Prevalence and Risk Factors for QTc Prolongation in Acute Psychiatric Hospitalization

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ABSTRACT

Objective: Prolongation of corrected QT (QTc) interval increases the risk of severe ventricular arrhythmias, in particular torsades de pointes. Patients with severe mental illness (SMI) represent a vulnerable population. This study aimed to measure the prevalence of QTc prolongation in inpatients with SMI and to identify risk factors for QTc prolongation.

Methods: Demographic, clinical, anthropometric, laboratory, and electrocardiographic information was extracted from the electronic records of a cohort of patients hospitalized in a psychiatry inpatient unit between July 1, 2017, and July 22, 2019. The primary outcome was the estimation of prevalence of QTc prolongation. The secondary outcome was the identification of risk factors for QTc prolongation.

Results: A total of 597 admissions were included. Only 1.4% had a QTc > 500 msec, while 11.6% had a QTc > 460 msec. The proportion of women with a QTc > 470 msec was 3.6% and men with a QTc > 450 msec was 7.3%. Several risk factors were individually associated with QTc prolongation. In the multivariate model explaining almost one-third of QTc variance, female sex ($P = .04$), older age ($P = .011$), heart rate ($P < .001$), systolic blood pressure ($P = .042$), potassium ($P = .012$), hemoglobin ($P = .006$), number of antipsychotics ($P = .026$), and treatment with clotiapine ($P = .012$) and clozapine ($P = .003$) were associated with QTc length. Several factors beyond pharmacologic treatment identify subjects at risk for QTc prolongation, and polypharmacotherapy does not seem to increase the risk of QTc prolongation.

Conclusions: QTc prolongation was rare in this cohort of SMI inpatients. Most of the risk factors involved in QTc prolongation are unchangeable elements or linked to general medical conditions, and only a few are modifiable factors, including psychotropic treatment.

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According to the literature, there is an association between antipsychotic drugs and prolongation of corrected QT (QTc) interval with Bazett's formula.[1–4] QTc interval represents an indirect marker of potential proarrhythmic toxicity, in particular of polymorphic ventricular arrhythmia called torsades de pointes (TdP), which can evolve into ventricular fibrillation and cause sudden cardiac death. While there is no international agreement on a safety threshold for the QTc interval, a consensus was reached considering QTc intervals > 440 msec as normal[5] and QTc prolongation > 500 msec as at increased risk for TdP.[2]

Among other factors, psychotropic drugs have been shown to be associated with QTc prolongation. Both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) are associated with QTc interval prolongation,[6] with SGAs being safer than FGAs,[7] with few exceptions.[3,8] The relationship between drug dose and risk of QTc interval prolongation is controversial,[7,9] and the relationship between antipsychotic polypharmacy and QTc remains uncertain.[2,4,10] QTc interval can also be significantly influenced by the route of administration of antipsychotic drug, with parenteral being less safe than oral administration, particularly for haloperidol.[11,12] Antidepressants have also raised concerns regarding the risk of QTc prolongation. More specifically, selective serotonin reuptake inhibitors (SSRIs) appear to be safe in general, with the exception of citalopram and escitalopram, which have a dose-dependent predictable negative effect on the QTc.[13] Tricyclic antidepressants (TCAs) are significantly associated with serious cardiovascular side effects, including prolongation of the QTc interval.[14] Among mood stabilizers, lithium in blood concentrations greater than 1.2 mmol/L may prolong the QTc interval, although no cases of TdP have been reported.[15] No risk of QTc prolongation with valproate or lamotrigine has been reported to the best of our knowledge.

In addition to psychotropic drugs, numerous other factors have been recognized as affecting QT interval, including both congenital and acquired conditions, as well as the use of various other drugs (antibiotics, antiarrhythmics, antifungal agents, methadone).[3] The primary aim of this study was to measure the prevalence of QTc interval prolongation in a real-world sample of

Clinical Points

- QTc interval prolongation is a rare event associated with identifiable factors.
- Consideration of the risk factors associated with QTc prolongation helps to minimize the risk of a critical event.

acute inpatients affected by and treated for severe mental illness. A secondary aim was to verify whether putative risk factors for QTc prolongation are confirmed in a real-world sample.

METHODS

Study Design

This study was a cross-sectional analysis of a cohort of patients with severe mental illness.

Participants

Among 898 patients admitted to the acute inpatient psychiatry unit of the psychiatry clinic at the Hospital of Padua (Padua, Italy) between July 1, 2017, and July 22, 2019, 597 patients with a valid electrocardiogram (ECG) performed during the hospitalization were included in the study. The severity of the patients' conditions is variable; they first pass through the emergency department and are then admitted to the inpatient unit. The setting is representative of Italian psychiatric inpatient units.

Source and Variables

Data were collected through electronic medical records. Age, sex, height (cm), body weight (kg), body mass index (BMI = kg/m^2), Clinical Global Impressions–Severity of Illness[16] (CGI-S) scores, systolic and diastolic blood pressure (mm Hg), and blood test results were extracted. A medical history was also collected from the patients' electronic charts, and possible concomitant medical conditions were reported. The pharmacologic treatment administered the day before ECG was noted. We also collected the dosage of antipsychotics and converted it into chlorpromazine equivalents.[17] Based on available literature,[2,18–20] antipsychotics were divided in relation to the risk of lengthening the QTc interval in 3 classes: low risk (aripiprazole, lurasidone, cariprazine, paliperidone, zuclopenthixol), moderate risk (quetiapine, perphenazine, fluphenazine, olanzapine, clotiapine, haloperidol), and high risk (chlorpromazine, promazine, clozapine, levomepromazine, ziprasidone). Long-acting injectable antipsychotics were considered as therapy administered the day before the ECG. For the sake of reporting, they were converted into daily dose equivalents.[21] Antidepressants were grouped into classes: SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), TCAs, and "other," which included mirtazapine, trazodone, bupropion, and vortioxetine. Based on current recommendations,[22,23] at-risk antidepressants have been identified based on the risk of lengthening the QTc interval: citalopram, escitalopram, and tricyclic antidepressants (clomipramine, amitriptyline). Each patient had a diagnosis at discharge formulated according to the *ICD-10*.

ECG Procedure

The day of admission or the day after each patient underwent a 12-lead ECG, the QT interval was automatically calculated and corrected for heart rate according to Bazett's formula. The ECG and QTc interval results were then studied and confirmed by a cardiologist. Unless alterations are found, the ECG is repeated after approximately 7–10 days of hospitalization, before discharge. If the QTc is lengthened instead, it is repeated sequentially over the subsequent days after treatment adjustments. If more ECGs were performed during the hospitalization, we considered the closest to admission.

Data Analysis

First, we calculated the primary outcome, namely the prevalence of QTc > 500 msec. Then, we assessed variable distribution with the Shapiro-Wilk test and tested the association between QTc length and binary (Mann-Whitney or *t* test depending on normality) and continuous (Pearson or Spearman correlation) variables. Furthermore, a multivariate linear regression model was created to test a model including putative risk factors for long QTc in a real-world setting. Statistical analyses were performed using Jamovi 2019 software (https://www.jamovi.org/). The level of statistical significance was set at $P < .05$.

RESULTS

A total of 597 patients were included in the study. Demographic, clinical, and pharmacologic characteristics are described in Table 1. The mean (SD) age of the sample was 45.7 (17.4) years, and 52.9% were female. The mean (SD) BMI was 26.1 (5.85) kg/m^2. Overall, 22.1% of the patients were admitted for agitation, 23.3% for schizophrenia spectrum disorder relapse, 37.2% for mood disorder episodes, 14.6% for suicide attempt, and 2.8% for other reasons. Also, 16.6% had a substance-related disorder. Diagnosis at discharge was schizophrenia spectrum disorder for 35%, mood disorders for 48%, and other reasons for 17%.

The QTc interval was > 500 msec in 1.4% of the sample; we describe the demographic, clinical, and pharmacologic characteristics of those 8 patients in Table 2. Furthermore, 11.7% of patients had a QTc > 460 msec; 3.6% of women had a QTc > 470 msec, and 7.3% of men had a QTc > 450 msec. The mean ± SD QTc was 429 ± 26.7 msec. The QTc interval was divided into 5 groups, and its distribution is reported in Table 3.

Also, prolonged QT distribution differed according to demographic factors, namely sex ($\chi^2 = 10.0$, $P = .040$) and age group ($\chi^2 = 19.2$, $P = .259$) (Table 3). Prevalence of QTc prolongation was not different based on antipsychotic QTc prolongation risk groups ($\chi^2 = 10.3$, $P = .242$) (Table 4).

Data on psychiatric and medical treatments were collected, including drugs at risk of QTc prolongation like

Table 1. Demographic and Clinical Characteristics

Variable	Total Patients (N = 597)
Mean ± SD	
Age, y	45.7 ± 17.4
Body mass index, kg/m^2	26.1 ± 5.85
CGI-S score	5.02 ± 0.99
Heart rate, bpm	78.3 ± 15.2
No. of diagnoses	1.33 ± 0.52
No. of comorbidities	1.23 ± 1.75
No. of medications	3.08 ± 2.21
Antipsychotics	1.00 ± 0.76
Antidepressants	0.43 ± 0.62
Mood stabilizers	0.39 ± 0.57
Frequencies, n (%)	
Age > 65 y	92 (15.4)
Female sex	316 (52.9)
ECG alterations	334 (55.9)
BMI > 25 kg/m^2	241 (40.37)
Substance use	99 (16.6)
Self-injury	105 (17.6)
Medical comorbidity	307 (51.4)
Comorbidities	
High blood pressure	104 (17.4)
Cardiovascular disease	43 (7.2)
Deep vein thrombosis	20 (3.4)
Diabetes mellitus	42 (7.0)
Thyroid disease	54 (9.0)
Gastrointestinal disease	30 (5.0)
Gynecologic disease	18 (3.0)
Other	361 (60.5)
Reason for admission	
Agitation	132 (22.1)
Psychosis	139 (23.3)
Mood	222 (37.2)
Suicide attempt	87 (14.6)
Other	17 (2.8)
Psychotropic medications	
Psychotropic drugs	517 (86.6)
Mood stabilizer	212 (35.5)
Lithium	82 (13.7)
Antipsychotics	446 (74.7)
Antipsychotic type	
FGA	84 (18.8)
SGA	281 (63.0)
FGA/SGA	81 (18.2)
Antipsychotic QTc risk	
Low	79 (17.7)
Moderate	246 (55.3)
High	121 (27.2)
Long-acting injectables	69 (11.6)
Antidepressants	221 (37.0)
Antidepressant type	
SSRI	88 (39.8)
SNRI	40 (18.1)
TCA	12 (5.4)
Other	56 (25.3)
SSRI/other	13 (5.9)
SNRI/other	10 (4.5)
TCA/other	1 (0.5)
SNRI/TCA	2 (0.9)
Antidepressant QTc risk	
Citalopram	4 (14.8)
Escitalopram	8 (29.6)
TCA	15 (55.6)

Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions–Severity, ECG = electrocardiogram, FGA = first-generation antipsychotic, QTc = corrected QT, SGA = second-generation antipsychotic, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 2. Characteristics of Subjects With QTc Trait > 500 msec

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, y	29	27	46	48	47	62	79	75
Sex	Female	Male	Male	Female	Male	Female	Female	Male
QTc (msec)	520	508	511	572	529	500	510	500
Reason for admission	Personality disorder + self-injury behavior	Schizophrenia	Psychomotor agitation	Mood disorder	Schizoaffective disorder	Psychosis	Psychosis	Bipolar disorder
Substance	No	No	Yes	Yes	No	No	No	No
Antipsychotics	Yes (haloperidol)	Yes (clozapine 400 mg, amisulpride 600 mg)	No	No	Yes (haloperidol)	No	No	Yes (aripiprazole)
Mood stabilizers	No	Yes (valproate)	No	No	No	No	No	Yes (valproate)
Antidepressants	No	No	No	No	No	No	No	Yes (trazodone)
Other medications	No	Yes (simvastatin)	Yes (methadone)	Yes (methadone)	No	No	Yes (ticlopidine, simvastatin, levothyroxine)	Yes (warfarin, amlodipine, olmesartan, omeprazole, tamsulosin)
Comorbidities	Yes (pregnancy)	Yes (hypercholesterolemia)	No	Yes (HIV, hepatitis C)	Yes (cardiomyopathy)	Yes (gastric resection)	Yes (hypothyroidism, hypercholesterolemia)	Yes (ischemic stroke, hypertension, BHS, spherocytosis)
Blood chemistry alterations	No	No	No	No	No	Yes (potassium: 2.1 mEq/L)	No	Yes (thyroid-stimulating hormone: 5.5 µU/mL)

Abbreviations: BHS = benign prostatic hyperplasia, QTc = corrected QT.

Table 3. Prevalence of QTc Prolongation in the Test Population in Relation to Sex and Age[a]

	QTc Value					*P*
	<450	450–459	460–479	480–499	>500	Value
Sex						
Female	237 (39.7)	37 (6.2)	31 (5.2)	7 (1.2)	4 (0.7)	.040
Male	238 (39.9)	16 (2.7)	19 (3.2)	4 (0.7)	4 (0.7)	
Age, y						
≤18	19 (3.2)	3 (0.5)	2 (0.3)	0 (0)	0 (0)	.259
19–24	53 (8.9)	2 (0.3)	11 (1.8)	3 (0.5)	0 (0)	
25–34	72 (12.1)	9 (1.5)	4 (0.7)	0 (0)	1 (0.2)	
35–64	257 (43.0)	31 (5.2)	28 (4.7)	6 (1.0)	4 (0.7)	
≥65	74 (12.4)	8 (1.3)	5 (0.8)	2 (0.3)	3 (0.5)	
Total	475 (79.6)	53 (8.9)	50 (8.4)	11 (1.8)	8 (1.3)	

[a]Data are presented as n (%).
Abbreviation: QTc = corrected QT.

Table 4. Prevalence of QTc Prolongation in Antipsychotic QTc Prolongation Risk Groups[a]

Antipsychotic	QTc Value					*P*
Risk	<450	450–459	460–479	480–499	>500	Value
Low	67 (15.1)	4 (0.9)	5 (1.1)	1 (0.2)	1 (0.2)	.242
Moderate	196 (44.0)	20 (4.5)	25 (5.6)	3 (0.7)	2 (0.4)	
High	88 (19.8)	20 (4.5)	10 (2.2)	2 (0.4)	1 (0.2)	
Total	351 (78.9)	44 (9.9)	40 (9.0)	6 (1.3)	4 (0.9)	

[a]Data are presented as n (%).
Abbreviation: QTc = corrected QT.

Table 5. Difference of QTc Length Across Binary Variables

Variable	Reference Group	Group 1, mean (SD)	Group 2, mean (SD)	*P* Value
Sex	Female vs male	433 (25.9)	426 (27.2)	<.001
Age, y	<65 vs >65	428 (26.2)	435 (28.7)	.026
Body mass index, kg/m^2	<25 vs >25	424 (26.3)	431 (25.2)	.002
Antipsychotics high risk	No vs yes	429 (27.0)	433 (25.2)	.035
Clotiapine assumption	No vs yes	429 (26.9)	441 (20.1)	.013
Clozapine assumption	No vs yes	429 (26.7)	440 (24.8)	.017
Zuclopenthixol assumption	No vs yes	429 (26.8)	443 (17.9)	.036
High blood pressure	No vs yes	428 (26.5)	437 (26.4)	<.001
Deep vein thrombosis	No vs yes	429 (26.6)	443 (26.8)	.023
Diabetes mellitus	No vs yes	429 (26.8)	441 (22.3)	<.001
Thyroid disease	No vs yes	429 (26.7)	438 (25.1)	.042
Gastrointestinal disease	No vs yes	429 (26.4)	440 (30.7)	.012
Gynecologic disease	No vs yes	429 (26.5)	445 (30.2)	.017
Comorbidity	No vs yes	425 (23.5)	434 (28.8)	<.001

Abbreviation: QTc = corrected QT.

methadone. There were 13 patients in methadone treatment; of these, 2 patients had a QTc > 500 msec, 3 patients had a QTc between 450 and 499 msec (459, 471, and 480 msec, respectively), and 8 patients had a QTc < 450 msec.

In the univariate analyses (Table 5), the QTc was longer in females (433 ± 25.9 vs 426 ± 27.2, $P < .001$) and in subjects aged > 65 years (428 ± 26.2 vs 435 ± 28.7, $P = .026$). QTc length was also significantly correlated with BMI ($\rho = 0.151$, $P = .001$), heart rate ($\rho = 0.393$, $P < .001$), clinical severity as measured with the CGI-S ($\rho = 0.111$, $P = .020$), and other variables reported in Table 6. The multivariate regression model ($R^2 = 31.7\%$) confirmed that female sex ($\beta = 5.30$ $P = .044$), age > 65 years ($\beta = 8.06$, $P = .011$), heart rate ($\beta = 0.62$, $P < .001$), systolic blood pressure ($\beta = 0.15$, $P = .042$), hemoglobin ($\beta = -0.24$, $P = .006$), potassium ($\beta = -7.27$, $P = .012$), lower antipsychotic number ($\beta = -3.77$, $P = .026$), clotiapine ($\beta = 15.46$, $P = .012$), and clozapine ($\beta = 14.43$, $P = .003$) were associated with QTc prolongation (Table 7).

Table 6. Correlation Between QTc and Continuous Variables

Variable	ρ	*P* Value
Body mass index	0.151	.001
Heart rate	0.393	<.001
CGI-S score	0.111	.020
No. of comorbidities	0.172	<.001
Systolic blood pressure	0.122	.003
Hemoglobin	−0.232	<.001
Glycemia	0.133	.002
Glomerular filtration rate	−0.09	.042
Potassium	−0.174	<.001
No. of medications	0.144	<.001
No. of antipsychotics	0.084	.040
Antipsychotic risk	0.096	.044

Abbreviations: CGI-S = Clinical Global Impressions–Severity, QTc = corrected QT.

Table 7. Multivariate Regression Model of Predictors of QTc (continuous) Duration

Variable	Estimate	T	95% CI	*P* Value[a]
Sex (female-male)	5.30	2.02	0.13 to 10.45	**.044**
Age ≥ 65 y (yes/no)	8.06	2.55	3.16 to 14.27	**.011**
Heart rate (continuous)	0.63	8.59	0.07 to 0.48	**<.001**
Body mass index (continuous)	0.28	1.26	−0.15 to 0.69	.207
Comorbidities (continuous)	1.26	1.73	−0.17 to 2.68	.084
Systolic blood pressure (continuous)	0.15	2.05	0.01 to 0.30	**.042**
Hemoglobin (continuous)	−0.24	2.76	−0.41 to −0.07	**.006**
Glycemia (continuous)	−0.19	0.28	−1.57 to 1.18	.781
Glomerular filtration rate (continuous)	−0.08	1.23	−0.20 to 0.05	.218
Potassium (continuous)	−7.27	2.54	−12.91 to −1.64	**.012**
No. of antipsychotics (continuous)	−3.77	2.22	−7.09 to −0.44	**.026**
Clotiapine (yes/no)	15.46	2.51	3.36 to 27.57	**.012**
Clozapine (yes/no)	14.43	3.01	5.01 to 23.86	**.003**
Zuclopenthixol (yes/no)	14.47	1.90	−0.51 to 29.46	.058

[a]Bolding indicates an association with QTc length.
Abbreviation: QTc = corrected QT.

DISCUSSION

The present study shows that female sex, age > 65 years, heart rate, systolic blood pressure, potassium, and hemoglobin were positively associated with QTc prolongation in the multivariate model. Also, only 2 antipsychotics, clozapine and clotiapine, were associated with QTc prolongation, while the others showed no statistical or clinical effect on QTc. Moreover, polypharmacotherapy with antipsychotics was not associated with increased risk of QTc prolongation.

The results of this study are relevant for the following reasons. First, they provide real-world evidence that clinically relevant QTc prolongation is a rare event that occurs in subjects with predisposing unmodifiable risk

factors such as older age and female sex, which is a finding that is consistent with previous literature.[4,24–27] Our study showed a low prevalence of QTc interval prolongation > 500 msec (only 1.4%). A larger percentage of patients (79.6%) had a QTc interval > 450 msec. These data agree with that of the literature,[28] wherein the prevalence of QTc > 500 msec is between 0.9%[29] and 2.6%.[30] An increase in the QTc with age may be due to several factors. The aging process may affect the molecular determinants of the QT interval or alter the myocardium with increased myocardial fibrosis.[31] Aging is also associated with alterations in the amount of sympathetic and parasympathetic tone,[32] which can alter myocardial repolarization and the duration of the QTc.[33,34] According to previous literature, women are at higher risk of drug-induced TdP than men.[35] Sex hormones modulate QTc and contribute to the longer QTc observed in the general population of women versus men and androgenized women.[36,37] Although the exact mechanisms underlying the influence of sex hormones on the repolarization and QTc interval are complex and still unresolved, androgens seem to have a protective role. Testosterone decreases the L-type calcium current and increases the potassium channel currents, resulting in a shorter QTc interval observed in both animal and human studies.[38]

Second, our results confirm previous findings about the role of hypokalemia on QT interval prolongation.[39] Potassium channel conductance decreases with decreasing extracellular serum potassium, leading to QTc prolongation[40–42] due to several factors. Hypokalemia may prolong the QT by activating calcium/calmodulin-dependent protein kinase and thereby increasing late sodium current.[43] Another important underlying mechanism is that the amplitude of rapid delayed rectifier (IKr) activated by depolarization to plateau potentials decreases as extracellular potassium is lowered. This unusual behavior reflects the very fast inactivation that open Kv11.1 channels undergo such that, with depolarizing pulses, channels are distributed between open and inactivated states. Decreasing extracellular potassium shifts this balance toward occupancy of inactivated states and thus decreases overall repolarizing current.[44] Further, the drug block of open channels is enhanced with low extracellular potassium, thereby further enhancing QT prolongation.[43]

Third, polypharmacotherapy does not seem to increase the risk of QTc prolongation, which is a result in contrast with previous literature.[2,4,10,26] In the literature, there are conflicting findings on antipsychotic polypharmacy and its role with respect to the QTc interval. Some research suggests that polypharmacy may be associated with an increased risk since greater cumulative doses would be given, thus suggesting a mainly dose-related action.[45] Other studies[26] conversely report a lower QT interval for patients receiving antipsychotic polypharmacy. Fourth, the dose-dependency ratio was not confirmed in our study,[46] probably because very high doses were hardly reached.

Regarding the specific role of medications, we found no increased risk with haloperidol,[47] which could be explained by the low doses and oral administration to comply with current safety warnings.[12] Aripiprazole was found to be safe, confirming data from previous literature,[47,48] as was lurasidone.[18] We also found no increased risk for long-acting formulations, which is in contrast with the study by Chong et al,[49] in which FGA long-acting drugs (fluphenazine and flupentixol) were used. In our study, clotiapine, an antipsychotic with the structure and properties of dibenzothiazepines similar to those of phenothiazines, appears to be significantly correlated with QTc lengthening.[29,50] Clozapine, which in our analysis correlated significantly with QTc prolongation, has been associated with an increased risk of sudden cardiac death,[3] but only rarely with QTc prolongation,[51–53] suggesting that another mechanism could mediate its relationship with sudden cardiac death. Since clozapine can cause myocarditis, it could act by sensitizing the myocardium to the effect of QT prolongation due to the concomitant use of other drugs.[54–58] On the other hand, the lack of association between sudden cardiac death with clozapine and QTc prolongation might be due to biases and nonsystematic reporting of QTc measures. Regarding antidepressants, SSRIs, SNRIs, mirtazapine, trazodone, bupropion, and vortioxetine have proved to be safe. Citalopram and escitalopram, despite the warning data of the US Food and Drug Administration,[59] were also found to be safe. TCAs, compared with other antidepressants, showed conversely a significant association with the lengthening of QTc and therefore seem to be the only antidepressants at risk for these conditions.[60,61] Mood stabilizers, lithium, valproate, and lamotrigine were safe with respect to QTc prolongation.[3]

Fifth, an important role seems to be played by medical comorbidities. According to our study, hypertension (also emerged from the correlation with systolic blood pressure)[50,62] and diabetes mellitus (and glycemia)[63–65] are associated with QTc prolongation. Our data also revealed an association with kidney function (expressed in terms of glomerular filtration rate)[66] and values of hemoglobin.

Despite the absence of TdP in our sample and the low incidence of TdP and QT in the general and psychiatric population, it should be emphasized that a risk exists, but that it is low in absolute terms and can be effectively reduced by adequate risk stratification.[66] Before starting antipsychotic treatment, an ECG should be recorded and examined. This is particularly important in subjects with established cardiovascular diseases or when a high-risk medication or parenteral therapy is considered.[67] Because over 85% of patients with drug-induced QT interval prolongation have 2 or more additional risk factors,[29] it is important to undertake a careful analysis of the concomitant risk factors to reduce risk: undertake a thorough medical and pharmacologic history, review the list of drugs that the patient takes, identify concomitant medical comorbidities, and monitor blood electrolyte levels.[54,68,69]

The present study has several limitations. First, the real-world nature of data, which can be considered a

strength of the work, also has inherent limitations such as lack of systematic collection of potential confounding factors, including smoking, calcium, and magnesium levels. Second, regarding antipsychotics, only a few patients were taking thioridazine, pimozide, sulpiride, droperidol, and ziprasidone, which have a higher QTc prolongation risk. Third, the cross-sectional design of the study limits any causal inference.

In conclusion, QTc prolongation seems to be a rare occurrence that affects only a small portion of the psychiatric population and is explained by demographic, clinical, and pharmacologic factors in one-third of these patients. Factors mostly implicated in the risk are unchangeable, such as age and sex, or are secondary to general medical conditions. Treatment with psychiatric drugs, on the other hand, would seem to have a marginal role.

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