Therapeutic Advances in Psychopharmacology Original Research

Prevalence of ECG abnormalities and risk factors for QTc interval prolongation in hospitalized psychiatric patients

Ther Adv Psychopharmacol
2019, Vol. 9: 1–13
DOI: 10.1177/2045125319891386

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Abstract

Background: Psychiatric patients are at risk of cardiovascular diseases, and many psychotropic drugs can prolong QTc interval. Requirements for electrocardiogram (ECG) monitoring have been set up in our psychiatric university hospital. The objective of this study was to determine the proportion of adult patients who had an ECG during their hospitalization, the prevalence of ECG abnormalities, the evolution of the QTc after admission, and the risk factors for QTc prolongation.

Methods: Retrospective analysis of ECGs and clinical data of all patients with a complete hospitalization in 2015. Assessment of the influence of covariates on QTc using linear mixed-effects models.

Results: At least one ECG ($n = 600$) was performed during 37.6% of the stays ($n = 1198$) and in 45.5% of the patients ($n = 871$). Among the patients with an ECG, 17.9% had significant ECG abnormalities, including 7.6% with a prolonged QTc. QTc measured at admission and during hospitalization did not change significantly ($n = 46$, 419.4 ± 29.7 ms, 417.2 ± 27.6 ms, $p = 0.71$). In the multivariate model (292 patients, 357 ECGs), the covariates significantly associated with the QTc were gender (+15.9 ms if female, $p < 0.0001$), age (+0.4 ms/year, $p = 0.0001$), triglyceride levels (+5.7 ms/mmol/l, $p = 0.005$), and drugs with known risk of torsades de pointes (+6.2 ms if ⩾1 drug, $p = 0.028$).

Conclusions: The prevalence of hospitalized psychiatric patients with an abnormal ECG indicates that ECGs should be performed systematically in this population. Prescription of psychotropic drugs should be done cautiously, particularly in patients with QTc prolongation risk factors.

Keywords: electrocardiogram, psychiatric inpatients, psychotropic drugs, QTc interval

Received: 5 July 2019; revised manuscript accepted: 21 October 2019.

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Introduction

Psychiatric patients have poor physical health and shortened life expectancy,[1] with a higher rate of sudden cardiac death than in the general population.[2,3] Of note, patients treated with antipsychotic drugs have twice the risk of cardiac death compared with nonusers,[4] and an association between antidepressant use and cardiac arrest has also been documented.[5]

Many psychotropic drugs can block the human ether-a-go-go-related gene (hERG) voltage-gated potassium channels that are implicated in the repolarization of the cardiac action potential.[6,7] This blockage can result in a prolongation of the QTc interval on an electrocardiogram (ECG), which may induce malignant polymorphic ventricular tachycardia, so-called torsades de pointes, associated with syncope and sudden death.[8] Other risk factors for QTc prolongation include female sex, increased age, congenital long QT syndrome, electrolyte abnormalities, heart (e.g. acute ischemia), and other medical conditions.[9]

In a study performed at admission in hospitalized psychiatric patients in Switzerland ($n = 6790$),

27.3% of the ECGs were classified as abnormal.[10] The prevalence of patients with a prolonged QTc interval (⩾470–499 ms) was 6.1%, and another 1.6% had long QTc interval (⩾500 ms), with 58% of the latter qualified as induced by a drug. Most importantly, 19.4% of the patients with drug-induced long QTc had torsades de pointes or sudden death within 72 h of detection.[10]

The National Institute for Health and Care Excellence (NICE) clinical guideline indicates an ECG should be offered before starting antipsychotic medication in hospitalized patients.[11] The Danish Society of Cardiology and the Danish Psychiatric Society developed a clinical guideline for reduction of the risk of arrhythmia induced by psychotropic drugs. The authors proposed a decisional algorithm that takes into account the individual risk factors of the patients, and the risk associated with the pharmacological treatments.[12] A medico–economic analysis showed that performing systematic ECG screening at admission in psychiatric hospitals helps to reduce the number of sudden cardiac deaths in a cost-effective way.[13]

Based on these publications, in the autumn of 2014, we introduced a clinical directive for the cardiac follow up of adult patients hospitalized in the service of General Psychiatry (Department of Psychiatry, Lausanne University Hospital).[14] This directive includes an ECG at admission, as well as later during the stay if a drug that poses a risk of cardiac toxicity is prescribed or after a significant dose increase.

In the current study, we retrospectively analyzed all ECGs performed during a 1-year period following the introduction of the directive. The aims were to determine the proportion of patients who had an ECG, the prevalence of ECG abnormalities, the evolution of the QTc interval during hospitalization, and the risk factors associated with QTc prolongation in this population.

Methods

Study design and patients

A retrospective, cross-sectional study was performed in the service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital. All adult patients aged 18–65 years with a complete hospital stay (admission and discharge) between 1 January and 31 December 2015, and at least one valid ECG, performed at admission or during the stay, were included. ECG measurements and laboratory analyses were part of the clinical monitoring of the patients. The study protocol, examining clinical data retrospectively, was approved by the Ethics Committee Vaud local Ethics Committee (approval number: 2015-00067).

Data extraction

Demographic (age, gender, length of stay, time elapsed between hospital admission and ECG recording), clinical (ECG parameters, psychiatric diagnoses), biological (potassium, creatinine, glucose, triglyceride, and cholesterol plasma levels), and pharmacological (drugs administered) data were extracted from the electronic medical records. Potassium and creatinine values were included if they were measured $\pm$ 3 days from the date of the ECG; in the case of more than one analysis, only the value closer to the ECG was selected for the analyses. For the other biological values, all measurements performed during the stay were considered, and mean values were included in the analyses. Drugs were included if they were administered within 5 days before the ECG recording. Psychiatric and somatic drugs potentially affecting the QTc interval were classified as known, possible, or conditional risks of torsades de pointes, according to CredibleMeds.[15] Drugs were also classified as strong inhibitors or strong inducers of cytochromes P450 (CYP).[16] Psychiatric diagnoses were based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

ECG assessment

All ECG recordings were performed using the Cardiovit-MS 2015 electrocardiograph (Schiller AG, Baar, Switzerland). ECGs recorded at 25 mm/s speed and 10 mm/mV amplification were initially interpreted automatically by the integrated measurement software. However, due to the limitations in diagnostic accuracy of computerized interpretation,[17] all ECGs were read over by a senior cardiologist (JS). All final ECG parameters were included in a database, and were double checked. ECGs that did not allow reliable measurement of the QTc interval (e.g. poor quality or agitated patients) were considered artifacts and excluded. ECGs performed within a short interval (i.e. less than 1 h for most cases) were considered duplicates, and only the first ECG was included unless the quality of the second was

Table 1. Classification of the 71 patients (17.9%) with at least one abnormal ECG, among the 396 patients with at least one valid ECG.

Description	Number of patients (%)[a]
Prolonged QTc (male: ⩾450 ms; female: ⩾460 ms)	30 (7.6)
Repolarization abnormalities (excluding prolonged QTc and early repolarization)	23 (5.8)
Atrioventricular conduction disturbances (PR <100 ms; PR > 200 ms)	10 (2.5)
Intraventricular conduction disturbances (QRS >120 ms)	5 (1.3)
Sinus bradycardia (<50 bpm)	13 (3.3)
Sinus tachycardia (>120 bpm)	2 (0.5)
Arrhythmias (premature beats; atrial fibrillation)	10 (2.5)
Remote myocardial infarction	3 (0.8)

[a]More than one type of ECG abnormality possible per patient.
bpm, beats per minute; ECG, electrocardiogram.

better. Automatic QT interval was defined as the interval between the earliest beginning of the QRS complex and the latest T-wave end taken from all 12 averaged leads. According to Postema and colleagues, the QT interval is measured manually in stable sinus rhythm from the beginning of the QRS complex to the end of the T-wave defined as the intersection of the tangent to the steepest slope of the last limb of the T-wave, and the baseline in lead II or V5.[18,19] Manual QT measurement was performed in only 13 cases of gross misinterpretation of the deepest slope of the T-wave descent by the automatic measure. Cardiac diagnoses were corrected for 28 ECGs. A significant U wave was present in only one patient with severe hypokalemia; in this case alone, the U wave was included in QT interval measurement. QT values were corrected for heart rate (QTc). As the commonly used Bazett's correction formula is known to undercorrect in cases of bradycardia and overcorrect in tachycardia, this formula was used for heart rates between 60 and 100 bpm[20]: $QTcB\ (ms) = QT\ (ms)/(RR)^{1/2}\ (s)$, where RR represents the duration of a cardiac cycle. For heart rates <60 or >100 bpm, Fridericia's correction formula, which is less sensitive to heart rate, was used: $QTcF\ (ms) = QT\ (ms)/(RR)^{1/3}\ (s)$. Additional analyses were also performed using Bazett's and Fridericia's correction formulas for all ECGs; these results are presented in the supplementary data. ECGs with irregular rhythms (marked sinus arrhythmias, atrial fibrillation) were excluded for the measurement of the QT interval, but were kept for the determination of the prevalence of ECG abnormalities. The defined ECG abnormalities used in the present study are enumerated in Table 1.

Statistical analyses

Mean values for continuous variables were compared using Student's *t* test for independent samples or the paired *t* test for dependent samples. To test for independence among the categorical variables, we used the Pearson Chi-square test. Differences in proportion of prolonged QTc were assessed using a generalized linear mixed model (logistic regression), fit by maximum likelihood to detect potential differences among the two groups, without adjusting these models for any covariates except for repeated measurements per admission. A linear mixed-effects model fit by restricted maximum likelihood was used to assess the influence of the covariates on QTc interval simultaneously.[21] Two nested random effects (one at the admission level nested in another random effect at the individual level) were used to take into account the repeated measurements of QTc per admission and for each individual. We used graphic tools to assess the fit and results were satisfactory. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata software, version 15.0 (StataCorp, College Station, TX, USA), and R language and environment for statistical computing 3.3.1.[22]

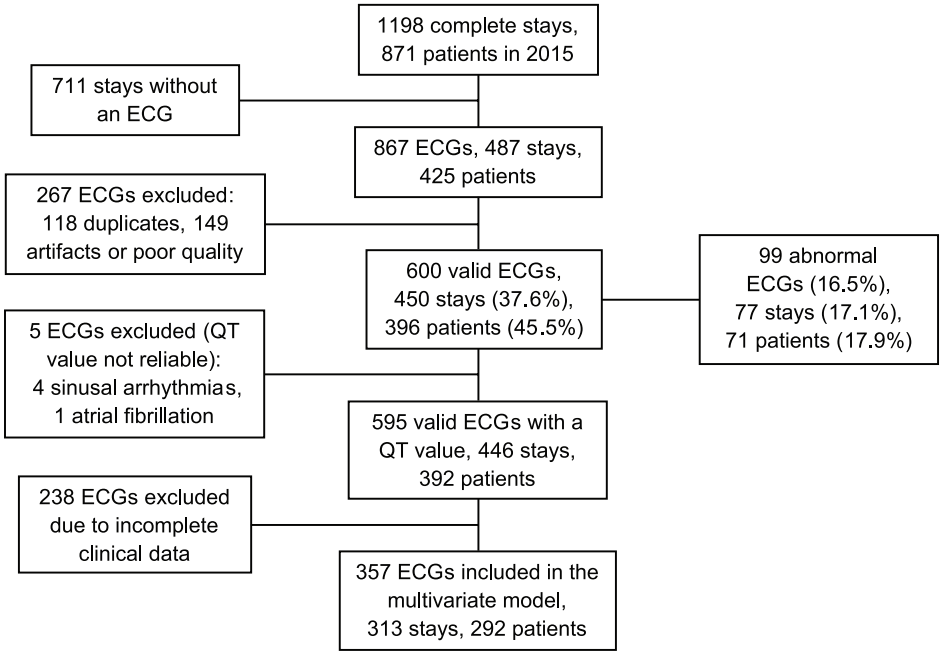

Figure 1. Flow chart for inclusion and exclusion of the ECGs in the various parts of the study.
ECG, electrocardiogram.

Results

Study population

During a total of 1198 complete hospital stays recorded in 2015 (871 patients), 867 ECGs were performed. After exclusion of 118 ECGs due to duplication, and 149 that were considered artifacts or of poor quality, 600 valid ECGs were included in the analysis of the prevalence of abnormalities, corresponding to 37.6% of the stays ($n=450$) and 45.5% of the patients ($n=396$) (see Figure 1).

The length of stay of the patients with at least one ECG was significantly longer (mean ± SD: 30.5 ± 26.5 days) than that of the rest of the patients (mean ± SD: 20.5 ± 22.5 days, $p<0.0001$). The proportion of females was significantly lower in the group of patients with an ECG (42.4%) compared with the rest of the patients (55.1%), $p<0.001$. The age of the patients with an ECG (mean ± SD: 38.4 ± 12.2 years) was similar to the rest of the patients (mean ± SD: 38.6 ± 11.8 years), $p=0.75$.

The mean ± SD number of ECGs per stay was 1.3 ± 0.7. The number of stays with 1, 2, 3, 4, and 5 ECGs were 347, 70, 20, 12, and 1, respectively. The mean ± SD time elapsed between hospital admission and the first ECG recording was 5.1 ± 10.6 days (range 0.02–138). The number of stays with an ECG performed within 24, 48, and 72 h after admission was 143 (11.9%), 251 (21.0%) and 302 (25.2%), respectively. The mean ± SD time elapsed between hospital admission and all ECGs was 8.9 ± 14.3 days (range 0.02–138).

Prevalence of ECG abnormalities

Among the 600 valid ECGs, an abnormality (as defined in Table 1) was detected in 16.5% of the ECGs ($n=99$), which corresponds to 17.1% of the stays ($n=77$) and 17.9% of the patients ($n=71$). A prolonged QTc interval (⩾450 ms for males; ⩾460 ms for females) was observed in 7.6% of the patients ($n=30$), including a patient with a very high risk QTc at 595 ms. This extreme value was observed in a 27-year-old female, with a low potassium value of 2.5 mmol/l (ref 3.5–4.6 mmol/l), and treated with psychotropic drugs at risk of QTc prolongation (lithium 24 mmol/d and amisulpride 400 mg/d) and magnesium. Detailed characteristics of the 30 patients (37 ECGs) with QTc prolongation, including at risk medications, are presented in supplementary Table S1. At least one and two drugs classified in any CredibleMeds' categories were present in 84% and 59% of these ECGs, respectively. However, due to multiple factors for QTc prolongation, it was not possible to

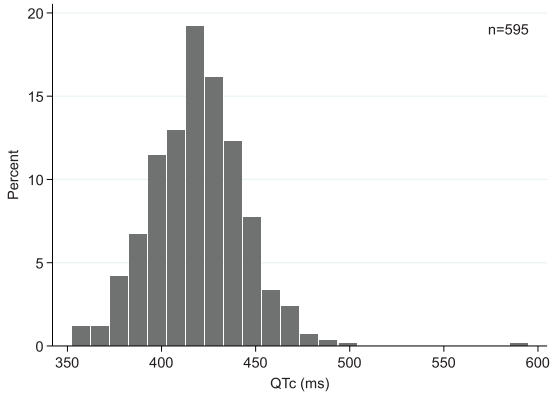

Figure 2. Distribution of the QTc values in the 595 valid ECGs.
ECG, electrocardiogram.

incriminate a particular drug, especially in patients taking several drugs. Nevertheless, it can be noted that, among the drugs classified in the highest QTc prolongation risk category, there were 10 ECGs with citalopram or escitalopram, 5 with methadone, and 4 with haloperidol. Other abnormalities, observed either in the same or in different patients, were repolarization abnormalities (other than QTc prolongation), sinus bradycardia and tachycardia, atrioventricular and intraventricular conduction disturbances, arrhythmias, and old myocardial infarction (see Table 1). Of note, no patients were treated with specific antiarrhythmic drugs, especially with amiodarone or sotalol, both drugs known to prolong QT interval. No case of acute ischemic ECG changes that could justify a specialized support or a transfer to an intensive care unit was documented, neither was there any case of torsades de pointes or sudden cardiac death. The prevalence of ECG abnormalities using Bazett's and Fridericia's corrections for all ECGs are presented in supplementary Tables S2 and S3, respectively.

Evolution of QTc interval during hospitalization

For the specific analysis of the QTc interval, 5 of the 600 valid ECGs were further excluded due to a normal but unreliable QTc value: 4 with pronounced sinus arrhythmias and 1 with atrial fibrillation (Figure 1). Bazett's correction was used for 478 ECGs that had a heart rate between 60 and 100 bpm, and Fridericia's correction for 63 and 54 ECGs that had a heart rate <60 or >100 bpm, respectively. Mean $\pm$ SD QTc interval in the 595 remaining ECGs was 419 $\pm$ 25 ms (range 352–595), see Figure 2.

The evolution of the QTc interval was studied in patients having an ECG recorded within 48 h after admission (considered the baseline value) and another ECG between 3 and 30 days later ($n = 46$). There were no significant differences between the two measurements: mean $\pm$ SD: 419.4 $\pm$ 29.7 ms *versus* 417.2 $\pm$ 27.6 ms, $p = 0.71$. When the proportion of patients with a QTc prolongation was considered, no significant change was observed between the two study periods: 10.9% *versus* 10.9%, $p = 1.0$. However, in the patients with a baseline value in the upper quartile ($n = 12$), a significant decrease was observed: 456.4 $\pm$ 14.1 ms *versus* 430.8 $\pm$ 27.5, $p = 0.025$. Among these patients, for those who had available data, six had a medical condition at admission that has been, or could have been, corrected later in the stay, and that could have therefore explained the shortening of QTc (two urinary screening positive for cocaine, two hypokalemia, one high amisulpride plasma level and one diagnosis of alcohol dependence, see Table S4). Similar results were obtained if cutoffs of 24 h ($n = 28$) and 72 h ($n = 54$) after admission were used for the baseline ECG (data not shown). The evolution of the QTc using Bazett's and Fridericia's corrections for all ECGs is presented in the supplementary data.

Risk factors for QTc prolongation

A total of 357 ECGs with complete clinical data sets were included in the multivariate model, corresponding to 313 stays and 292 patients (Figure 1 and Table 2). Bazett's correction was used for 295 ECGs that had a heart rate between 60 and 100 bpm, and Fridericia's correction for 34 and 28 ECGs that had a heart rate <60 or >100 bpm, respectively. The covariates significantly associated with the QTc interval in the multivariate model were (β, p): gender (+15.9 ms if female, $p < 0.0001$), age (+0.4 ms/year, $p = 0.0001$), triglyceride plasma levels (+5.7 ms/mmol/l, $p = 0.005$), and administration of at least one drug with known risk of torsades de pointes (+6.2 ms if ≥ 1 drug, $p = 0.028$), see Table 3. The results of the multivariate model obtained using Bazett's and Fridericia's corrections for all ECGs are presented in the supplementary data (Table S5). Other psychiatric diagnoses (F20-29, F30-31 and F32-34) were also tested in the multivariate model, but they were not significantly associated with QTc interval (data not shown).

Table 2. Description of the covariates included in the linear mixed-effects model ($n = 357$ ECGs).

Covariates	Values
Females, *n* (%)	149 (41.7)
Age (years), mean ± SD (range)	39 ± 12 (18–64)
Potassium (mmol/l, ref. 3.5–4.6), mean ± SD (range)	4.0 ± 0.4 (2.3–5.3)
Glucose (mmol/l, ref. 3.7–5.6), mean ± SD (range)	5.1 ± 1.1 (2.5–12.9)
Triglycerides (mmol/l, ref. < 2.0), mean ± SD (range)	1.3 ± 0.7 (0.4–7.8)
Cholesterol total (mmol/l, ref. < 5.0), mean ± SD (range)	4.8 ± 1.1 (2.6–10.1)
Creatinine (µmol/l, ref. 62–106), mean ± SD (range)	75 ± 19 (39–302)
At least one drug with known risk of TdP, *n* (%)[a]	102 (28.6)
At least one drug with possible risk of TdP, *n* (%)[b]	139 (38.9)
At least one drug with conditional risk of TdP, *n* (%)[c]	137 (38.4)
At least one strong CYP inhibitor, *n* (%)[d]	17 (4.8)
At least one strong CYP inducer, *n* (%)[e]	5 (1.4)
Time between admission and ECG (days), mean ± SD (range)	5.4 ± 10.8 (0.02–87.7)
F10-F19 ICD diagnosis, *n* (%)	106 (29.7)
QTc (ms), mean ± SD (range)	418 ± 24 (352–487)

Drugs classified according to their risk of TdP (www.crediblemeds.org):
[a]Known risk: haloperidol ($n = 38$), escitalopram ($n = 32$), methadone ($n = 19$), citalopram ($n = 15$), levomepromazine ($n = 6$), domperidone ($n = 2$).
[b]Possible risk: olanzapine ($n = 40$), risperidone ($n = 29$), mirtazapine ($n = 25$), aripiprazole ($n = 20$), venlafaxine ($n = 19$), clozapine ($n = 10$), lithium ($n = 10$), buprenorphine ($n = 4$), tizanidine ($n = 2$), paliperidone ($n = 1$), clomipramine ($n = 1$).
[c]Conditional risk: quetiapine ($n = 70$), amisulpride ($n = 33$), sertraline ($n = 18$), trazodone ($n = 12$), fluoxetine ($n = 6$), hydroxyzine ($n = 5$), pantoprazole ($n = 4$), paroxetine ($n = 3$), indapamide ($n = 2$), amitriptyline ($n = 1$), hydrochlorothiazide ($n = 1$), metoclopramide ($n = 1$), ritonavir ($n = 1$).
Drugs classified according to their CYP inhibitor or inducer profile (www.pharmacoclin.ch):
[d]Strong inhibitors: fluoxetine ($n = 6$), levomepromazine ($n = 6$), paroxetine ($n = 3$), darunavir ($n = 1$), fluvoxamine ($n = 1$), ritonavir ($n = 1$).
[e]Strong inducers: oxcarbazepine ($n = 2$), dexamethasone ($n = 1$), phenobarbital ($n = 1$), ritonavir ($n = 1$).
CYP, cytochrome P450; ECG, electrocardiogram; F10-F19, ICD diagnosis: mental and behavioral disorders due to psychoactive substance use; SD, standard deviation; TdP, torsades de pointes.

Discussion

Proportion of patients with at least one ECG recorded

Among the 1198 stays recorded during a 1-year period in a psychiatric university hospital (871 patients), a total of 600 valid ECGs were analyzed retrospectively. The proportion of stays with at least one ECG performed within 24 h after admission was 11.9%, which is relatively low, but this proportion increased to 25.2% after 72 h, and to 37.6% during the whole stay. Taking into account that some patients were hospitalized more than once during the study period, the proportion of patients with at least one ECG was 45.5%. These results are satisfactory, considering the psychiatric context (e.g. agitation of the patients, particularly at the beginning of the hospitalization), and the introduction of the ECG directive in our hospital a few months before the study started. A significantly longer length of stay was observed for patients with at least one ECG compared with the rest of the patients, suggesting that the patients with more complex situations were more susceptible to having an ECG during the

Table 3. Linear mixed-effects model (357 ECGs, 313 stays, 292 patients).

Covariates	QTc	
	Beta [a] (ms)	*p*
Females	+ **15.9**	<**0.0001**
Age (years)	+ **0.4**	**0.0001**
Potassium (mmol/l)	– 3.7	0.28
Glucose (mmol/l)	+ 1.3	0.26
Triglycerides (mmol/l)	+ **5.7**	**0.005**
Cholesterol total (mmol/l)	– 1.6	0.22
Creatinine (µmol/l)	+ 0.006	0.93
At least one drug with known risk of TdP [b]	+ **6.2**	**0.028**
At least one drug with possible risk of TdP [b]	+ 3.6	0.13
At least one drug with conditional risk of TdP [b]	+ 3.6	0.14
At least one strong CYP inhibitor [c]	+ 6.4	0.21
At least one strong CYP inducer [c]	– 0.01	0.99
Time between admission and ECG (days)	– 0.1	0.54
F10-F19 ICD diagnosis	+ 0.5	0.87

[a]Effect of the covariate on the QTc.
[b]Based on the classification of CredibleMeds (www.crediblemeds.org).
[c]Based on the classification of the Geneva University Hospitals (www.pharmacoclin.ch).
CYP, cytochrome P450; ECG, electrocardiogram; F10-F19, ICD diagnosis: mental and behavioral disorders due to psychoactive substance use; TdP, torsades de pointes.

stay, but we cannot exclude the possibility that a longer stay increases the likelihood of receiving an ECG.

Our results are in accordance with a study that reviewed records of mental health inpatient admissions and revealed that an ECG was performed in 19% of the patients.[23] In another study including patients who had been prescribed antipsychotic drugs on hospital admission, a higher proportion of patients (40% in the baseline audit and 70% in the reaudit) had ECG monitoring before or after taking antipsychotics.[24] Different protocols for ECG monitoring of psychiatric patients and management plans for patients with abnormal ECG findings have been proposed recently to reduce the risk of arrhythmia.[12,24–27]

Prevalence of ECG abnormalities

Among the 396 patients with a valid ECG, the prevalence of patients with an abnormal ECG was 17.9%. The most frequently observed abnormalities were linked to the QTc values. This prevalence of abnormal ECGs justifies routine recordings in hospitalized psychiatric patients. In a study by Girardin and colleagues, performed at admission in hospitalized psychiatric patients, 27.3% of the ECGs were classified as abnormal.[10] The most frequent abnormalities identified were supraventricular tachycardia (6.6% of all ECGs), followed by QTc lengthening (6.1%) and repolarization abnormalities other than QTc prolongation (4.1%).[10] In nonpsychiatric patients (age 35–74 years), major ECG abnormalities were identified in 7.9% and 11.3% of women and men, respectively.[28] In

primary care patients, the prevalence of ECG abnormalities in the age group from 20 to 39.9 years was 19.4% in females and 29.3% in males, and increased in older age groups.[29] Comparison of these results with ours is difficult, however, as the populations are not the same, and the categories used for the classification of the abnormalities are different.

A prolonged QTc interval was observed in our study in 7.6% of the patients, but only one case had a QTc interval ⩾500 ms, which is the threshold considered to be a strong predictor of drug's risk to cause torsades de pointes in both sexes.[30] This prevalence is consistent with the observed rates of QTc prolongation reported in the main studies performed in hospitalized psychiatric patients, with the majority of the values ranging between 2% and 17%,[10,23,25–27,31–43] but up to 38% in some studies.[33,44] In somatic inpatients, the prevalence of QTc prolongation seems to be higher than in psychiatric inpatients, with rates varying between 22% and 35%. These differences may be explained by older populations and a higher prevalence of cardiovascular comorbidities in somatic inpatients.[45–47]

The mean QTc (419 ± 25 ms) values measured in our study are in accordance with values reported in other studies performed in psychiatric inpatients. The mean QTc values in these studies ranged between 391 ms and 423 ms,[25,32,35,36,38,39,43,48,49] but a higher mean QTc of 451 ms was also reported in one study.[44]

Comparison across studies is limited due to different factors such as the heterogeneity in cut-off values used for the definition of QTc prolongation (421–480 ms), study designs, characteristics of patients (inclusion and exclusion criteria, gender, age, ethnic origin, comorbidities), drugs prescribed (first- or second-generation antipsychotics, doses, polymedications), and QT correction methods (Bazett, Fridericia or nomogram), which could explain the large range of values reported. Other QT correction formulas exist, such as Framingham or Hodges, but were not used in these studies.[50,51]

Evolution of the QTc interval during hospitalization

When the ECGs performed at admission were compared with the ECGs later in the stay, the QTc interval, as well as the proportion of patients with a prolonged QTc, were not significantly different. These results suggest that, in our study, hospitalization of patients was not a risk factor for QTc prolongation nor a protective situation. However, in patients with a baseline value in the upper quartile, QTc values decreased significantly after admission, suggesting for these patients a risk reduction due to hospitalization, but a regression to the mean cannot be excluded. In a cross-sectional study performed in 74 hospitalized patients in a general psychiatry ward in Iran, the proportion of patients with a prolonged QTc interval increased between admission and 1 week of hospitalization, from 14% to 37% in males (QTc > 450 ms) and from 6% to 26% in females (QTc > 470 ms). A significant increase in the mean QTc interval was also observed between admission (436 ± 26 ms) and 1 week of hospitalization (451 ± 30 ms). Due to the small sample size, no possible cause was identified.[44] In another study performed in 95 patients acutely admitted to an emergency ward for psychosis in Norway, the proportion of prolonged QTc interval (>450 ms for males and >470 ms for females) decreased from 11.6% at admission to 4.2% at discharge or after 6 weeks of hospitalization at the latest. A positive association was observed between the QTc interval and the agitation score.[39]

Risk factors for QTc prolongation

A highly significant association between female gender and QTc interval was observed in our study using a multivariate model. This result is in accordance with previous studies performed in psychiatric inpatients,[32,38,41] although discordant results have been published.[39,42] A suggested mechanism in sex difference is the presence of androgens in males between puberty, and around the age of 50 that may shorten the QTc interval.[38,52]

A significant association between age and QTc interval was observed in the present study. Similar results were observed in some other studies performed in psychiatry,[37,41,42] but not all.[40] The increase in QTc interval with age might be explained by the physiological changes in the heart observed in healthy elderly subjects, which include, among others, cardiac hypertrophy or fibrosis and alterations in the sympatho-vagal balance.[53,54]

We observed a significant association between triglyceride plasma levels and QTc interval. This parameter has been studied less frequently than other well-known risk factors. In a large

cross-sectional study that determined the association between QTc interval and metabolic syndrome and its components, using a multiple linear regression analysis, QTc was positively associated with triglyceride levels in men, but not in women. After adjusting for covariates, QTc interval increased with increasing numbers of metabolic syndrome components in a dose-response manner.[55] In another cross-sectional survey, triglycerides were significantly associated with QTc interval in unadjusted regression analyses, but not in multivariate analysis.[56] In a retrospective study that included patients with type 2 diabetes, triglyceride levels were associated with prolonged QTc only in the univariate analyses.[57] The explanation regarding the association between triglyceride levels and QTc prolongation is not clear. It has been suggested that dyslipidemia may induce atherosclerotic changes accompanying oxidative stress and can subsequently cause endothelial dysfunction and damage.[55]

Our multivariate model showed that patients who received at least one drug with known risk of torsades de pointes had significantly higher QTc intervals than the other patients. Using the classification from CredibleMeds, significant associations between drug prescriptions with known risk of torsades de pointes and QTc prolongation were also observed in other studies.[25,40,47] A large cross-sectional survey in Italy found that first-generation antipsychotics, age, gender, alcohol misuse, and concurrent risky drugs prolonged QTc interval.[58] In a retrospective review of antipsychotic overdoses, there appeared to be a significant risk of QTc prolongation with amisulpride and thioridazine.[59] These results indicate that use of psychotropic drugs should be undertaken with caution, particularly in patients with other risk factors for QTc prolongation. However, a comprehensive review concluded that current literature does not provide sufficient and consistent information to stratify second-generation antipsychotics and antidepressants for their potential to prolong QTc interval or cause torsades de pointes.[30] QTc prolongation associated with these drugs is, in itself, not sufficient to cause torsades de pointes, which can occur at therapeutic doses and with QTc interval $<$500 ms.[30]

Hypokalemia is a well-known risk factor for QTc prolongation, as observed in some previous studies,[10,27,41] but not all.[39] Potassium plays an important role in maintaining the electrical potential across the cellular membrane, as well as in depolarization and repolarization of the cardiac myocytes. Alterations in potassium levels may lead to ECG changes and severe arrhythmias.[60] In our study, potassium plasma levels were not significantly associated with QTc, except when Bazett's formula was used for all ECGs (supplementary Table S5). An explanation could be that potassium was included if it was measured at $\pm$ 3 days from the ECG. In unstable patients, a modification of this parameter between the ECG recording and laboratory measurement cannot be excluded. Of note, this might concern a minority of patients, as around half of the measurements were performed the day of the ECG and three-quarters at $\pm$ 1 day.

Different scores for QTc prolongation have been developed in recent years. A risk score for QT prolongation in hospitalized patients was, for example, developed by Tisdale and colleagues.[61] The Mayo Clinic also created a pro-QTc score that reflects patients' multimorbidity and polypharmacy. This score has been shown to be an age-independent predictor of mortality.[62] A genetic QT score was also developed, which explained a significant proportion of the variability in drug-induced QT prolongation. This score was a significant predictor of drug-induced torsades de pointes.[63]

Limitations

The classification from CredibleMeds was used in this study, but different results might have been obtained if a different classification was used. Due to the retrospective design of the study, all clinical and biological parameters possibly linked to the QTc interval were not measured systematically for all patients. For example, due to a low number of observations, calcium or magnesium plasma levels were not studied, and only the ECGs with all covariates were included in the multivariate model, corresponding to 60% of the valid ECGs. To increase the amount of available data, potassium and creatinine plasma levels were included if they were measured at $\pm$ 3 days from the ECG, which could have decreased the accuracy. Another limitation is the representativeness of the sample included. A selection bias is possible, as an ECG was performed in less than half of the eligible subjects. An ECG could have been performed more frequently in patients with known cardiovascular risk factors, which could have overestimated the

prevalence of abnormal ECGs. On the other hand, an underestimation of abnormal ECGs was also possible because of the impossibility of performing ECGs in very agitated patients, some of which might have been under the influence of drugs or alcohol, which can increase the QTc interval. Our results can therefore not be generalized to the whole hospitalized psychiatric population. In addition, the sample size of the subgroup of patients included in order to study the evolution of the QTc during hospitalization was small, limiting the statistical power of these results. Finally, due to the design of the study (cross-sectional), only associations between clinical factors and QTc prolongation were observed, rather than causal relationships.

Conclusion

In the current study, performed over a 1-year period, 45.5% of hospitalized psychiatric patients had at least one ECG recording. Among them, 17.9% had a significantly abnormal ECG and 7.6% a prolonged QTc interval, which confirms the utility of performing ECGs in this population. The QTc of the patients with an ECG performed at admission, and a second during hospitalization, did not change significantly, which suggests that the hospitalization of the patients was not a risk factor for QTc prolongation. However, in the patients with a baseline value in the upper quartile, the QTc decreased significantly. The covariates that were positively associated with QTc interval were female gender, age, triglyceride levels, and administration of at least one drug with known risk of torsades de pointes. Psychotropic drugs should thus be prescribed with caution in psychiatric inpatients, particularly in those with other risk factors for QTc prolongation.

Acknowledgements

We wish to thank the Data Science and Research Group (Lausanne University Hospital) for the extraction of the data from the electronic medical records.

Authors' note

Part of this work was presented at the 20th Journées Franco-Suisses de Pharmacie Hospitalière, 1–2 December 2016, Bern, Switzerland.

Ethical Approval

The study protocol, examining clinical data retrospectively, was approved by the local Ethics Committee Vaud (approval code is 2015-00067).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: This work has been funded in part by the Swiss National Research Foundation (CE and PC: 320030-120686, 324730-144064, and 320030-173211). The funding sources had no role in the writing of the manuscript or in the decision to submit it for publication.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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