, Reeves K, Cutler N et al. (2004) A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. Int Clin Psychopharmacol, 24(1):62-69.

Harvey PD, Strassing M (2012) Predicting the severity of everyday functional disability in people with schizophrenia: Cognitive deficits, functional capacity, symptoms, and health status. World Psychiatry, 11(2):73-79.

Hennekens CH, Hennekens AR, Hollar D, Casey DE (2005) Schizophrenia and increased risks of cardiovascular disease. Am Heart J, 150:1115-1121.

İlhan A, Özcan ME, Tuncer C, Kali S, Boztepe V, Pekdemir H (1999) Antipsikotik kullanımının ventriküler repolarizasyon parametreleri üzerine etkileri. Klinik Psikofarmakol Bulteni, 9:112-117.

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull, 13:261-276.

Kinagi S, Nagangouda N, Mahesh M (2014) ECG changes in patients on antipsychotics medication. J Evol Med Dent Sci, 3(62):13655-13661.

Kostakoğlu E, Batur S, Tiryaki A, Göğüs A (1999) Pozitif ve negatif sendrom ölçeğinin (PANSS) Türkçe uyarlamasının geçerlik ve güvenilirliği. Türk Psikoloji Dergisi, 14:23-32.

Kumsar N, Dilbaz N (2012) Practices of antipsychotic polypharmacy in schizophrenia: a review. Journal of Neurobehavioral Science, 1:28-37.

Michelsen JW, Meyer JM (2007) Cardiovascular effects of antipsychotics. Expert Rev Neurother, 7:829-839.

Moss AJ (1993) Measurement of the QT interval and the risk associated with QTc interval prolongation: A review. Am J Cardiol, 72:23-25.

Moss AJ (1996) Correct the QT interval correctly: QTc should be expressed in the same unit as the QT interval. Pacing Clin Electrophysiol, 19:881–882.

Meyer JM, Loeber AD, Schweizer E (2009) Lurasidone: A new drug in development for schizophrenia. Expert Opin Investig Drugs, 18:1715–1726.

Özalmete ÖA, Özalmete OE, Ceylan ME, Sevim ME (2009) Şizofreni tedavisinde çoklu ilaç kullanımının nedenleri. Klinik Psikofarmakol Bulteni, 19:68-74.

Passman R, Kadish A (2001) Polymorphic ventricular tachycardia, long QT syndrome, and torsades de pointes. Med Clin North Am, 85:321-341.

Stollberger C, Hubera JO, Finsterer J (2005) Antipsychotic drugs and QT prolongation. Int Clin Psychopharmacol, 20:243-251.

Takeuchi H, Suzuki T, Remington G, Uchida H (2015) Antipsychotic polypharmacy and corrected QT interval: A systematic review. Can J Psychiatry, 60:215-222.

Taylor DM (2003) Antipsychotics and QT prolongation. Acta Psychiatr Scand, 107:85–95.

Van Noord C, Sturkenboom MC, Straus SM, Witteman JC, Stricker BH (2011) Noncardiovascular drugs that inhibit hERG-encoded potassium channels and risk of sudden cardiac death. Heart, 97:215–220.

Vink SA, Sally ABC, Arthur AMW AB, Nico AB (2017) Effect of age and gender on the QTc-interval in healthy individuals and patients with Long-QT syndrome age and gender on QTc interval. Trends Cardiovasc Med, 28:64-75.

Authors Contributions: All authors attest that each author has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript.
Ethical Approval: The study was approved by the Local Ethics Committee. Written informed consent was obtained from all participants.
Peer-review: Externally peer-reviewed.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study has received no financial support.