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Impact of Psychotropic Drugs on QT Interval Dispersion in Adult Patients

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Abstract

Background: Drug-induced increase in QT dispersion has been associated with potentially fatal ventricular arrhythmias. Little is known about the use of psychotropic substances, alone or in combination with other drugs on QT dispersion.

Objectives: To evaluate the impact of psychotropic drugs on QT interval dispersion in adults.

Methods: An observational cohort study was designed involving 161 patients hospitalized from an emergency department at a tertiary hospital, divided into psychotropic users or non-users. Demographic, clinical, laboratory data and drugs used on a regular basis were collected on admission, in addition to 12-lead electrocardiogram with QT dispersion measurement.

Results: QT dispersion was significantly higher in the psychotropic user group compared to non-users (69.25 ± 25.5 ms vs. 57.08 ± 23.4 ms; p = 0.002). The QT interval corrected by Bazzett formula was also higher in the psychotropic drugs user group, with statistical significance. (439.79 ± 31.14 ms vs. 427.71 ± 28.42 ms; p = 0.011). A regression analysis model showed a positive association between the number of psychotropic drugs used and QT interval dispersion, with r = 0.341 and p < 0.001.

Conclusions: The use of psychotropic drugs was associated with increased QT dispersion and this increase was accentuated, as the number of psychotropic drugs used was higher. (Arq Bras Cardiol. 2014; 102(5):465-472)

Keywords: Electrocardiography; Cardiovascular diseases; Torsades de Pointes; Ventricular fibrillation; Death, Sudden.

Introduction

The perception and interest in unexpected death are secular. Sudden cardiac death received its first scientific definition in 1707 with Giovanni Lancisi[1], in his work *De mortibus subitaneis*. The most prevalent cause of sudden death is coronary artery disease, followed by cardiomyopathies and primarily electrical cardiac causes, especially the long QT syndrome, either congenital or acquired – the latter induced by drugs, in most cases. Data indicate that QT prolongation is a major contributor to the genesis of polymorphic ventricular tachycardia or torsades de pointes, even in structurally normal hearts[2]. This prolongation is not a pharmacological property attributed only to antiarrhythmic drugs. A recent American cohort showed that 5 million Americans are exposed to drugs that prolong the QT interval, with antibiotics and psychotropic drugs, especially antipsychotics, being the most common[2,3].

However, not all drugs that prolong the QT interval increase the risk of ventricular arrhythmias[4]. It is currently accepted that the electrical disturbance genesis is related to blockage of ionic currents of potassium channels, notably in M cells of the human ventricle, with subsequent QT interval prolongation and dispersion (QTD) on the electrocardiogram (ECG), closely related to the onset of torsades de pointes[4-7].

The concept of "QT interval dispersion", defined as the difference between the maximum and minimum QT interval measured at the 12-lead ECG, was introduced by Higham and Campbell[8] in the early 1990s. Initially proposed as an index of electrical instability, it represents the expression of physiological regional variation of myocardial excitability recovery.

Since then, the analysis of QTD was accepted as a noninvasive method for the detection of ventricular repolarization heterogeneity, being a marker of arrhythmogenesis, especially in the presence of an ischemic substrate and drug-induced ventricular arrhythmias. Additionally, there have been studies associating it as a prognostic index in heart failure and hypertrophic cardiomyopathy[8,9].

Little is known about the impact on QTD with the specific use of antipsychotics and its associations with other drugs acting on the central nervous or cardiovascular system.

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Methods

Study characterization

The present was a prospective, multicenter, observational cohort study, carried out in a private hospital in Rio de Janeiro, with an open emergency room, from September 2009 to January 2013. The research protocol was approved by the Institutional Research Ethics Committee (REC) (number 148/09).

Study population

Of the total number of patients admitted at the institution, necessarily admitted through the emergency room, 194 met the initial eligibility criteria for the study. After careful evaluation, 33 patients were excluded and population sample comprised 161 patients.

The subjects of the investigation were not submitted to any interventions resulting from the study. A liability form was completed by the main investigator on the use of information contained in medical records and database, thus making it unnecessary for patients to sign the Informed Consent form.

Inclusion criteria

The following inclusion criteria were used: age > 40 years; emergency care and subsequent hospital admission for more than 24 hours, regardless of the reason for admission; performance of ECG with at least 12 leads in the emergency room; performance of basic complementary laboratory tests (glucose, potassium and magnesium).

Exclusion criteria

The exclusion criteria were: patients with artificial cardiac pacing, either temporary or permanent; patients with congenital long-QT syndrome; patients with calcium metabolism alterations; patients with atrial fibrillation of any cause and/or frequent ventricular arrhythmia; patients using antiemetics, prokinetics and antibiotics that alter ventricular repolarization.

According to the study design and construction of methodology, the use of concomitant drugs that would influence QT interval and its dispersion was cause for careful analysis. Thus, we excluded patients on continuous use of other drugs that prolong the QT interval, especially domperidone, bromopride and metoclopramide.

The sample population was stratified into two groups according to the use or nonuse of psychotropic drugs. Group 1 (G1) consisted of patients who were not taking psychotropic drugs, while Group 2 (G2) consisted of patients taking psychotropic drugs.

Investigation procedures

Demographic data, present and past medical history, information on regular use of drugs and diagnostic hypotheses were collected on admission. Any drug that had more than seven days of uninterrupted use before hospital admission was defined as continuous use.

All antipsychotics, anticonvulsants, antidepressants and drugs used in dementia syndromes used by the sample population were taken into account. All drugs subject to classification according to Vaughan Williams were considered antiarrhythmic drugs.

A 12-lead ECG was performed on patient admission, while still in the emergency department, being a routine procedure for any patient older than 40 years of age, symptomatic or not (hospital accreditation process protocol by the Joint Commission).

Laboratory assessment

Laboratory evaluation consisted of measurements of plasma glucose, potassium and magnesium, also assessed on admission. Glycemia levels did not take into account any criterion of fasting. Calcium ion was measured when requested by the emergency team. A Vitros 250 analyzer (Johnson & Johnson, New Brunswick, USA) was used for biochemical measurement of magnesium and glucose, with the dry-chemical method. The measurements of potassium and calcium ion were performed using a Gem Premier 3000 analyzer (Instrumentation Laboratory, Bedford, USA) using the selective electrode method. Normal values of these tests were determined according to the institution protocols.

QT dispersion measurement

Each patient's ECG was recorded in three-channel conventional ECG equipment (HP - Hewlett Packard Company, Palo Alto, United States) with recording speed of 25 mm/s and recording of the 12 leads considered as conventional (D1, D2, D3, aVR , aVL, aVF, V1, V2, V3, V4, V5, V6). ECGs that did not have at least nine leads with a QT interval technically capable of being measured were excluded. The QT interval is measured from the first deflection of the QRS complex to the end of the T wave, defined as the meeting point of the descending branch of T to the isoelectric line. In the presence of a U wave, the end of the T wave is considered as the base of deflection formed by the two waves. The presence of bundle branch block did not exclude patients from the study.

Cardiac cycles succeeding early beats (extrasystoles) were abandoned[10]. "QT interval dispersion" is defined as the difference between the maximum and minimum QT interval measured on the 12-lead (at least nine leads).

The digitized ECGs were analyzed with the help of Preview® software, version 5.5.2 (719.25) (Apple Inc ®, Cupertino, USA). Tracings were submitted to a 300% magnification and QT measurement was made digitally. All ECG tracings were digitalized with a 200 dpi resolution and saved in JPEG format to allow use of the Preview® program measuring tool. ECGs were captured by an Epson Stylus TX105 scanner (Long Beach, United States) and amplified during digitalization.

However, in daily clinical practice, the measurements of QT interval and QTD can be performed simply with the aid of a triplicate magnifying glass[8,9]. Two QT interval and QTD measures were performed by four examiners blinded to the clinical characteristics of patients and the arithmetic mean of the values were considered for the analysis.

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Several methodologies have been described for the measurement of QT interval [10, 11]. In this study, we used the difference between the second largest and the second smallest QT interval (minimum of nine leads)[10,11] to measure QTD, a methodology also used by Campbell et al[12]. Studies can be found in the literature[13,14] that used the standard measure of QTD or that corrected by heart rate. In the present study, we used the default QT dispersion.

Statistical Analysis

Univariate, bivariate, covariance and multivariate analysis were used for the statistical analysis of the data.

Univariate analysis was used for the description of the studied variables, using simple frequency and percentage tables for discrete variables and mean (minimum-maximum), and graphical representation of histograms and box-plots for continuous variables. Bivariate analysis was used for discrete variables, using contingency tables and chi-square, Fisher exact and ML chi-square tests, when indicated; the Student's *t* test, paired or not, and Mann-Whitney test were used for continuous variables,.

Levene's test was used to test whether the studied samples had homoscedasticity, that is, whether they had the same variance. A significant F ratio in this test indicates that the differences in mean, or effects, probably exist between the groups. In the case of heteroscedastic samples, non-parametric tests were used according to the characteristics of the studied variable. Welch and Brown-Forsythe tests were used in the assessment of the mean magnesium levels between groups.

Analysis of covariance was used with regression models and analysis of variance (ANOVA), using the partial ETA squared ($\eta 2$), which allows inferring what proportion of the total variance is attributed to the studied variable (effect size). Multivariate analysis was used from a log-linear model for discrete variables aiming to detect and resolve the confusion effects. Pearson's correlation coefficient was used to demonstrate the correlation between two or more variables. The ANOVA model was chosen for the analysis of variance between the studied groups.

Results

Sample population

Of a total of 194 initially selected patients, 161 met the inclusion criteria and constituted the sample population of this study. The most prevalent cause of exclusion was the presence of atrial fibrillation (11) in the electrocardiogram, followed by artificial cardiac stimulation (7), calcium replacement without the measured serum level of calcium ion (5), frequent ventricular extrasystoles (4), incapacity of analyzing the ECG due to technical problems (3), and documented hypercalcemia.

The sample population (n = 161) was stratified into two groups according to the use or nonuse of psychotropic drugs: G1 consisting of patients who did not use psychotropic drugs (n = 85 patients) and G2 consisting of users of psychotropic drugs (n = 76 patients).

The reasons for hospital admission of patients are shown in Table 1, per group. There was no statistical significance between the groups.

Drugs used by the sample population

Tables 2 and 3 show the frequency of psychotropic drugs and antiarrhythmic drugs used by the sample population. This use may have been isolated or in associations. None of the patients from the sample population used digitalis.

Clinical and epidemiologic characteristics of the sample population

Female gender were more prevalent in G2, with statistical significance (p = 0.04). We sought to determine whether, in G2, the gender difference would have an impact the QTD, as there was no difference between men and women regarding psychotropic drug use (p = 0.642). There was a positive correlation between age and the use of psychotropic drugs.

The prevalence of hypertension, diabetes mellitus and known coronary artery disease showed no statistically significant difference between G1 and G2.

Regarding the laboratory variables, all patients (n = 161) had serum potassium, magnesium and glucose levels measured on admission at the emergency service, with no statistical difference between the two groups. The study excluded patients with hyper- and hypocalcemia. It is noteworthy that plasma glucose levels were not measured in fasting. Levene's test was used to better understand the behavior of variance in the two groups.

Therefore, glucose and potassium showed a homoscedastic distribution, whereas magnesium had a heteroscedastic distribution, after using the appropriate statistical test for each situation. The results are shown in Table 4.

QT interval dispersion behavior

QTD was significantly higher in the group of psychotropic drug users compared to non-users (p = 0.002). The QT interval corrected by the Bazett's formula was also higher in the group using psychotropic drugs, with statistical significance (p = 0.011), as shown in Table 5. The variance was homogeneous in QTD, in the corrected QT interval and heart rate between the groups.

The analysis of covariance between age and use of psychotropic drugs was performed aiming to determine the adjusted mean of the QTD. As measure of analysis of variance, $\eta 2$ was used. After adjusting the mean (G2 = 68.38 ± 8.11 milliseconds - ms and G1 = 57.85 ± 7.22 ms), the difference between the groups remained significant (p = 0.009).

Analysis of use of multiple psychotropic drugs on QT dispersion

In the sample population, 85 patients were not taking any psychotropic drugs, 52 used one drug, 16 patients used two drugs simultaneously, three patients used three drugs, four used four psychotropic drugs and one patient in the study used five psychotropic drugs simultaneously.

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Table 1 – Distribution of groups according to the reasons for hospital admission

Reasons for hospital admission	Total	Group 1 n (%)	Group 2 n (%)	Chi-square
Orthopedic surgical admissions	96	51 (60)	45 (59.21)	p = 0.19
Admissions for general and urological surgery	32	20 (23.53)	13 (17.11)	p = 0.065
Pulmonary sepsis	21	8 (9.41)	12 (15.79)	p = 0.085
Urinary sepsis	12	6 (7.06)	6 (7.89)	p = 0.32
Total	161	85 (100)	76 (100)	

Table 2 – Psychotropics used by the sample population

Salt name	Patients using it	Salt name	Patients using it
Haloperidol	1	Phenobarbital	1
Chlorpromazine	1	Phenytoin	2
Levomepromazine	3	Lamotrigine	2
Risperidone	3	Carbamazepine	4
Clozapine	1	Oxcarbazepine	2
Quetiapine	23	Gabapentin	6
Olanzapine	2	Valproic acid	4
Ziprasidone	0	Topiramate	2
Aripiprazole	0	Venlafaxine	4
Promethazine	3	Memantine	7
Amitriptyline	3	Mirtazapine	4
Imipramine	1	Duloxetine	3
Clomipramine	2	Fluoxetine	3
Doxepin	1	Paroxetine	1
Desipramine	0	Sertraline	4
Nortriptyline	1	Citalopram	6
Trazodone	1	Citalopram	3
Bupropion	2	Donepezil	2
Maprotiline	1	Rivastigmine	4
Nefazodone	0	Galantamine	1

A linear regression model showed a positive association between the number of psychotropic drugs used and QTD, with r = 0.341. (Chart 1)

The intensity of the linear association between variables was quantified. Pearson's linear correlation showed a positive correlation between the number of psychotropic drugs and patient age in QTD (Table 6). In the regression model, when the data are analyzed together, R = 0.329.

To better understand the association between these two variables in QTD, a regression model was proposed, followed by an ANOVA model, to allow the measurement of the adjusted Beta of the number of psychotropic drugs and age, with QTD being the dependent variable.

When the coefficients are adjusted, only the number of psychotropic drugs shows statistical significance with QTD (p <0.001).

Of the original sample population, the impact of concurrent use of psychotropic and antiarrhythmic drugs was evaluated, compared to the isolated use of antiarrhythmics. Table 3 details the type of antiarrhythmic drug used according to the classification of Vaughan Williams, with no statistical difference between the studied subgroups. The combined use of both classes of drugs showed a statistically significant increase in the QT interval. However, there was no statistical difference in QTD between the two subgroups (Table 7).

Discussão

Aiming to assess the impact of psychotropic drug use on QTD, it was necessary to study separately the clinical and demographic variables, identifying the isolated and combined action of these drugs with other cardiovascular action drugs.

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Table 3 – Antiarrhythmic drugs used by the sample population

Vaughan-Williams	Class I	Class II	Class III		Class IV		Total
	----	Beta-blockers	Amiodarone	Sotalol	Diltiazen	Verapamil	
Psychotropics + Antiarrhythmics	0	9	6	1	4	0	20
Antiarrhythmics	0	7	4	1	2	1	15

Table 4 – Demographic, clinical and laboratory data

Variable	G1 (n = 85)	G2 (n = 76)	Statistical test	p value
Age (years), mean ± standard deviation	67.68 ± 12.68	74.43 ± 11.37	t = 3.540	0.001
Male gender, %	50.60	34.20	X^2 = 4.395	0.04
Female gender, %	49.40	65.80		
SAH, %	40	39.50	X^2 = 0.005	1
DM, %	25.90	23.70	X^2 = 0.104	0.885
CAD, %	21.20	13.20	X^2 = 1.796	0.214
Potassium, mean ± standard deviation (mEq/L)	4.29 ± 0.55	4.31 ± 0.69	F = 0.493	0.852
Magnesium, mean ± standard deviation (mg/dL)	1.88 ± 0.21	1.95 ± 0.34	F = 6.444*	0.109
Glycemia, mean ± standard deviation (mg/dL)	115 ± 40	123 ± 46	F = 1.194	0.191

* Heteroscedastic sample. SAH: systemic arterial hypertension; DM: diabetes mellitus; CAD: coronary artery disease; F: Levene F ratio.

Table 5 – Electrocardiographic data and behavior of QT interval dispersion

Variable	Group 1 (n = 85)	Group 2 (n = 76)	t Test
			p value
QT interval dispersion, mean ± standard deviation (ms)	57.08 ± 23.4	69.25 ± 25.5	0.002
Corrected QT interval, mean ± standard deviation (ms)	427.71 ± 28.42	439.79 ± 31.14	0.011
Heart rate, mean ± standard deviation (bpm)	79 ± 15	77 ± 18	0.379

Over the past 25 years, the QTD has been studied by several authors in different clinical scenarios, in normal subjects and patients with heart disease. Tran et al[15] in a study that evaluated the influence of age and sex on QTD, concluded that estrogen, athought it does not change the QT interval, significantly reduces its dispersion. In a healthy population, Alici et al[16] also confirmed these findings. In the population evaluated in this study, the results were similar.

The use of psychotropic drugs is more common in elderly women[17,18] and this population had a significantly higher number of women in G2.

In this context, we expected to find a higher number of females in the group of psychotropic drug users. For this reason, the QTD was analyzed separately in men and women in the group of psychotropic drug users and it was greater in men (71.15 ± 26.91 ms) than in women (68.26 ± 24.96 ms), with no statistical significance. It is known that in the age range of the female population, estrogen protection is not as present any more. Thus, other mechanisms were studied to understand this phenomenon.

Ebert et al[19] demonstrated in an animal model that ionic currents in females, specifically in potassium channels, are significantly smaller than in males of the same species of rats. This effect is accentuated in the presence of class III antiarrhythmic drugs, increasing the QTD. Therefore, elderly women are particularly susceptible to changes in the QT interval and this fact should be considered when prescribing psychotropic drugs.

Regarding comorbidities found in the population, there was no statistical difference between the groups of non-users and users of psychotropic drugs on the prevalence of hypertension, diabetes mellitus and coronary artery disease. There was a high prevalence of these comorbidities in this population, respectively 60.2%, 24.8% and 17.4%. This may be related to the age of the sample, as well as the patient selection method, carried out in the emergency room. The profile of emergency patients and institution alignment explain the high number of orthopedic surgical patients. It is noteworthy that no patient was admitted for acute coronary syndrome, which is therefore, not a bias.
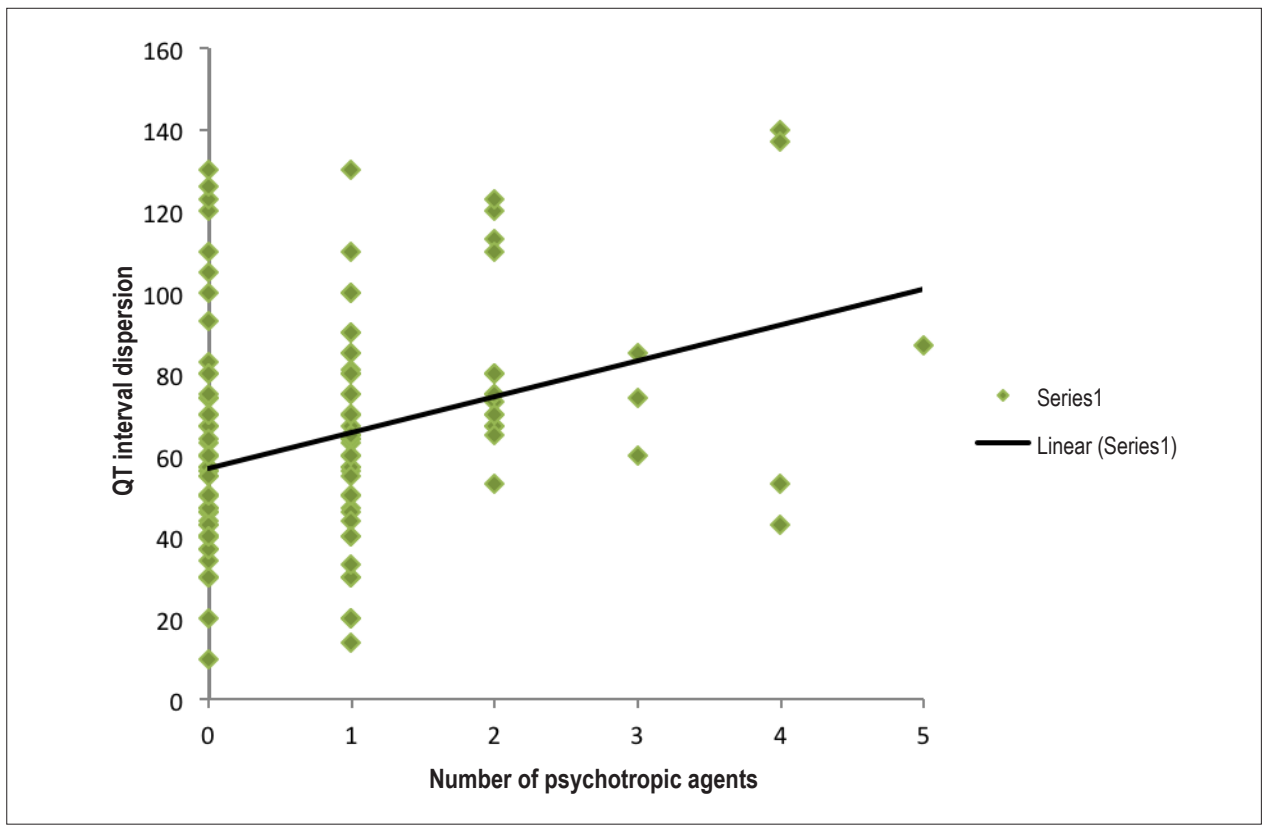
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Chart 1 – *Correlation between number of psychotropic agents and QT interval dispersion. r = 0.341, p value < 0.001.*

Table 6 – Pearson's linear correlation between the studied variables

	Number of psychotropic agents	Age	Heart rate	Potassium	Glucose	Magnesium
Pearson's	0.341	0.177	-0.103	0.057	-0.054	0.095
p value	< 0.001	0.024	0.195	0.471	0.495	0.232

Table 7 – Impact of concurrent use of psychotropic agents and antiarrhythmic drugs vs. isolated use of antiarrhythmic drugs

Analysis of subgroups	Sample (n. of patients)	QT Interval	p value	QT dispersion	p value
Psychotropic + antiarrhythmic drugs	20	445.1 ± 23.77	0.023	63.55 ± 21.11	0.715
Antiarrhythmics	15	421.7 ± 24.01		66.60 ± 23.22	

It is also worth mentioning that the doses used were not considered, as it was not considered reliable information, either due to the patient's underlying disease or the frequent presence of caregivers with little information about the drugs being used.

This factor, together with the large number of users of domperidone, bromopride and metoclopramide in continuous use justifies the extended time of patient selection, aiming at attenuating a possible selection bias.

In the present study, we observed a positive correlation between use of psychotropic drugs and increased QTD at the ECG. There was also a positive correlation between age and QTD. The population studied had a minimum age of 40 years; however, in practice, both groups had mean age > 65 years (G1 = 67.68 ± 12.68 years and G2 = 74.43 ± 11.37 years). The use of psychotropic drugs increases with age, according to data collected by Maia et al[17], similarly to the sample studied here. After adjusting for age, as well as analyzing separately the influence of age and the use of psychotropic drugs on QTD, it was observed that only the use of psychotropic drugs persisted with a statistically significant difference.

Other authors also confirmed these findings. Mangoni et al[20] demonstrated that age has no association with QTD. In the present sample, both the use of psychotropic drugs and the number of psychotropic drugs had a positive correlation with QTD. Of the 76 patients in the psychotropic user group, 24 used a combination of more than one psychotropic drug, corresponding to 31.5% of the group. Thus 114 uses were documented, with the most frequent drug being Quetiapine (20%).

Dispersion values > 60 ms were found in the group using psychotropic drugs, which, in most studies performed to date, are associated with increased cardiovascular death. The Rotterdam Study[21] evaluated a cohort of 2,358 men and 3,454 women during a mean period of four years and observed that the presence of QTD > 60 ms was associated with a 2.5-fold higher risk of cardiac death, 1.9-fold higher risk of sudden death and a 40% higher risk of overall death than in the group with QTD <60 ms.

In our study, after adjusting for age, the mean QT interval dispersion was 57.85 ± 7.22 ms in the group of non-users and 68.38 ± 8.11 ms in the group of psychotropic drug users, confirming the risk involved in using these drugs.

It is noteworthy that digitalization, followed by enlargement of electrocardiographic recordings, allowed a high level of resolution, enabling a manual, easy, quick and effective acquisition of the QT interval and its subsequent dispersion, with negligible interobserver variation.

Thus, the QTc interval and its dispersion should be thoroughly investigated in the general population, in outpatient, as well as surgical and emergency settings[22,23]. Health professionals involved in drug prescription and monitoring of patients taking psychotropic drugs, especially the elderly, should routinely include the ECG in the diagnosis routine of this population, in addition to carefully assess the combination of drugs used.

Conclusion

In the sample population studied, the use of psychotropic drugs, used alone or with other drugs, is associated with increased QT interval dispersion. The greater the number of psychotropic drugs used, the greater the QT dispersion. There was a positive correlation between the number of psychotropic drugs used per patient and increased QT dispersion. The simultaneous use of psychotropic and antiarrhythmic drugs is associated with the increase in the corrected QT interval, but not QT dispersion, when compared to the subgroup of patients that use only antiarrhythmic drugs.

Author contributions

Conception and design of the research: Claudio BQ, Albuquerque DC; Acquisition of data: Claudio BQ, Penna F, Konder MT, Celoria BMJ, Souza LL; Analysis and interpretation of the data: Claudio BQ, Costa MAN, Penna F, Celoria BMJ, Souza LL, Schneider RS, Albuquerque DC; Statistical analysis: Claudio BQ, Pozzan R, Albuquerque FN, Albuquerque DC; Writing of the manuscript: Claudio BQ, Albuquerque DC; Critical revision of the manuscript for intellectual content: Claudio BQ, Costa MAN, Albuquerque DC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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