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Psychotropic Medications and QTc Parameters in a Nigerian Cohort

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Authors' contributions

This work was carried out in collaboration with all authors. PMK designed the study, acquired electrocardiograms, statistical analysis, wrote first draft and was the corresponding author. POA conceived the study and together with ADY assessed patients for psychiatric diagnosis and literature search. ABO wrote study protocol and was involved in interpretation of electrocardiograms. EOO participated in statistical analysis and data interpretation. All authors read and approved the final manuscript

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ABSTRACT

Aims: Evidence is increasing to indicate that individuals with mental illness may be at risk of premature death. We studied the prevalence of QTc prolongation, QT dispersion (QTd) and cardiac arrhythmias in patients on psychotropic drugs.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Medicine and Department of Behavioral Sciences, University of Ilorin Teaching Hospital, Nigeria Between Januaryand June 2010.
Methodology: One hundred and ninety-one consecutive patients on psychotropic medications with 121 controls were studied. All the subjects had detailed clinical examination and resting electrocardiogram (ECG) at 25mm/sec. QTc was determined using Bazett formula and QTd by subtracting shortest from longest QTc in 12-lead ECG.
Results: Mean QTc of the patients (450±46msc) was longer (p=0.0001) than that of the controls (390±27msc) but mean QTd was similar (p=0.13) in both groups. QTc was

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prolonged in 68(35.6%) patients compared to 11(9.1%) controls, p=0.0001. LVH, arrhythmias and abnormal T-wave morphology occurred more (p=0.01, 0.01 and 0.001 respectively) in the patients than controls. Age, duration of treatment and total daily doses of antipsychotics were independent predictors of QTc. Cardiac arrhythmias were seen in 24.1% of the patients but none had ventricular arrhythmias.
Conclusion: Psychotropic drug use is a risk factor for QTc prolongation and cardiac arrhythmias. We suggest periodic electrocardiography, discourage polypharmacy and recommend drug holiday in stable patients.

Keywords: Psychotropic drugs; QTc parameters; cardiac arrhythmias; Nigerians.

1. INTRODUCTION

Evidence is increasing to indicate that individuals with mental illness and in care may be at risk of premature death (Abbasi et al., 2006; Allebeck, 1989; Hansen et al., 1997). Incidentally, several studies (Ruschena et al., 1998; Corten et al., 1991; Mehtonen et al., 1991) conducted in American and European populations suggest a link between unexpected deaths and the use of psychotropic medications. Specifically, QTc prolongation has been demonstrated to underlie some of such deaths (Straus et al., 2004; Haddad et al., 2002).

Whether this observation plays any major role in such sudden death is not clear. However, abnormal QTc parameters have been reported to degenerate into malignant arrhythmia over time and precipitate sudden death (Haddad et al., 2002; Huston et al., 1966). Unfortunately, many of these studies cited above were in populations different from Nigerians, therefore it is not clear whether these observations could apply toour patient population. For these reasons, the present study was undertaken to determine whether a link exists between QTc parameters and cardiac arrhythmia in subjects exposed to psychotropic medications.

2. MATERIALS AND METHODS

2.1 Patients

One hundred and ninety one consecutive patients on various psychotropic medications with one hundred and twenty one normal individuals were recruited for the study. A detailed history including symptom complex, pre-morbid personality, family and social history, duration of illness and drug history was obtained from the patients. History of systemic hypertension, diabetes mellitus, hyperlipidaemia and family history of sudden unexpected death (SUD) were elicited. A focused clinical and mental state examination was performed to determine the nature of mental illness in the patients. Psychiatric diagnosis was based on World Health Organization criteria (ICD-10, WHO, 1992). All the subjects were recruited if they gave consent, were 18 years and above, did not suffer from central nervous system diseases such as stroke, subarachnoid haemorrhage, and were not using non-psychotropic medications known to prolong QTc such as halofantrin, itraconazole and amiodarone. All patients and controls with hypokalaemia were excluded from the study. However, there was no facility to assess serum magnesium in our hospital. The weight and blood pressure of all the subjects were measured as extensively detailed previously (Okoro, 2004). Hypertension was defined using the JNC VII (BP≥140/90 mmHg or anti-hypertensive use as previously

reported elsewhere (Chobanian et al., 2003). Control subjects with hypertension and diabetes were excluded. However, patients with cardiovascular co-morbidities such as systemic hypertension were not excluded so that their QTc parameters might be compared with those without these risk factors. Total dose of antipsychotic medication was calculated using the chlorpromazine (CPZ) equivalent and antidepressant as maprotiline equivalent (Ito et al., 2004; Woods, 2003).

2.2 Electrocardiography

A 12-lead ECG was obtained from each subject using Schiller Cardiovit-10 machine at a paper speed of 25mm/sec. A rhythm strip was taken in lead II. The latter was used to determine the observed QT (QTo) and the R-R interval. QTo was measured from the beginning of the QRS complex to the visual return of the T-wave to the iso-electric line. QTc was calculated by applying the Bazett's formula (Bazett, 1920). QTc = QTo/√R-R. QTd is the difference between the maximum and minimum QT interval in 12 lead ECG. One of us, KPM, a cardiologist blinded to the clinical status of the subjects read the ECG tracings. Prolonged QTc was defined in females (≥454msc) and males (≥424msc) respectively using Mean +2 standard deviation of the QTc in control subjects. Left ventricular hypertrophy (LVH) was determined using methods previously validated (Araoye, 1982) in black Africans of Nigerian extraction. Any cardiac arrhythmia was noted.

2.3 Statistical Analysis

Statistical analysis was performed using the SPSS Version 15 and the numerical values were presented as mean ± SD. Student t-test was used to compare means of continuous variables while chi-square test was used to compare means of proportions. Test of correlation was done using the Pearson or Spearman's Rank correlation method. Stepwise regression analysis using 0.05 as entry probability and 0.10 as removal probability was used to determine predictors of QTc. A statistically significant association was set at $P<0.05$

3. RESULTS AND DISCUSSION

The mean age of the patients (41.3±11 years) and that of the controls (40.2±12 years) were similar, p=0.48. One hundred and fifty-three (80.1%) patients had schizophrenia, 16 (8.4%) depression, 14(7.3%) bipolar affective disorder, 6 (3.1%) psychotic depression and 2 (1%) somatoform disorder. Mean duration of taking psychotropic medication was 9.4±8.5 years and mean dose of antipsychotic (CPZ equivalent per day) was 835±826 mg and antidepressant dose was 68.8±33.9 mg. As to the group of psychotropic medication, 161 (84.3%) patients were on antipsychotics, 12(6.3%) patients on antidepressants and 18 (9.4%) patients on both. Ninety-five (49.7%) patients were placed on single drug, 76(39.8%) on two drugs, 18(9.4%) on three drugs and 2(1.0%) on four drugs. The clinical and electrocardiographic characteristics of the study group are shown in Table 1. The mean weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate and QTd were similar between the patients and the controls. However, mean QTc of the patients (450±46msc) was significantly longer than that of the controls (390±27msc), p=0.0001. When patients with history of hypertension were excluded from analysis, the mean QTc of the patients (447±44msc) was still higher (p=0.0001) than that of the controls. The prevalence of LVH, arrhythmias and abnormal T-wave morphology was significantly (p=0.01, 0.01 and 0.001 respectively) higher in the patients compared with controls. QTc was prolonged in 68(35.6%) patients compared with 11(9.1%) controls, p=0.0001.

Table 1. Clinical and electrocardiographic characteristics of the study group

Variable	Patients mean ±SD	Control mean ±SD	P-value
Number	191	121	
Age (years)	41.3 ±11	40.2 ±12	0.48
Weight (KG)	63 ±13.4	62 ±12.6	0.32
SBP (mmHg)	116.8 ±16	109 ±15	0.06
DBP (mmHg)	76.9 ±12	74.7 ±13	0.07
HR (beats/min)	78.3 ±19	80.6 ±12	0.45
QTc	450 ± 46	390 ± 27	0.0001*
QTc (HBP excluded)	447 ± 44	390 ± 27	0.0001*
QTd	37 ± 06	35 ± 05	0.13
LVH (ECG) %	27 (14.1)	6 (4.9)	0.01*
Arrhythmias (%)	46 (24.1)	8 (6.6)	0.01*
Abnormal T-wave (%)	28 (14.7)	3 (2.5)	0.001*
Prolonged QTc (%)	68 (35.6)	11 (9.1)	0.001*

*¥SBP-systolic blood pressure, DBP-diastolic blood pressure, HR-heart rate, QTc-corrected QT, HBP-history of high blood pressure, QTd-QT dispersion, LVH-left ventricular hypertrophy, ECG-electrocardiography.*significant.*

Gender differences in clinical and electrocardiographic parameters of patients on psychotropic medications are presented in Table 2. The female patients were older (p=0.02) and had higher (p=0.012) SBP than males. However, mean DBP was similar between females and males. Twelve (11-9%) females had history of hypertension compared with 4 (4.4%) males, p=0.06. Mean heart rate, QTc, QTd and prevalence of cardiac arrhythmias were similar between the two groups but more males smoked cigarette and abuse ethanol (P=0.03, 0.001 respectively). Daily antipsychotic dose and duration on medication were similar between males and females.

Table 2. Gender differences in clinical and electrocardiographic parameters of patients

Variable	Males	Females	P-value
Number	90	101	
Age (years)	38.3±11.9	43.1±9.9	0.02*
SBP (mmHg)	113.8±13.9	119.4±16.5	0.012*
DBP (mmHg)	75.8±12.8	77.9±11.7	0.228
HR (beats/min)	76.9±19.3	80.1±16.9	0.29
QTc	444± 50	455± 38	0.08
Prolonged QTc (N %)	28 (31.1)	40 (39.6%)	0.2
QTd	36± 10	38± 10	0.6
Increased QTd (N %)	24 (26.7)	22 (21.8)	0.43
Cardiac arrhythmias (N %)	10 (11.1)	18 (17.8)	0.19
Hypertension (N %)	4 (4.4)	12 (11.9)	0.06
Smoking (N %)	6 (6.7%)	0 (0%)	0.03*
Alchohol (N %)	18 (20%)	4 (4%)	0.001*
Antipsychotic dose (mg)/day	916±907	882±755	0.8
Duration on treatment (Years)	9 ±7.9	9.7 ±9.1	0.6

*¥SBP-systolic blood pressure, DBP-diastolic blood pressure, HR-heart rate, QTc-corrected QT, QTd-QT dispersion.*significant*

Antipsychotic drugs, mean daily doses (CPZ equivalent/ADD) and QTc are displayed in Table 3. Haloperidol either as mono or combination therapy is the commonest antipsychotic used in our patients. Others include trifluroperazine, fluphenazinedecanoate and CPZ. Very few patients were on thioridazine and risperidonemonotherapy. The longest QTc (0.53) was recorded in 2 patients on CPZ monotherapy (CPZ equivalent=100mg/day). However, these two patients also had hypertension as co-morbidity. All patients with mean QTc ≥0.46 were on at least 600mg/day CPZ equivalent of antipsychotics.

Table 3. Shows drug(s), daily dose and QTc

Drug (s)	No of Patients	Daily dose (mg) (CPZ equivalent/ADD)	QTc (Mean ±SD)
HDL	59	683	430 ± 40
TDZ	2	125	430 ± 20
TFP	18	300	440 ± 50
CPZ	2	100	530 ± 20
AMT	6	95.8	460 ± 30
RISP	2	175	450 ± 20
IMP	6	41.7	470 ± 20
HDL, MOD	18	1567	480 ± 40
HDL, MOD, CPZ	8	2425	520 ± 50
HDL, CPZ	14	2350	460 ± 20
HDL, CPZ, AMT	4	475	450 ± 30
HDL, CBZ	12	916	440 ± 60
HDL,AMT	8	656	480 ± 50
MOD, TFP	10	1400	460 ± 50
MOD, TFP, CPZ	2	600	380 ± 20
MOD, CBZ, RISP	2	350	430 ± 20
TFP, CPZ	4	800	500 ± 20
TFP, CPZ, CBZ	2	1000	440 ± 20
TFP, CBZ	4	300	450 ± 30
TFP, AMT	4	100	450 ± 30
CBZ, RISP	2	175	420 ± 20
HDL,MOD, CPZ, AMT	2	1150	510 ± 20
Total (mean)	191	898	450 ± 46

¥HDL-haloperidol, TDZ-thioridazine, TFP-trifluroperazine, CPZ-chlorpromazine, AMT-amitryptiline, RISP-risperidone, IMP-imipramine, MOD-modecate, CBZ-carbamazepine, ADD-antidepressant dose.

Correlates of QTc in patients on antipsychotic drugs are presented in Table 4. Significant positive correlation was observed between age, history of hypertension, SBP, DBP, abnormal T-wave and QTc. The number of drugs, dose and duration of antipsychotic medication use also showed positive association with QTc. However, no significant association was seen between LVH, psychiatric diagnosis and QTc.

Table 4. Correlates of QTc in patients on antipsychotics

Parameters	R	P-value
Age and QTc	0.346	0.001*
Hypertension and QTc	0.242	0.001*
SBP and QTc	0.207	0.004*
DBP and QTc	0.209	0.004*
Psychiatric diagnosis and QTc	0.107	0.14
Number of drugs and QTc	0.305	0.001*
Dose of antipsychotics and QTc	0.224	0.003*
Duration on antipsychotics and QTc	0.294	0.001*
LVH and QTc	0.037	0.6
Abnormal T-wave	0.344	0.001*

*¥ QTc-corrected QT, SBP-systolic blood pressure, DBP-diastolic blood pressure, LVH-left ventricular hypertrophy; *significant.*

Table 5. Shows coefficients of regression equation relating QTc to its correlates

Variable	Coefficient	P-value
Age	0.001	0.001
Duration on medications	0.001	0.026
Dose of antipsychotics	0.00016	0.001
Constant	0.373	0.001

Spectrum of cardiac arrhythmias seen in the patients is shown in Table 6. One hundred and forty-five (75.9%) patients had normal sinus rhythm, 18(9.4%) had sinus bradycardia while 10(5.2%) patients each had sinus tachycardia and premature atrial contraction. Six (3.1%) patients suffered from atrial fibrillation and 2(1.1%) from supraventricular tachycardia. None of the patients had premature ventricular contraction or high grade ventricular arrhythmias. In the regression analysis, age, duration on psychotropic medications and total dose of psychotropic drugs in chlorpromazine equivalent were predictors of QTc. The derived regression equation is shown below:

QTc = 0.373 + 0.001 x Age + 0.001 x Duration + 0.000016 x Dose of antipsychotic

Where Age is the age of patient in years, Duration being duration of treatment with drugs while dose of antipsychotic is the total dose of antipsychotic drugs in CPZ equivalent.

The present study showed that mean QTc was significantly higher in those exposed to psychotropic drugs. Specifically, nearly 36% of individuals with mental illness on treatment with this class of medication had abnormal QTc compared to only 9% in similar individuals not on these medications (Table 1). This difference persisted even after those with hypertension were excluded from analysis (Table 1). More importantly, the scatter plot shown in Fig. 1 could indicate that the degree of QTc prolongation could be a function of length of drug exposure. Recently we (Kolo et al., 2008) observed QTc prolongation of up to 494msc in Nigerians with chronic heart failure to accurately predict early deaths but those patients were older and were in New York Heart Association class 4. This implies that patients on psychotropic drugs with QTc prolongation may have a greater risk of early mortality than similarly treated patients without this abnormality (Auquier et al., 2006). The age, duration on treatment and the total dose of psychrotropic medication per day in CPZ equivalent predicted QTc in our study cohort. It therefore means that patients with normal

QTc at the commencement of treatment with psychotropic drugs have substantial risk of developing abnormal QTc parameters after prolonged therapy (Sala et al., 2005). Although, it was not feasible to determine the effect of each drug on QT interval because a significant number of patients were on more than one medication, most patients with QTc ≥460msc were on at least 600mg CPZ equivalent per day (Table 3). Poly-pharmacy and the use of high doses of psychotropic drugs to achieve mental stability are common in our patients. This poses a great danger especially in elderly patients (Reilly et al., 2000; Llerena et al., 2002).

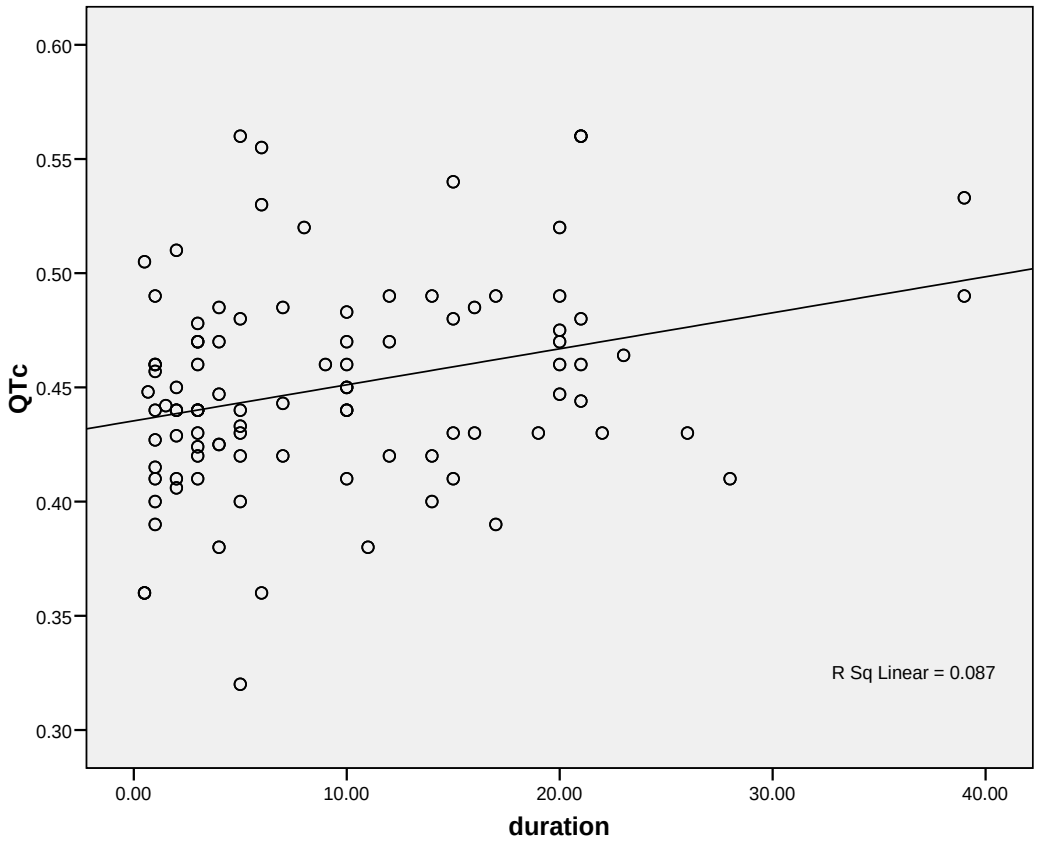

Fig. 1. Scatter diagram of QTc versus duration on medication in years

Table 6. Spectrum of cardiac arrhythmias in the patients

Arrhythmia type	Number (%)	QTc (Mean ±SD)
Normal sinus	145 (75.9)	0.45 ±0.04
Sinus bradycardia	18 (9.4)	0.42 ±0.05
Sinus tachycardia	10 (5.2)	0.46 ±0.02
PAC	10 (5.2)	0.44 ±0.048
PVC	none	-
AF	6 (3.1)	0.51 ±0.049
SVT	2 (1.1)	0.54
VT	none	-

¥PAC-premature atrial contraction, PVC-premature ventricular contraction, AF-atrial fibrillation, SVT-supraventricular tachycardia, VT-ventricular Tachycardia.

Although female gender has been implicated as a risk factor for QTc prolongation and torsades de pointes in patients on psychotropic medications (Warner et al., 1996; Makkar et al., 1993), there were no significant gender differences in electrocardiograms of our patients (Table 2). However, HBP, SBP and DBP were positively associated with QTc in our patients (Table 4). Significantly, Table 5, shows the coefficients of regression equation relating QTc to its correlates and the strength of their influence. Of note, left ventricular hypertrophy was higher in those using medications compared to controls. Strikingly, the prevalence of arrhythmia and abnormal T-wave patterns were also higher in those using medications compared to controls. Fortunately, most of these arrhythmias were benign. This observation raises the possibilities that continental Africans may be more tolerant of the adverse cardiovascular consequences of prolonged use of psychotropic medications compared to their African American cousins and individuals of European descent. However, the mean duration of treatment was about 9.5 years. Therefore, it is not entirely clear whether the benign arrhythmia noted could progressively degenerate into life threatening patterns given that duration of treatment and total dose of antipsychotics in CPZ equivalent significantly correlate with abnormal QTc parameters observed.

4. CONCLUSION

Psychotropic drug use is associated with increased risk of QTc prolongation and cardiac arrhythmias. Age, duration on treatment and total daily doses of antipsychotics in CPZ equivalent predicted QTc in our population. We suggest periodic electrocardiography in patients on psychotropic medications, poly pharmacy should be discouraged and drug holiday should be considered in patients who are mentally stable.

CONSENT

Written informed consent was obtained from each of the subjects before they were recruited to participate in the study.

ETHICAL APPROVAL

All authors hereby declare that all experiments were examined and approved by the Ethics Committee of University of Ilorin Teaching Hospital, Ilorin and had therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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