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The Effect of Psychotropic Medications and Their Combinations on the QTc Interval Among Jordanian Outpatients: A Cross-Sectional Study

ABSTRACT

Objective: To investigate the effect of psychotropic drugs and their combinations on the QTc interval as well as the prevalence of long QTc (LQTc) among ambulatory patients with psychiatric illness in Jordan.

Methods: A cross-sectional study that included patients treated in an outpatient psychiatric clinic was conducted. The QTc duration was calculated using a combined QT correction (Bazett's formula for heart rate 60-100 and the Framingham formula for extremes of HR).

Results: Among 307 patients, about 60% received multiple psychotropic drugs. The LQTc frequency was 1.2%. QTc interval prolongation was observed in patients receiving selective serotonin reuptake inhibitors (SSRIs) (P = .011), tricyclic antidepressants (TCAs) (P = .033), citalopram (P = .044), or psychotropic polytherapy (P = .005). The addition of SSRIs to second-generation antipsychotics (SGAs) also lengthened the QTc interval (P = .029). There was a correlation between the number of psychotropic medications and the QTc length (P = .018). All patients with LQTc carried at least one risk factor for it other than the use of psychotropic medication(s), 3 of 4 patients had a combination therapy, all patients were prescribed SSRIs, and 2 of them had comorbid conditions.

Conclusion: There is a high prevalence of psychotropic drugs polytherapy, and it is clearly associated with LQTc. Citalopram, SSRIs, and TCAs prolong QTc interval. It is recommended to assess non-pharmacological factors for LQTc and, if necessary, to obtain an electrocardiogram before starting patients on psychotropic drugs known to prolong the QTc interval.

Keywords: Electrocardiography, psychotropic drugs, antidepressive agents, antipsychotic agents, serotonin uptake inhibitors, polypharmacy

Introduction

A number of psychotropic drugs, including antipsychotics and antidepressants, are shown to prolong the QT interval (QTc) (i.e., the interval reflecting electrical depolarization and repolarization of the ventricles).[1] Different formulas (Bazett's, Framingham, Hudges, etc.), each with its own set of limitations, are used to correct the QT interval for heart rate (HR). As none are ideal, there is a lack of consensus as to which method is optimal.[2]

Prolongation of the corrected for the HR QT interval may herald a life-threatening polymorphic ventricular tachyarrhythmia, torsade de points (TdP) that, in turn, may lead to sudden cardiac death (SCD). The mortality risk associated with TdP is high, estimated to be approximately 10%,[3] and SCD is one of the top causes of premature death among psychiatric patients.[4] Most cardiologists, however, use the QTc cutoff value of <450 m/s for men and <460 m/s for women before any intervention.[5]

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In a study that explored the frequency of the use of the QTc interval prolonging agents and QT-prolonging drug–drug interactions among patients in a psychiatry outpatient department, almost half of patients (47.9%) were identified as receiving interacting medications with the ability to induce TdP. In comparison, 36.8% of the interacting medications were associated with a known risk of TdP, 27.3% were associated with a possible risk, and 26.7% were associated with a conditional risk, as per AZCERT (Arizona Center for Education and Research on Therapeutics) classification (CredibleMeds TdP risk-stratification lists).[6,7]

A systematic review found that among antipsychotics, thioridazine, ziprasidone, and haloperidol (the latter given intravenously in high doses) are associated with the highest risk of a long QTc interval (LQTc) and/or TdP. TdP has also been associated with the use of second-generation antipsychotics (SGAs), mainly quetiapine and amisulpride, most of the tri- and tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine, and paroxetine), and venlafaxine.[8] The reported overall prevalence rates of polypharmacy in psychiatry vary between 13 and 90%.[9] However, only a few studies investigated the effect of psychotropic drug combinations on the electrocardiogram (ECG).[1,10-12] In a systematic review that summarized the results of different clinical study types involving antipsychotic polypharmacy, it was concluded that the evidence was scarce and inconsistent and depended on the type of the clinical study (i.e., randomized clinical trial, observational study, or case report) and that the currently available evidence fails to confirm worsening QTc prolongation by antipsychotic polypharmacy in general.[13]

This study aimed to investigate the effect of psychotropic drugs such as antidepressants and/or antipsychotics and their combinations on QTc duration, in addition to the prevalence of LQTc among ambulatory patients with psychiatric illness in Jordan, in order to accumulate knowledge in this area of research.

Methods

Study Participants and Design

This cross-sectional study was conducted in the outpatient psychiatric clinic at Jordan University Hospital (JUH) from March 2018 till March 2019. All eligible patients were invited to participate. The study received ethical approval from the Institutional Review Board of the JUH.

Inclusion Criteria: The patient had to fit the following criteria:

- Adult (18-65 years old),
- Jordanian,
- Informed consent signed by the patient or his/her caregiver,
- Diagnosed with mental illness according to DSM-5 by a psychiatrist and is receiving antipsychotic and/or antidepressant medication(s).

Exclusion Criteria: The patient was excluded for the following:

- Pregnant or breast-feeding,
- On medications other than psychotropic that are known to be associated with QTc prolongation (antiarrhythmics, fluoroquinolones, macrolides, antihistamines like diphenhydramine or loratadine, and antiemetics, such as domperidone, ondansetron, dolasetron, or granisetron),
- Uncooperative or aggressive.

Data Collection

Demographic and clinical data were obtained from patients' medical files and via direct patient interview, including psychiatric diagnosis, comorbidities, alcohol use, history of cardiovascular disorders, drug treatment for psychiatric and other disorders, and alcohol and caffeine intake.

A surface ECG was recorded in a supine position after a 5-minute rest using a 12-lead Mortara ELI 230 portable ECG recorder (25 mm/s paper speed, 10 mm/mV amplitude). The ECG records were analyzed by a fellow in cardiology who was blind to the patient's condition, study hypothesis, and treatment status and was not involved in the patient's care.

The ECG was assessed in all 12 leads; however, it was decided to focus on the lead II measurement. Several successive beats were measured with the maximum interval taken.

QTc was calculated using Bazett's, Fridericia, Framingham, and Hodges formulas. In addition, we used combined QT correction (using the Bazett's formula for HR 60-100 and the Framingham formula for extremes of HR as the most reliable method of QT correction according to the American Heart Association guidelines for ECG interpretation).[14] The LQTc frequencies obtained using different formulas were compared.

Prolonged QTc was defined as >450 milliseconds in men and >460 milliseconds in women. The threshold of QTc (>500 milliseconds) was also taken into consideration as it is regarded by the Food and Drug Administration to be of particular concern.[15]

Statistical Analysis

All statistical analyses were performed using SPSS version 22 (IBM Corp.; Armonk, NY, USA). The Kolmogorov–Smirnov and Shapiro–Wilk tests were conducted for the normality of data distribution. Frequencies and mean values with standard deviations (SD) were calculated. A Pearson correlation coefficient was assessed for the study of the relationship between 2 linear variables. Paired sample statistics were used to compare the QTc intervals obtained by different equations and methods. Independent sample *t*-test and one-way

MAIN POINTS

- *Long QTc interval frequency in our study was 1.2% as detected by the combined QT correction (Bazett's formula for heart rate 60-100 and the Framingham formula for extremes of HR).*
- *Selective serotonin reuptake inhibitors, tricyclic antidepressants, citalopram, and psychotropic polytherapy were associated with QTc interval prolongation .*
- *The addition of selective serotonin reuptake inhibitors to second-generation antipsychotics lengthened the QTc interval.*
- *There was a correlation between the number of psychotropic medications and the QTc length.*
- *All patients with LQTc carried at least one risk factor for it other than the use of psychotropic medication(s), 3 of 4 patients had a combination therapy, all patients were prescribed SSRIs, and 2 of them had comorbid conditions.*

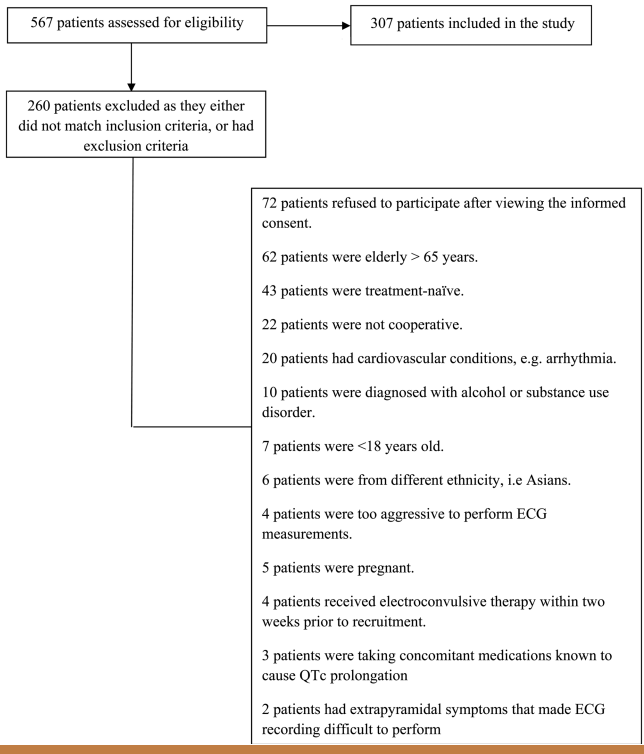

Figure 1. Patient recruitment flowchart.

analysis of variance (ANOVA) test were conducted for the comparison between the treatment groups. The Kruskal–Wallis test, followed by Mann–Whitney *U* tests, was conducted to assess the differences in continuous variables between multiple groups for non-normally distributed data. *P*-values < .05 were considered statistically significant.

Results

Patient Demographic and Clinical Data

Among 567 patients diagnosed with mental illness, 307 patients met the eligibility criteria and were included in the study. The reasons for patients' exclusions are shown in the study flowchart (Figure 1). Around 46% (141) patients were males, and 54% (166) were females; the mean age was 36.3 (SD = 13.5) years (Table 1).

Anxiety disorder was the most common psychiatric condition among study participants (127 patients, 41.4%), followed by major depressive disorder (88 patients, 28.7%), bipolar disorder (53 patients, 17.3%), and schizophrenia (15 patients, 4.9%). The most common comorbidities were hypertension (26 patients, 8.4%), diabetes mellitus (17 patients, 5.6%), hypothyroidism (5 patients, 1.6%), and asthma (4 patients, 1.3%).

Table 1. General Characteristics of the Study Participants (n = 307)

Patient Characteristic	
Gender, n (%)	
Male	141 (45.9)
Female	166 (54.1)
Age, Mean (SD) (range)	36.26 (13.48) (18-81)
BMI, Mean (SD) (range)	26.66 (5.07) (16.40-47.94)
Smoker,[a] n (%)	113 (36.8)
Alcohol,[a] n (%)	10 (3.3)
Caffeine,[a] n (%)	233 (75.9)
Physical activity,[a] n (%)	61 (19.9)

[a]Most days of the week of any amount.

Description of Psychotropic Medications

The mean number of psychotropic medications was 1.81 (SD = 0.81), ranging between 1 and 5. Most of the patients received either 1 (123 patients, 40.1%) or 2 (128 patients, 41.7%) psychotropic medications, while 48 patients (15.6%) received 3 and 8 patients (2.7%) received more than 3 psychotropic medications. A total of 242 patients (79.1%) received antidepressants, and 178 patients (58.3%) received antipsychotic drugs.

SSRIs were prescribed to 226 patients (73.6%), most commonly citalopram (118 patients, 38.4%), followed by fluoxetine (65 patients, 21.2%). SGAs were prescribed to 159 patients (51.8%), most commonly, quetiapine (73 patients, 23.8%) and olanzapine (144 patients, 4.3%). Mood stabilizers were prescribed to 69 patients (22.4%) (Table 2).

Among psychotropic drug combinations, the most frequent was SSRI + SGA (101 patients, 32.9%), followed by SGA + mood stabilizer (44 patients, 14.3%) and SSRI + mood stabilizer (30 patients, 9.8%). A triple combination of an SSRI, an SGA, and a mood stabilizer was prescribed to 21 patients (6.8%) (Table 2).

QTc Interval Assessment Results

QTc Assessment Formulas Comparison

Different QT correction formulas gave unequal QTc results, with the Framingham and Hodges equations producing the shortest QTc intervals (401.1 [SD = 18.2] and 401.1 [SD = 18.7] milliseconds, respectively) and the Bazett's equation producing the longest interval (416.2 [SD = 23.3] m/s); there is approximately a 15 m/s difference between formulas (Table 3). Paired sample statistics of QTc intervals showed significant differences between equations and methods ($P < .001$ for all comparisons).

The frequency of long QTc intervals ranged from 0 (0%; by the Framingham equation and automated method) to 6 patients (2%; by Bazett's equation). The combined method showed the LQTc in 4 patients (1.2%). Of note, there was a strong correlation of QTc intervals obtained by different methods (Pearson correlation: $r = .65$ between the automated QTc and Bazett's equation, $r = .84$ between the automated QTc and the Framingham equation, $r = .81$ between the automated QTc and Hodges equation, $r = .72$ between the automated QTc and the corrected method, $r = .86$ between Bazett's and the Framingham equations, $r = .89$ between Bazett's and Hodges equations, $r = .91$ between Bazett's equation and the corrected method, $r = .96$ between the Framingham and Hodges equations, and $r = .90$ between the Framingham equations and the corrected method; $P < .001$ for all pairs studied).

Association of Patient Anthropometric Characteristics and QTc Interval

Females had longer QTc intervals than males (by 10 m/s, $P < .001$) (Table 4). There was a correlation between the QTc length and the age ($r = .20$; $P < .001$) but not between the QTc length and the BMI ($r = .28$; $P = .284$).

Table 2. Frequency of Psychotropic Medications/Combinations (n = 307)

Name of class and medication	Frequency (%)
SSRIs	226 (73.6)
Citalopram	118 (38.4)
Fluoxetine	65 (21.2)
Fluvoxamine	19 (6.2)
Escitalopram	17 (5.5)
Sertraline	4 (1.3)
Paroxetine	3 (1.0)
SNRIs	3 (1.0)
Venlafaxine	2 (0.7)
Duloxetine	1 (0.3)
TCAs	35 (11.4)
Melitracen	18 (5.9)
Amitriptyline	13 (4.2)
Clomipramine	4 (1.3)
Other antidepressants	
Mirtazapine	8 (2.6)
FGAs	33 (10.8)
Flupentixol	26 (8.5)
Haloperidol	3 (1.0)
Sulpiride	1 (0.3)
Zuclopentixol	3 (1.0)
SGAs	158 (51.5)
Quetiapine	73 (23.8)
Olanzapine	44 (14.3)
Risperidone	29 (9.4)
Amisulpiride	7 (2.3)
Aripiprazole	2 (0.7)
Clozapine	2 (0.7)
Ziprasidone	1 (0.3)
Mood stabilizers	69 (22.4)
Valproate	27 (8.8)
Lamotrigine	21 (6.8)
Lithium	13 (4.2)
Carbamazepine	8 (2.6)
Benzodiazepines	24 (7.8)
Bromazepam	17 (5.5)
Alprazolam	5 (1.6)
Clonazepam	2 (0.7)
SSRI + FGA	21 (6.8)
SSRI + SGA	100 (32.6)
SSRI + TCA	23 (7.5)
SSRI + Mood stabilizer	30 (9.8)
TCA + FGA	17 (5.5)
TCA + SGA	14 (4.6)
TCA + Mood stabilizer	3 (1.0)
FGA + Mood stabilizer	7 (2.3)
SGA + Mood stabilizer	44 (14.3)
FGA + SGA	13 (4.2)
SSRI + SGA + Mood stabilizer	21 (6.8)
FGA + SGA + Mood stabilizer	5 (1.6)

FGAs, first-generation antipsychotics; TCAs, tricyclic antidepressants; SGAs, second-generation antipsychotics; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Assessment of Psychotropic Medications and Other Factors Effect on QTc Interval

Assessment of Individual Drug Classes Effect on QTc Interval

Among patients receiving different classes or selected individual psychotropic medications only those on SSRIs or TCAs had prolonged QTc intervals (by 7.3; $P = .011$ and 8.6 m/s; $P = .033$, respectively, by independent sample *t*-test) compared to patients who did not receive these medications (Table 4).

Effect of SSRI and SGA Combination on the QTc Interval

The Kruskal–Wallis test was conducted to examine the effect of the most common psychotropic drug combinations of SSRIs and SGAs, in comparison to either SSRIs or SGAs alone or none of these medications on QTc intervals. The test provided strong evidence of a difference ($P < .01$) between the mean ranks of at least 1 pair of groups. Afterwards, pairwise Mann–Whitney *U* tests were carried out for the above 4 pairs of groups; the median (min–max values) for QTc intervals are shown in Table 5. The QTc interval was significantly longer in patients who received SSRI and SGA combinations—when compared to those treated with SGAs alone ($P = .029$) or those who received none of these 2 treatments ($P = .001$).

Assessment of Citalopram Effect on QTc Interval

Patients on citalopram (n = 118) had significantly longer QTc intervals (by 5.1 m/s) than those not receiving citalopram ($P = .044$) (Table 4).

The study of the correlation between a citalopram dose and the QTc length found no association ($r = 0.16$; $P = .063$ by Pearson correlation). Furthermore, the comparison of the QTc interval length between patients who received a citalopram dose of 40 mg or more (n = 10) and those who received a smaller citalopram dose (n = 108) found no significant difference ($P = .406$ by the Mann–Whitney *U*-test).

Assessment of Polytherapy Effect on QTc Interval

Table 4 shows that patients who received more than one psychotropic medication had a significantly longer QTc interval (by 8 milliseconds) than those on monotherapy ($P = .005$). Furthermore, there was a significant correlation between the number of psychotropic medications and the QTc interval length ($r = .14$; $P = .018$ by Pearson correlation).

Summary of Patients with Long QTc Interval

The details of patients detected to have LQTc interval are shown in Table 6. All patients with LQTc carried at least one risk factor for QTc

Table 3. Frequencies of Long QTc and Mean QTc Values Using Different Formulas[14] (n = 307)

Formula	Equation	Frequency, n (%) of long QTc[a]	Frequency, n (%) of QTc > 500 milliseconds	Mean (SD) QTc (m/s)
Automated		0 (0)	0 (0)	401.2 (19.7)
Bazett	QTc = QT/√RR	6 (2.0)	0 (0)	416.2 (23.3)
Framingham	QTc = QT + 0.154 (1 – RR)	0 (0)	0 (0)	401.1 (18.2)
Hodges	QTc = QT + 0.00175 (60/RR – 60)	2 (0.7)	0 (0)	400.1 (18.7)
Combined QT correction[b]	Combined use of Bazett formula for normal HR (60-100 BPM) and Framingham formula for extremes of HR	4 (1.3)	0 (0)	414.1 (22.5)

[a]It denotes >450 milliseconds (men) and >460 milliseconds (women); [b]When HR was between 60-100 BPM, Bazzet formula was used, while for extreme values, the Framingham formula was used.
RR', interval between 2 R waves measured in seconds (RR interval = 60/heart rate).

Table 4. Factors Affecting QTc Interval (n = 307)

Patient factor/Psychotropic medications/Classes	n (%)	Mean QTc Interval (SD), milliseconds	*P*[a]
Male	141 (45.9)	408.80 (21.92)	<.001
Female	166 (54.1)	418.83 (21.60)	
SSRIs	226 (73.6)	416.00 (14.9)	.011
No SSRI	81 (26.4)	408.7 (34.3)	
Citalopram	118 (38.4)	417.26 (22.47)	.044
No citalopram	189 (61.6)	412.15 (22.12)	
TCAs	35 (11.4)	421.8 (26.2)	.033
No TCA	272 (88.6)	413.2 (21.8)	
FGAs	33 (10.8)	417.5 ± 25.1)	.361
No FGA	274 (89.2)	413.7 ± 22.2)	
SGAs	158 (51.5)	415.7 (22.3)	.195
No SGA	149 (48.5)	412.4 (22.7)	
Mood stabilizers	69 (22.4)	410.3 (20.4)	.114
No mood stabilizer	238 (77.6)	415.2 (23.0)	
Monotherapy	123 (40.1)	409.64.05 (22.37)	.005
Polytherapy[b]	184 (59.9)	417.05 (22.18)	

[a]Independent sample *t*-test; [b]Two or more psychotropic medications.
FGAs, first-generation antipsychotics; TCAs, tricyclic antidepressants; SGAs, second-generation antipsychotics; SSRIs, selective serotonin reuptake inhibitors.

prolongation along with the use of psychotropic medication(s). In total, 3 of 4 patients had combination therapy. All patients were prescribed SSRIs, either citalopram or fluoxetine. In this study, 2 of them had comorbid conditions (Familial Mediterranean Fever with hypothyroidism in one case and type 2 diabetes mellitus with chronic kidney disease stage 2 in the other case). None of the patients encountered TdP at the time of the study.

Table 5. Comparison of QTc Intervals for SSRI-SGA Combinations and Monotherapy with These Drugs

Group	n	QTc interval, median (min–max) (m/s)	*P*[a]
SSRI + SGA	100	420 (373-485)	
SSRI only	126	413 (360-471)	.094
SGA only	57	412 (360-461)	.029
No SSRI or SGA	23	400 (377-465)	.001

[a]In comparison to SSRI + SGA group by Mann–Whitney test.

Discussion

QTc interval prolongation is one of the major issues for patients who were prescribed psychotropic medication.[16] A number of psychotropic agents are known to increase the risk of ventricular arrhythmias and SCD by lengthening the QT interval and/or inducing TdP.

The Resource Document on QTc Prolongation and Psychotropic Medications by the American Psychiatric Association emphasizes the importance of the QTc interval measurement method (Bazett's, Fridericia, etc.) interpreting results of the QTc interval prolongation reported.[17] The Resource Document considers reporting mean QTc interval prolongation less important than the proportion of individuals who experience clinically meaningful QTc interval prolongation. In compliance with the latter statement, we compared in our study different QT correction formulas and found the frequency of LQTc intervals to range between 0% (using the Framingham and automated method) and 2% (using Bazett's method) among outpatients

Table 6. Characteristics of Patients with Long QTc Interval

Number	Gender	Age	BMI	Smoking*	Alcohol intake[a]	Caffeine intake[a]	Main psychiatric diagnosis	Comorbid conditions	Psychotropic medications	QTc interval, milliseconds	Number of risk factors[c] for LQTc
1	Male	49	25.39	No	No	No	Anxiety disorder	Hypothyroidism, FMF	Citalopram 20 mg and risperidone 1 mg	459	1
2	Male	65	22.03	No	No	Yes	MDD	None	Citalopram 40 mg, olanzapine 5 mg, quetiapine 200 mg and amitriptyline 50 mg	459	1
3	Female	33	21.77	No	No	Yes	Anxiety disorder	CKD stage 2, DM	Fluoxetine 20 mg	485	2
4	Female**	35	32.4	No	No	Yes	Anxiety disorder	None	Fluoxetine 20 mg and Quetiapine 200 mg	471	2

[a]QTc interval assessed by the combined method; *Most days of the weeks of any amount; **Other than the use of psychotropic medications. Risk factors include female gender, age >40 years old, comorbid conditions, and polytherapy.
FMF, Familial Mediterranean Fever; MDD, Major Depressive Disorder; CKD, Chronic Kidney Disease; DM, Diabetes Mellitus; LQTc, long QTc interval.

who receive psychotropic drugs and their combinations. According to the APA, the most widely used correction formula Bazett's is not a consistently reliable method of QT interval correction as it overestimates the QTc interval at high HRs and underestimates it at low HRs.[2] Thus, we used the combined QT correction method (Bazzet's formula for HR 60-100 and the Framingham formula for extremes of HR), with the resulting LQTc frequency of 1.3% (4 patients). Although the frequencies of LQTc intervals varied with different QTc correction formulas used in our study, all of the formulas were highly correlated with each other, being in line with the previous observations.[17] Regardless of the formula used, the LQTc interval frequency was lower than that in the study in hospitalized psychiatric patients (12.8%)[18] which could be explained by the fact that our subjects were outpatients, who are usually prescribed lower doses and less number of psychotropic medications and usually take their medication by an oral rather than parenteral route, as well as the fact that the patients on other medications known to prolong the QTc interval (e.g., antihistamines) were excluded. Additionally, the relatively younger mean age of our patients (36 years) as compared to other studies may be related to the absence of LQTc risk factors such as cardiovascular diseases.

There is substantial inconsistency among previous population studies investigating the effect of antidepressants and antipsychotics on QTc interval duration. The results range from shorter QTc interval durations obtained in a longitudinal study involving 8222 individuals treated by a number of psychotropic drugs previously known to cause QTc prolongation (e.g., phenothiazines as a group, quetiapine, and clozapine)[19] to no associations found between the use of haloperidol, citalopram, or escitalopram as well as antipsychotic drugs and QTc prolongation in a cross-sectional population study involving 2411 patients.[12] On the other hand, in a survey of 6790 psychiatric inpatients, haloperidol, phenothiazines, fluoxetine, and citalopram (including escitalopram) were significantly associated with LQTc and potentially fatal ventricular arrhythmias.[20] Similarly, there were significant increases in QTc among patients receiving haloperidol, thioridazine, imipramine, citalopram, venlafaxine, clozapine, ziprasidone, sertraline, quetiapine, nortriptyline, and risperidone in a study by Iribarren et al.[21] In our study, among patients receiving different classes of psychotropic medications, only those on SSRIs or TCAs had significantly longer QTc intervals (by 7 and 9 m/s, respectively) compared to patients who did not receive these medications. Furthermore, patients on citalopram had significantly longer QTc intervals (by 5.1 m/s) than those not receiving this drug. Our data are consistent with the results of a meta-analysis where TCAs, SSRIs, and citalopram caused significant QTc prolongation.[16]

In a retrospective review involving patients ≥18 years old who received a new prescription or a dose increase of citalopram, QTc prolongation was identified in 16.4% of patients, and in the subgroup of patients ≥60 years old, QTc prolongation was identified in 21.9% of patients. The prevalence of QTc prolongation increased with a dose in the entire study population.[22] Nose et al[12] also identified a dose–response association with QTc prolongation for some antidepressants, including citalopram, as opposed to our results. The use of antipsychotics alone did not significantly prolong the QTc interval in our study; however, the addition of SSRIs to SGAs lengthened the interval, as opposed to the lack of difference in the QTc interval for the whole sample of patients receiving no antipsychotics, antipsychotic

monotherapy, or antipsychotic polypharmaceutical treatment.[23] Our data regarding antipsychotics support the results of a randomized head-to-head trial of the SGAs risperidone, olanzapine, quetiapine, and ziprasidone in patients with acute psychosis at admission and with follow-up visits at discharge, where none of the SGAs produced significant QTc prolongation.[24]

In our study, 42 and 16% of patients received 2 or 3 psychotropic medications, respectively. Our results are quite comparable to those from the 2006 cross-sectional National Ambulatory Medical Care Survey, where visits with 2 or more medications comprised 59.8% in 2005-2006.[25] A few studies have investigated the effect of psychotropic drug combinations on ECG changes. Our data are resembling the results of a cross-sectional population study that included 2411 patients where the use of 2 or more antipsychotic drugs was positively associated with QTc prolongation.[12] On the contrary, in a study involving adults treated with atypical antipsychotics, patients on polytherapy and monotherapy were similar with regard to QTc duration and proportion of patients with gender-adjusted QTc prolongation (7.9% vs. 9.6%, respectively).[10] In another study that involved hospitalized women with psychiatric disorders divided into a monotherapy group (either an antipsychotic or an antidepressant) and a polytherapy group (an antipsychotic agent plus an antidepressant), the QTc interval length did not differ significantly between the monotherapy and the polytherapy groups.[26] The discrepancy between the results of the above studies may be explained by the difference in the study populations (gender differences, outpatient vs. inpatient status, psychotropic drug classes, and individual drugs used).

In a study that involved 729 Japanese patients diagnosed with a mood disorder, the authors found that the use of tricyclic antidepressants and concomitant use of antipsychotics, as well as advanced age and being female (known factors for prolonged QTc interval), significantly prolonged the QTc interval, the latter 2 findings being supported by our data. The SSRIs investigated in their study (fluvoxamine, paroxetine, and sertraline) were not associated with risk of QTc prolongation,[27] as opposed to our results, probably because citalopram was the most commonly used SSRI.

Notably, all 4 patients detected to have the LQTc interval in this study received an SSRI (citalopram or fluoxetine), 3 patients received combination therapy containing a SSRI with either the SGA quetiapine or amitriptyline, and, similar to the Shao et al[18] study, all patients had at least 1 additional risk factor for QTc prolongation, including comorbidities. Noteworthy, the comorbidities present among our patients (hypothyroidism, Familial Mediterranean Fever, chronic kidney disease stage 2, and diabetes mellitus) are not traditionally considered the risk factors for LQTc,[28] and only diabetes mellitus was recently listed among significant independent predictors of QTc prolongation.[18] The fact that the majority of our patients with LQTc interval received combination psychotropic therapy is particularly important in the view of the results of the case–control study where the use of antipsychotics and antidepressants was more common among the victims of SCD than among the survivors of an acute coronary event.[11]

In addition to medications, non-pharmacological variables may affect QTc duration and, consequently TdP that heralds SCD risk, such as gender, age, genetics, electrolyte disorders, endocrine, and metabolic and cardiovascular diseases.[15] According to the APA, in the presence of a significant cardiac disease and/or other risk factors for QTc interval prolongation, cardiology assessment should be considered.[2] More recently, a literature-based algorithm was proposed with a stepped-based approach for the assessment, monitoring, and management of QTc prolongation in psychiatric patients receiving pharmacotherapy. The algorithm includes the use of CredibleMeds[6] as an evidence-based resource, along with cardiac risk stratification.[4] Our data confirm that a substantial proportion of ambulatory psychiatric patients receives multiple psychotropic medications, and the most commonly prescribed classes, such as SSRIs, prolonging the QTc interval. Thus, it is essential that clinicians follow such guidelines to optimize the safety of psychotropic drug prescriptions.

In our opinion, in order to make a definite conclusion regarding the effect of psychotropic agents on the ECG, there is a need for a large prospective multicenter study to evaluate LQTc prevalence in patients prescribed psychotropic medications in comparison with the general population, using a standardized approach such as choosing the most reliable method for QT correction, using the ECG leads and the cutoff values for LQTc consistently, studying the patient genotypes, excluding reversible factors that may affect QTc prolongation (e.g., other medications known to lengthen QTc interval) and cardiovascular, metabolic, and electrolyte disturbances, and considering the doses, routes, and/or serum drug levels. Also, studying different psychotropic drug combinations in similar settings in a large number of patients is recommended.

Our results should be interpreted considering some study limitations. First of all, the cross-sectional nature of the study does not allow access to the baseline QTc interval before starting each medication or combination. Therefore, we cannot rule out the impact of a psychiatric diagnosis on the QTc interval. The prevalence of LQTc was not compared with the age-, ethnicity-, and gender-matched general population. We did not investigate the serum electrolyte levels or presence of renal or hepatic dysfunction. Another limitation is the small number of patients receiving particular individual medications or their combinations. We did not study other surrogate markers for TdP QTc dispersion, TpTe, flattened T-waves, etc.[30]

There is a high prevalence of psychotropic drugs polytherapy and it is clearly associated with LQTc, particularly the SSRIs-SGAs combination. Citalopram, SSRIs, and TCAs prolong QTc interval. It is recommended to assess non-pharmacological factors for LQTc and, if necessary, to obtain an ECG before starting patients on psychotropic drugs known to prolong the QTc interval.

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References

1. Corponi F, Fabbri C, Boriani G, et al. Corrected QT interval prolongation in psychopharmacological treatment and its modulation by genetic variation. *Neuropsychobiology*. 2019;77(2):67-72. [CrossRef]
2. Funk MC, Beach SR, Bostwick JR, et al. Resource document on QTc prolongation and psychotropic medications. https://www.psychiatry.org/psychiatrists/search-directories-databases/library-and-archive/resource-documents. 2018. American Psychiatric Association.
3. Dapro B. Spectrum of drugs prolonging QT interval and the incidence of torsade de points. *Eur Heart J*. 2001;3(suppl K):K70-K80. [CrossRef]
4. Zolezzi M, Cheung L. A literature-based algorithm for the assessment, management, and monitoring of drug-induced QTc prolongation in the psychiatric population. *Neuropsychiatr Dis Treat*. 2019;15:105-114. [CrossRef]
5. Postema PG, Wilde AA. The measurement of the QT interval. *Curr Cardiol Rev*. 2014;10(3):287-294. [CrossRef]
6. CredibleMeds. [Homepage on the Internet). *FAQs on QTdrugs List*. https://www.crediblemeds.org/everyone/articlesbrochures-library/consumerfaq. Accessed March 3, 2021.
7. Das B, Rawat VS, Ramasubbu SK, Kumar B. Frequency, characteristics and nature of risk factors associated with use of QT interval prolonging medications and related drug-drug interactions in a cohort of psychiatry patients. *Therapie*. 2019;74(6):599-609. [CrossRef]
8. Wenzel-Seifert K, Wittmann M, Haen E. QTc prolongation by psychotropic drugs and the risk of torsade de pointes. *Dtsch Arztebl Int*. 2011;108(41):687-693. [CrossRef]
9. Kukreja S, Kalra G, Shah N, Shrivastava A. Polypharmacy in psychiatry: A review. *Mens Sana Monogr*. 2013;11(1):82-99. [CrossRef]
10. Correll CU, Frederickson AM, Figen V, et al. The QTc interval and its dispersion in patients receiving two atypical antipsychotics. *Eur Arch Psychiatry Clin Neurosci*. 2009;259(1):23-27. [CrossRef]
11. Honkola J, Hookana E, Malinen S, et al. Psychotropic medications and the risk of sudden cardiac death during an acute coronary event. *Eur Heart J*. 2012;33(6):745-751. [CrossRef]
12. Nosè M, Bighelli I, Castellazzi M, et al. Prevalence and correlates of QTc prolongation in Italian psychiatric care: cross-sectional multicentre study. *Epidemiol Psychiatr Sci*. 2016;25(6):532-540. [CrossRef]
13. Takeuchi H, Suzuki T, Remington G, Uchida H. Antipsychotic polypharmacy and corrected QT interval: A systematic review. *Can J Psychiatry*. 2015;60(5):215-222. [CrossRef]
14. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for computerized Electrocardiology. *J Am Coll Cardiol*. 2009;53(11):982-991. [CrossRef]
15. Castro VM, Clements CC, Murphy SN, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ*. 2013;346:f288. [CrossRef]
16. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry*. 2014;75(5):e441-e449. [CrossRef]
17. Peles E, Bodner G, Kreek MJ, Rados V, Adelson M. Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: A cross-sectional study. *Addiction*. 2007;102(2):289-300. [CrossRef]
18. Shao W, Ayub S, Drutel R, Heise WC, Gerkin R. QTc prolongation associated With psychiatric medications: A retrospective cross-sectional study of adult inpatients. *J Clin Psychopharmacol*. 2019;39(1):72-77. [CrossRef]
19. van Noord C, Straus SM, Sturkenboom MC, et al. Psychotropic drugs associated with corrected QT interval prolongation. *J Clin Psychopharmacol*. 2009;29(1):9-15. [CrossRef]
20. Girardin FR, Gex-Fabry M, Berney P, et al. Drug-induced long QT in adult psychiatric inpatients: the 5-year cross-sectional ECG Screening Outcome in Psychiatry study. *Am J Psychiatry*. 2013;170(12):1468-1476. [CrossRef]
21. Iribarren C, Round AD, Peng JA, et al. Validation of a population-based method to assess drug-induced alterations in the QT interval: a self-controlled crossover study. *Pharmacoepidemiol Drug Saf*. 2013;22(11):1222-1232. [CrossRef]
22. McClelland J, Mathys M. Evaluation of QTc prolongation and dosage effect with citalopram. *Ment Health Clin*. 2016;6(4):165-170. [CrossRef]
23. Elliott A, Mørk TJ, Højlund M, et al. QTc interval in patients with schizophrenia receiving antipsychotic treatment as monotherapy or polypharmacy. *CNS Spectr*. 2018;23(4):278-283. [CrossRef]
24. Olsen RE, Kroken RA, Bjørhovde S, et al. Influence of different second generation antipsychotics on the QTc interval: A pragmatic study. *World J Psychiatry*. 2016;6(4):442-448. [CrossRef]
25. Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch Gen Psychiatry*. 2010;67(1):26-36. [CrossRef]
26. Sumić JČ, Barić V, Bilić P, et al. QTc and psychopharmacs: are there any differences between monotherapy and polytherapy. *Ann Gen Psychiatry*. 2007;6:13. [CrossRef]
27. Okayasu H, Ozeki Y, Fujii K, et al. Pharmacotherapeutic determinants for QTc interval prolongation in Japanese patients with mood disorder. *Pharmacopsychiatry*. 2012;45(7):279-283. [CrossRef]
28. Vandael E, Vandenberk B, Vandenberghe J, Willems R, Foulon V. Risk factors for QTc-prolongation: systematic review of the evidence. *Int J Clin Pharm*. 2017;39(1):16-25. [CrossRef]
29. de Hert M, Vancampfort D, Correll CU, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. *Br J Psychiatry*. 2011;199(2):99-105. [CrossRef]
30. Gupta P, Patel C, Patel H, et al. T (p-e)/QT ratio as an index of arrhythmogenesis. *J Electrocardiol*. 2008;41(6):567-574. [CrossRef]