ORIGINAL RESEARCH

PREVALENCE OF VENTRICULAR REPOLARIZATION ABNORMALITIES IN SUBJECTS ON PSYCHOTROPIC DRUGS IN NIGERIA: A CROSS-SECTIONAL COMPARATIVE STUDY

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Abstract

Introduction: Patients on psychotropic medications are at high risk of cardiac adverse effects and sudden death. However, the adverse effect burden of these drugs is grossly underreported in most African countries including Nigeria. The study aimed to evaluate the prevalence of ventricular repolarization electrocardiographic abnormalities (QTc, QTd, TpTe, and TpTe/QT) among patients taking psychotropics.

Methods: This study was conducted among 150 psychiatric patients on psychotropics and 75 controls. All subjects had resting electrocardiogram. QTc was determined using Bazett formula, QT dispersion was determined by subtracting shortest from longest QT in a 12-lead ECG, and Tpeak to Tend was measured from Tpeak to Tend in V5.

Results: The prevalence of prolonged QTc and QT dispersion in patients were significantly higher than the controls (24.7% vs. 4%; p<0.001 and 17.3% vs. 1.3%; p<0.001 respectively). The mean QTc and QT dispersion were significantly higher than the control group (418.5±28.1 ms vs 390.4±21.9ms; p<0.001 and 53.17±23.1ms vs. 43.7113.4ms; p=0.001 respectively). There was no statistically significant difference in the mean TpTe and TpTe/QT in both study groups.

Conclusion: Psychotropic drugs influence QTc and QT dispersion prolongation. This study showed that chronic use of psychotropics is associated with increased risk of ventricular repolarization abnormalities among this population.

Key words: **Keywords:** Psychotropic drugs, ventricular repolarization, sudden cardiac death, Adverse effects, QTc, QTd, TpTe

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INTRODUCTION

Globally, there is a high burden of cardiovascular disease among psychiatric patients on psychotropic medications.[1-3] Psychotropic medications which play an important role in the management of various forms of mental illness have been associated with cardiac adverse effects.[4] Some of the cardiovascular adverse effects include orthostatic hypotension, tachycardia, atrioventricular nodal delay, arrhythmias, prolonged QTc, myocarditis, cardiomyopathy, and sudden cardiac death.[4] Of particular interest is sudden cardiac death (SCD) which has long been established to be associated with antipsychotics especially phenothiazines.[5,6] Cardiac arrhythmia such as torsades de pointes has gained increasing concern over the years as an important factor in sudden death among patients on antipsychotics because some antipsychotics and antidepressants prolong QTc interval.[5] Beyond QT interval prolongation, other electrocardiogram (ECG) markers associated with an increased risk of SCD are QT dispersion (QTd), T-peak to T-end (TpTe) interval, and TpTe/QT.[6]

The QT interval is the interval from the beginning of the Q wave to the end of the T wave. As a result of the variability of QT value with heart rate (varies inversely with heart rate), various group-derived formulae are used to correct/normalize the QT value (QTc). The Bazett formula is the most popular and commonly used of them all.[7] QT dispersion (QTd) is the difference between the longest (QTmax) and the shortest (QTmin) QT intervals within a 12-lead ECG. It has also been shown as a good predictor of sudden cardiac death.[6]

T-peak to T-end (TpTe) refers to the interval from the peak of the T wave to its end on the 12-lead ECG. This is a measure of transmural dispersion of repolarization in the left ventricle (LV) and when prolonged, it represents a period of potential vulnerability to reentrant ventricular arrhythmias.[8] A prolonged Tpeak–Tend interval (TpTe) measured in lead V5 seems to be independently associated with sudden cardiac death, even with a normal QTc or when QTc is not measurable.[6, 8] TpTe might be a novel marker of SCD and only a few studies have explored the effect of psychotropics on TpTe.[9] The TpTe to QT interval ratio (TpTe/QT) has also been proposed to provide an estimate of dispersion of repolarization and is considered better predictor of ventricular arrhythmia than QTc.[10]

Many developing countries in Africa including Nigeria have a high burden of mental disorders.[11] However, the burden of associated cardiovascular adverse effects and risk of SCD in patients on psychotropic drugs is grossly underreported in Nigeria and other low-and middle-income countries (LMICs). The aim of this study is to evaluate the prevalence of the ECG markers of ventricular repolarization (QTc, QTd, TpTe, and TpTe/QT) among psychiatric patients taking psychotropic drugs.

MATERIALS AND METHODS:

Study settings

This was a hospital-based cross-sectional descriptive case-control study. The study was carried out in EKSUTH, Ado Ekiti. Ado Ekiti is the capital of Ekiti State in the South Western geopolitical zone of Nigeria.

Selection of subjects:

A total of 225 participants were recruited. This included 150 patients who had been on psychotropic medications for at least 6 months and 75 age and sex-matched apparently healthy individuals as controls. Relevant history including symptom complex, family and social history, duration of

illness, and drug history was obtained from the patients as well as important examination findings. Their Psychiatric diagnosis was based on World Health Organization criteria.[12] All the subjects were recruited if they gave informed consent, were 18 years and above, did not suffer from central nervous system diseases such as stroke, liver disease, renal disease, and were not using non-psychotropic medications known to prolong QTc such as antihistamines, macrolides, imidazoles, quinine, classes 1A, 1C and III antiarrhythmic. All patients and controls with risk factors for ventricular repolarization abnormalities including systemic hypertension, diabetes mellitus, history of heart failure based on history of symptoms and signs of heart failure in the past or at the time of evaluation using the Framingham criteria, pregnancy, and hypokalaemia were excluded from the study. The study protocol was approved by the Ethics and Research Committee of Ekiti State University Teaching Hospital, Ado-Ekiti, Ekiti State, Nigeria. The ethical clearance protocol number is EKSUTH A67/2018/11/009.

Study Instruments

These include a structured data collection form adapted from Kolo *et al*,[13] medical records of subjects, materials for blood sample collection to assay serum potassium, and 12 lead ECG machine (Zoncare ZQ 1203G)

Electrocardiography evaluation

A resting 12-lead ECG (Zoncare ZQ 1203G) was obtained at a paper speed of 25mm/sec and vertical calibrations of 1mV=10mm from each subject lying in a supine position and in a noise-free environment. Standardization of leads and specification was done according to the recommendations of the American Heart Association/American College of Cardiology (AHA/ACC).[14-16]

Definition of ECG terms

The ECG parameters of interest were RR interval, maximum QT interval, minimum QT interval, and TpTe interval. Derived parameters were: QTc interval corrected by Bazett,[17] QTd and TpTe/QT ratio. Observed QT (QT_o) was measured from the beginning of the QRS complex to the visual return of the T-wave to the iso-electric line using lead II and the preceding R-R interval was also determined. QTc was calculated by applying the Bazett's formula[17] QTc = QTo/√R-R. At least three consecutive cycles were measured and then averaged. Prolonged QTc was defined in females (≥434msec) and males (≥432msec) respectively using the Mean +2 standard deviation of the QTc in control subjects. QT dispersion (QTd) was measured as the difference between the longest (QTmax) and the shortest (QTmin) QT intervals within a 12-lead ECG. At least three consecutive cycles were measured for each lead and then averaged. Prolonged QTd was defined in females (≥63msec) and males (≥75msec) respectively using the Mean +2 standard deviation of the QTd in control subjects. Tpeak to Tend (TpTe) was measured from Tpeak to Tend in V5. V5 was used to measure Tpeak to Tend as it has been considered the lead that best predicts torsades de pointe (TdP) based on earlier studies.[18] When V5 was not suitable, leads V4 and V6 in that order were used. TpTe was measured as previously detailed by Panikkath *et al.*[19] At least three consecutive cycles were measured for each lead and then

averaged. The TpTe/QT ratio was calculated as the ratio of TpTe in that lead to the corresponding QT interval without performing the correction for the heart rate.

Statistical Analysis

Using IBM SPSS statistics version 25 computer software package, continuous variables were summarized into means and standard deviations (SD) while Categorical variables were summarized as proportions. Bivariate analysis was done with the use of Chi-square and Fisher's exact test for categorical variables as appropriate while the student t-test was used to compare means of continuous variables. Parametric data such as means of QTc, QTd, TpTe, and TpTe/QT in both groups were analyzed using the student's t-test. 95% confidence interval (CI) was used while statistical significance was set at $P < 0.05$.

Ethical approval: The study protocol was approved by the Ethics and Research Committee of Ekiti State University Teaching Hospital, Ado-Ekiti, Ekiti State, Nigeria. The ethical clearance protocol number is EKSUTH A67/2018/11/009

RESULTS

A total number of 225 subjects completed the study. These included 150 subjects on psychotropic medications and 75 apparently healthy control subjects well matched for age and gender distribution. No statistically significant difference was found in the mean age, body weight, and BMI of the patients and that of the controls. The patient's group consisted of 71 males (47.3%) and 79 females (52.7%) while the control group consisted of 41 males (54.7%) and 34 females (45.3%) (p =0.30). The details are summarized in Table I.

Diagnoses of the patients are as shown in Table II with the majority of patients diagnosed with schizophrenia. The most common drug used either singly or in combination is risperidone while the most common antidepressant used is amitriptyline

Table I: Demographic and clinical characteristics of both study groups

Characteristics	Patients (150) N (%)	Control (75) N (%)	Significance
Gender			
Male	71 (47.3)	41 (54.7)	$\chi 2$=1.076
Female	79 (52.7)	34 (45.3)	P=0.300
Smoking	3 (2)	0 (0)	¥P=0.218
Alcohol	4 (2.7)	2 (2.7)	¥P=1.000
	Mean ± SD	**Mean ± SD**	**P-value**
Age (years)	35.4±10.8	32.7±10.9	0.08
Weight (Kg)	72.7±45.2	68.1±8.1	0.383
BMI (Kg/m^2)	25.4±3.9	24.7±2.8	0.132

$\chi 2$ – Chi-square, ¥= Fisher's exact test, pressure, BMI- body mass index. *-Significant

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Table II: Distribution of psychiatric diagnoses among patients

Psychiatry diagnoses	Frequency
Schizophrenia	93 (62.00%)
Depression	37 (24.67%)
Bipolar	16 (10.67%)
Substance-related disorder	3 (2.00%)
Somatoform disorder	1 (0.67%)

Characteristics of psychotropic drugs used by patients either singly or in combination are shown in Table III.

Table III: Characteristics of Psychotropic drugs used by patients either singly or in combination (n=150)

Psychotropic drugs	Frequency N (%)
Antipsychotics	
Risperidone	94 (62.7%)
Chlorpromazine	27 (18%)
Trifluoperazine	16 (10.7%)
Fluphenazine (oral)	1 (0.7%)
Haloperidol	8 (5.3%)
Olanzapine	14 (9.3%)
Clozapine	7 (4.7%)
Fluphenazine (depot),	7 (4.7%)
Depixol	3 (2%)
Antidepressants	
Amitriptyline	20 (13.3%)
Fluoxetine	11 (7.3%)
Escitalopram	1 (0.7%)
Mood stabilizers	
Carbamazepine	20 (13.3%)
Valproate	1 (0.7%)

For the patient group, the mean QTc (418.5 ±28.1 ms) and QTd (53.2± 23.1 ms) were statistically significantly higher than the QTc (390.4±21.9 ms) and QTd (43.7 ±13.4 ms) of the control group (p-value <0.001 and 0.001 respectively). Likewise, the prevalence of prolonged QTc and QTd was 24.7% and 17.3% respectively in the test group and statistically significantly higher than the control group (p<0.001 for both parameters). Across both study groups, the mean Tpeak-to-Tend, as well as TpTe/QT were not statistically significantly different. The details of the above findings are shown in Table IV.

Table IV: Ventricular repolarization ECG characteristics of the study population

Variables	Patients (150) Mean ± SD		Control (75) Mean ± SD		Statistical indices
QTc (ms)	418.5±28.1		390.4±21.9		P<0.001*
QTd (ms)	53.2±23.1		43.7±13.4		P=0.001*
TpTe (ms)	85.9±18.9		81.8±14.7		P=0.078
TpTe/QT	0.239±0.05		0.233±0.04		P=0.364
	Patients (150)		Controls (75)		
	N	%	N	%	
Prolonged QT_c interval	37	24.7	3	4	¥p<0.001*
Prolonged QTd	26	17.3	1	1.3	¥p<0.001*

*- significant, ¥= Fisher's exact test

The gender differences in the ventricular repolarization electrocardiographic parameters of the patient on psychotropic drugs are shown in Table V. Female patients on psychotropic drugs had higher mean QTc and prolonged QTd while the male patients had higher mean Tpeak-to-Tend and TpTe/QT. For both genders, the mean QTd and prevalence of prolonged QTc were not statistically different.

Table V: Gender difference in the ventricular repolarization ECG characteristics of patients on psychotropic drugs

Variables	Male (71) Mean ± SD		Female (79) Mean ± SD		Statistical indices
QTc (ms)	408.8±24.3		427.2±28.7		p<0.001*
QTd (ms)	51.4±16.5		54.8±27.7		P=0.358
TpTe (ms)	90.6±13.8		81.6±21.8		P=0.003*
TpTe/QT	0.252±0.04		0.227±0.06		P=0.002*
	Patients (150)		**Controls (75)**		
	N	**%**	**N**	**%**	
Prolonged QTc	18	25.4	19	24.1	$\chi2$ = 0.034 p = 0.854
Prolonged QTd	5	7	21	26.6	$\chi2$ = 9.964 p = 0.002*

*- significant, $\chi2$= chi square

DISCUSSION

This study showed that mean QTc and QTd as well as the prevalence of both prolonged QTc and QTd were significantly higher in those exposed to psychotropic drugs. Although patients in this study were without pre-existing cardiovascular conditions, the study showed a significant proportion are already at increased cardiovascular risk as a result of the significant increased prevalence of prolonged QTc and QTd among them. Kolo *et al* reported similar findings about the higher mean QTc and prolonged QTc among the patients' group, however, the mean QTd was similar in both groups.[13] QTc interval prolongation is an indicator of prolonged repolarization of the myocardium resulting in early after-depolarization. This can eventually lead to polymorphic ventricular tachycardia and sudden cardiac arrest.[20,21] Blockade of delayed rectifier cardiac potassium current (I_{kr}) has been proposed to be the mechanism of psychotropic drug-induced QTc prolongation.[22, 23] Although various factors influence the susceptibility of individuals to drug-induced QT prolongation and Torsades de Pointes (TdP), two of these factors are said to be key determinants. Firstly, the variation (polymorphisms) in genes encoding potassium ion channels may cause an increase in the sensitivity of these channels to drugs blocking I_{Kr}. Secondly, the polymorphisms in genes encoding enzymes metabolizing psychotropic drugs may increase serum levels of the drugs leading to excessive blockade of the channel.[23]

This study also showed similar mean TpTe and TpTe/QT in both study groups and this observation is similar to another study which shows that the mean TpTe and TpTe/QT in patients on antidepressants were not significantly higher than the controls. In contrast, the study by Acciavatti *et al* showed increased TpTe in patients on lithium (a mood stabilizer) and antipsychotics (clozapine) while reduced TpTe was observed in those on valproic acid (another mood stabilizer).[9] This study possibly did not demonstrate significant TpTe changes in patients on psychotropics, because only a few of our patients were on the above-listed medication that has been associated with significant changes in TpTe. None of our patients was on lithium.

The female gender had been implicated as a risk factor for QT prolongation and Torsades de Pointes in patients on psychotropic medications.[24,25] This observation is consistent

with this study which showed female patients had higher mean QTc and increased QTd prevalence compared to the male patients. Sex hormones have been hypothesized as a likely factor responsible for the gender difference in QTc value as women are said to be more sensitive to drugs that prolong QTc interval.[20, 26] In contrast, male patients had significantly higher mean TpTe than female patients. This is consistent with studies that showed men have longer TpTe than women.[27,28]

There are some limitations to this study. Due to the study design, we were able to describe the associations and prevalence but we were unable to assign specific ECG abnormalities to specific medication. A prospective design that will evaluate changes in QTc, QTd, TpTe, and TpTe/QT ratio pre- and post-treatment initiation would probably be more informative.

CONCLUSION

Treatment with psychotropic drugs influences QTc and QTd prolongation. This study showed that chronic use of psychotropic drugs is associated with significant effects on ventricular repolarization which may increase the risk of sudden cardiac death among this population.

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