QTc Prolongation Associated With Psychiatric Medications

A Retrospective Cross-Sectional Study of Adult Inpatients

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Abstract:

Objective: The aim of our study was to assess the impact of psychiatric medications and concomitant risk factors on the prevalence of QTc prolongation and torsades de pointes (TdP) in hospitalized subjects. We examined the association between individual risk scores and QTc prolongation and proposed an evidence-based protocol for electrocardiogram monitoring on psychotropic medications.

Method: Electrocardiograms (ECGs) of subjects hospitalized over a 1-year period were analyzed for QTc prolongation, associated risk factors, and use of medications. Analysis was performed using logistic regression to identify independent predictors of QTc prolongation, and the Pearson χ^2 test was used for risk score assessment.

Results: A total of 1249 ECGs of 517 subjects were included in this study. Eighty-seven subjects had QTcB intervals greater than 470 milliseconds for females and greater than 450 milliseconds for males. Twelve (2.3%) subjects had QTcB of 500 milliseconds or greater, or greater than 60 milliseconds of change from baseline. Of these subjects, only 1 case of QTc interval change was related to routine use of psychiatric medications. There were no incidents of TdP. Age, diabetes, hypokalemia, overdose, diphenhydramine, and haloperidol were significant independent predictors of QTc prolongation. Risk scores were significantly correlated with QTc prolongation ($P = 0.001$).

Conclusion: Our retrospective review study found that the occurrence of TdP and QTc prolongation was low in this subject population. QT abnormalities were associated with known risk factors, and risk scores correlated well with QTc prolongation. Providers can use the protocol proposed in this study, which incorporates risk scores and the CredibleMeds classification system to determine the need for ECG monitoring and to guide treatment.

Key Words: ECG, TdP, sudden cardiac death, prolonged QTc, psychopharmacology

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Psychiatric medications are associated with QTc interval prolongation, which can lead to torsades de pointes (TdP). Because of this risk, electrocardiograms (ECGs) are used during treatment for monitoring QTc; however, this practice varies greatly among clinicians. The use of ECG as a biomarker for TdP has also been disputed given the natural variations in QTc intervals.[1,2] Currently, the American Psychiatric Association provides clear ECG monitoring recommendations only for thioridazine, pimozide, mesoridazine, and ziprasidone.[3]

Some experts believe that psychiatric medications can be prescribed safely without routine ECGs in low-risk subjects,[1,2] especially as the practice of psychiatry moves away from first-generation antipsychotic to potentially safer second-generation agents.[4] Conversely, a large study by Ray et al[5] found the incidence of sudden cardiac death in users of both atypical and typical antipsychotics to be twice that of nonusers. Such studies prompted the clinical practice of obtaining pretreatment ECGs on all patients. However, the methodologies of such studies have been questioned. Dr Lieberman, of the American Psychiatric Association Council on Research, noted that the study by Ray et al used an unvalidated cardiovascular risk score, and the retrospective nature of this study leads to an overestimation of sudden cardiac death compared with prospective studies.[4] In addition, Ray et al attempted to exclude subjects with known coronary heart disease; however, they could not exclude those with undiagnosed heart disease or differentiated TdP from other malignant arrhythmias such as asystole. Given these discrepancies and the rise of atypical antipsychotic use, a formal model of decisional analysis in ECG monitoring on psychiatric medication is needed.[6]

The aim of our study was to examine the impact of psychiatric medications and concomitant risk factors for TdP on the prevalence of QTc prolongation in hospitalized subjects. We also reviewed the use of the Mayo Clinic Pro-QTc Risk Score to predict QTc prolongation. Finally, our article concludes with an evidence-based protocol for ECG monitoring for clinical practice by combining previously validated risk scores and the Arizona CredibleMeds classification system.

METHODS AND PROCEDURES

Study Population

The survey population consisted of 517 adult consecutive subjects hospitalized at a university medical center behavioral health unit from January 1, 2015, through January 1, 2016. All subjects received 1 or more ECGs during their stay and took at least 1 psychiatric medication with risk for TdP or QT prolongation (as defined by the Arizona CredibleMeds QT drug list).[7] We documented each subject's ECGs and individual risk factors for TdP, and all medications were taken with the potential to prolong QTc (psychiatric medications and other medications).

Data Collection of ECGs, Associated Risk Factors, and Risk Scores

A baseline ECG and blood samples (thyrotropin, complete blood cell count, comprehensive metabolic panel, hepatitis panel, fasting glucose, and HA1c) were obtained within 24 hours of admission, before starting new medications, and subsequently based

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on clinical need. Trained technicians collected all ECGs. QTc morphology was analyzed on 12-lead ECGs by computer algorithm and then verified by cardiology fellows. The QT interval was corrected for heart rate using the Bazett formula ($QTcB = QTc/(RR)^{0.5}$). QTcB between 470 and 500 milliseconds in females and between 450 and 500 milliseconds in males were considered borderline prolonged. QTcB equal to or above 500 milliseconds or with greater than 60 milliseconds of change from baseline were considered prolonged. These cutoffs were selected based on previous studies demonstrating higher risk of sudden cardiac death or arrhythmia.

The following risk factors associated with QTc prolongation were collected: sex, age (>60), dialysis, infection with human immunodeficiency virus or hepatitis C, hypothyroidism, cardiovascular heart disease, diabetes, hypokalemia (serum potassium, <3.5 mEq/L), hypocalcemia (serum calcium, <4.5 mg/dL), hypomagnesaemia (serum magnesium, <1.7 mg/dL), history of traumatic brain injury, recent overdose, and concurrent antibiotic use or infection.

All data were gathered manually by 8 reviewers. For quality control, 1 researcher randomly checked the data to ensure homogeneity and accuracy in collection. The risk scores used to determine individual subject risks were analogous to the Mayo Clinic Pro-QTc Risk Score,[8] in which each associated risk factor and QTc prolonging medication present on the Arizona CredibleMeds QT drug list was considered equipotent and was assigned 1 point.

Data Analysis

Analysis was performed using logistic regression to identify independent predictors of QTc prolongation and Pearson χ^2 test for risk score assessment. Significance was set at $P < 0.05$.

RESULTS

Subject Population and Medications

A total of 1249 ECGs were obtained on 517 hospitalized subjects. Clinical characteristics and risk factors of study subjects are summarized in Table 1. Subjects were treated with 31 different psychiatric medications with varying degrees of risk for QTc interval prolongation or TdP, and 60.3% of the patients took more than 1 medication. The frequencies of individual medication use and risk classification are shown in Table 2.

TABLE 1. Clinical Characteristics of Subjects (N = 517)

Total Subjects	**517**	
Male	246	48%
Female	271	52%
Mean age	38	
Age > 60 y	26	5.0%
Dialysis	4	0.8%
CVD	37	7.1%
Diabetes	73	14%
HIV	23	4.4%
Hepatitis C	38	7.3%
Low K	67	13%
Low Mg	56	11%
Low Ca	149	29%
Hypothyroid	68	13%
TBI	8	1.5%
Antibiotics	57	11%

CVD indicates cardiovascular disease; TBI, traumatic brain injury.

TABLE 2. Psychiatric Medications Used in This Study and Risk Category Based on the CredibleMeds Classification System

	n
Known risk	
Chlorpromazine	3
Citalopram	37
Escitalopram	42
Haloperidol	40
Ondansetron	28
Thioridazine	1
Conditional risk	
Diphenhydramine	34
Fluoxetine	29
Hyroxyzine	210
Olanzapine	81
Paroxetine	8
Quetiapine	142
Sertraline	75
Trazodone	60
Ziprasidone	7
Possible risk	
Aripiprazole	50
Asenapine	5
Clozapine	1
Fluphenazine	7
Iloperidone	1
Imipramine	1
Lithium	43
Lurasidone	9
Mirtazapine	33
Nortriptyline	1
Paliperidone	16
Promethazine	9
Risperidone	62
Venlafaxine	36
Not classified	
Buproprion	25
Buspirone	12

CredibleMeds Classify Drugs into 3 Categories: known risk—drugs that prolong QT and are associated with TdP when used as recommended; conditional risk—drugs that are associated with TdP but only under certain conditions of their use; possible risk—drugs that prolong QT but lack evidence for TdP when used as recommended.

Prevalence of TdP and QTc Prolongation

There were no incidents of TdP. Of 517 subjects, 87 (16.8%) subjects had QTcB greater than 450 milliseconds for males (55%) and greater than 470 milliseconds for females (45%). Of these, 19 (3.7%) subjects had a final QTcB, obtained after medication titration, greater than their initial QTcB obtained on admission. Twelve (2.3%) subjects had QTcB equal to or greater than 500 milliseconds or greater than 60 milliseconds of change from baseline. Of these, only 1 case was associated with routine use of psychiatric

TABLE 3. Characteristic of Subjects With QTcB ≥500 Milliseconds or ≥60 Milliseconds of Change From Baseline (n = 12)

Risk Factors	Risk Score	Medications	Cause of QTc Prolongation	Initial QTcB	Final QTcB	Longest QTcB
F, TSH, OD	9	Chlorpromazine, haloperidol, hydroxyzine, ondansetron, mirtazapine, promethazine	Psychiatric medications	407 (HR 66)	468 (HR 99)	468
Low K, OD	4	Venlafaxine, trazodone	OD	378	455	455
Age, low Mg, low Ca, OD	7	Lithium, bupropion, hydroxyzine	OD	513	421	513
F, low K, OD	7	Quetiapine, sertraline, lithium, hydroxyzine	OD	505	448	505
F, low Ca, CVD	6	Fluoxetine, risperidone, hydroxyzine	OD	501	465	501
F, low Ca, hep C, OD	9	Risperidone, haloperidol, olanzapine, hydroxyzine, ondansetron	OD	512	443	512
F, low Ca, TSH	5	Haloperidol, hydroxyzine	OD LVH	502	445	502
DM, low K, hep C, low Ca	6	Quetiapine, hydroxyzine	RBBB	470	485	501
Dialysis, DM	4	Sertraline, hydroxyzine	LVH	510	495	510
F, low Ca	3	Hydroxyzine	LBBB	500	517	517
F, low Mg, low Ca, hep C	6	Haloperidol, diphenhydramine	Unknown	480	480	511
None	1	Sertraline	Unknown	463	406	528

OD indicates overdose; LVH, left ventricular hypertrophy; BBB, bundle branch block; F, female; CVD, cardiovascular disease; TSH, hypothyroid; DM, diabetes mellitus; LBBB, left bundle branch block; RBBB, right bundle branch block.

medications rather than other factors, such as acute overdose or bundle branch block (Table 3).

Risk Score Analysis

Subject risk scores were significantly associated with incidence of QTc prolongation ($P = 0.001$; Fig. 1, Table 4). Figure 1 shows a plot of escalating incidence of QTc prolongation concurrently with increasing risk scores. Age [odds ratio (OR), 1.033], diabetes (OR, 2.233), hypokalemia (OR, 2.277), overdose (OR, 2.857), diphenhydramine (OR, 4.394), and haloperidol (OR, 3.086) were significant independent predictors of QTc prolongation equal to or greater than 500 milliseconds or greater than 60 milliseconds of change from baseline (Table 4). A significant protective association was found for the female sex (OR, 0.540). No other risk factors or medications were found to be significantly associated with QTc prolongation.

DISCUSSION

In this 1-year retrospective cross-sectional study, 1249 ECGs were obtained from 517 subjects admitted to our hospital. Prevalence of drug-induced QTc interval equal to or greater than 500 milliseconds or greater than 60 milliseconds of change from baseline was 2.3%. This value is within the range of the 0.9% to 2.6% prevalence reported by previous studies.[9,10] However, there were no incidents of TdP, and only 1 (0.002%) subject in our study met the criteria for QTc prolongation under conditions of routine psychiatric medication use (outside of acute overdose or other causes of QTc prolongation such as right bundle branch blocks). This subject's risk score was 9; initial QTcB was 407 milliseconds, and final QTcB was 468 milliseconds before discharge. Her medication regimen consisted of chlorpromazine, haloperidol, mirtazapine, hydroxyzine, ondansetron, and promethazine. She

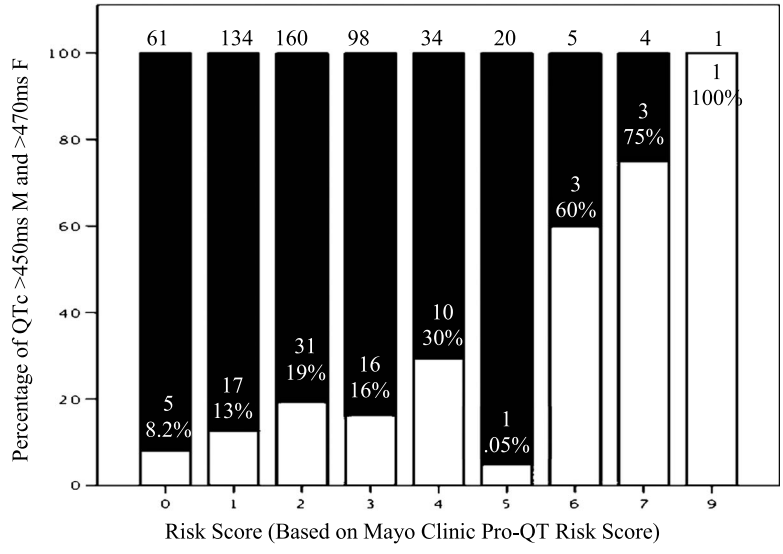

FIGURE 1. Predictive performance of subject risk scores.

TABLE 4. Logistic Regression Predicting QTcB >450 Milliseconds for Males or >470 Milliseconds for Females (n = 87)

Variables	*B*	SE	Significance	OR
Age (>60)	0.033	0.011	0.002	1.033
Diabetes	0.803	0.338	0.018	2.233
low K (<3.5 mEq/L)	0.823	0.333	0.013	2.277
Overdose	1.050	0.331	0.001	2.857
Diphenhydramine	1.480	0.449	0.001	4.394
Haloperidol	1.127	0.418	0.007	3.086
Female	−0.615	0.273	0.024	0.540

also had risk factors of hypothyroidism, acute overdose, and female sex (Table 3).

These findings are in agreement with the overall low incidence of TdP in the general clinical population.[11] Although the true incidence of TdP is largely unknown, a study by Sarganas et al[12] estimated the incidence of TdP to be 2.5 per million per year for males and 4 per million per year for females. The low occurrence of QTc prolongation in our study is also congruent with other contemporary studies[10,13] and could be explained by the shift in the spectrum of psychotropics used in modern psychiatry. Only 1 subject in our study took thioridazine, a higher-risk medication, whereas 50 subjects were treated with aripiprazole. Aripiprazole, per the CredibleMeds Classification System, can cause QTc prolongation but currently lacks evidence for a risk of TdP when used as recommended.[7] Other medications used frequently by our subject population and believed to have lower risk included risperidone (n = 62), lithium (n = 43), venlafaxine (n = 36), and mirtazapine (n = 33). These medications have been associated with QTc prolongation but not with TdP under normal conditions of their use. A portion of our subjects were treated with higher-risk medications such as haloperidol (n = 40), citalopram (n = 37), and escitalopram (n = 42); however, because of enhanced awareness of the cardiac risks of these medications, only Food and Drug Administration–recommended dosages were used. Dosages of citalopram were kept under 40 mg daily, and the dosage of escitalopram was kept under 20 mg daily.

Contrary to previous studies, we found diphenhydramine to be an independent predictor of QTcB prolongation. This finding is probably due to the higher heart rates associated with the antimuscarinic activity of diphenhydramine, which is overcorrected by the Bazett formula.[14,15] For this reason, some clinicians recommend using either the Friderica or Framingham formula over the Bazett formula when heart rate is greater than 80 bpm.[13] A large study by Vandenberk et al[15] found both the Framingham and Friderica formulas to be a superior predictors of mortality at 30 days and 1 year than the Bazett formula. The use of the optimal correction formula may improve care by providing greater allowance for clinically indicated QTc prolonging medications. For example, the QTcF was normal across 3 ECG readings (initial QTcF was 401 milliseconds and final was 430 milliseconds) for the single subject in our study who met criteria for QTcB prolongation under routine use of psychiatric medications. Therefore, no medication changes were made based on the abnormal QTcB findings.

Clinical Practice Guideline and ECG Monitoring Recommendations

Our study also identified independent predictors of QTc prolongation and evaluated the association between risk scores and QTc abnormality. Congruent with many previous studies, age, overdose, haloperidol use, and hypokalemia were found to be independent predictors of QTc prolongation. Hypokalemia, hypomagnesemia, and hypocalcaemia are well-known risk factors for TdP.[9] Electrolyte depletion may be caused by conditions such as malnutrition/anorexia, diuretic use, renal dysfunction, pituitary and thyroid insufficiency, central nervous system injury, diabetes, and dialysis. Haloperidol is known to cause TdP even at therapeutic dosages in both the intravenous and oral formulation.[7] This medication falls under the "known risk" CredibleMeds category, indicating its propensity to prolong QTc even when taken as recommended.

Awareness of individual medication risk and cardiac risk factors for TdP is essential for appropriate ECG monitoring and clinical treatment. Torsades de pointes rarely occurs in subjects without risk factors.[16] The Mayo Clinic study found the proQTc Risk Score to be an independent predictor of mortality with a hazard ratio of 1.18 [95% confidence interval (CI), 1.05–1.32; P = 0.006]. In this study, 99% of the subjects with QTc

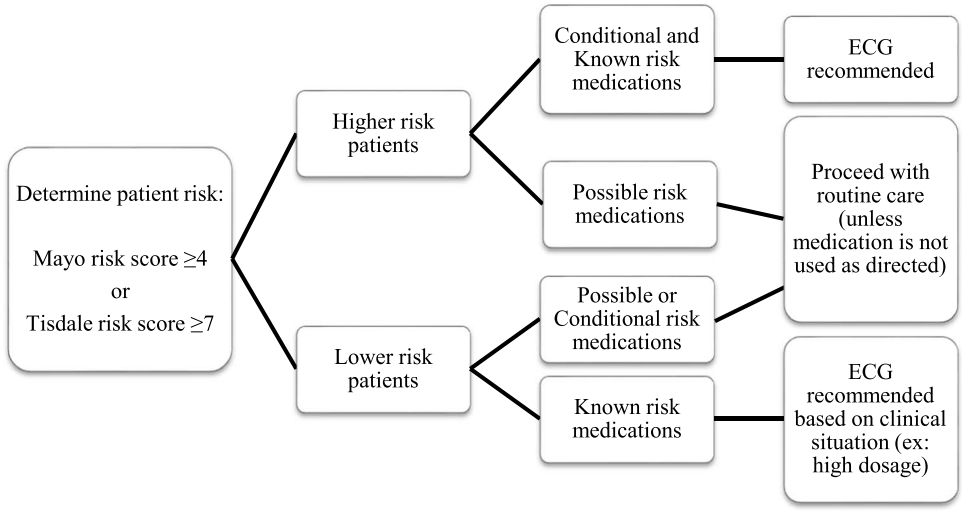

FIGURE 2. Protocol for ECG monitoring incorporating risk scores (predicting individual patient risk) and the CredibleMeds Classification System.

prolongation had at least 1 risk factor and a pro-QTc score of 4 or higher significantly predictive of mortality, with a hazard ratio of 1.72 (95% CI, 1.11–2.66; $P < 0.001$).[8] The study by Tisdale et al[16] also showed that the incidence of QTc prolongation is rare in subjects without risk factors and QTc interval increases exponentially with cumulating risk factors. The study by Tisdale et al divided risk scores into 3 groups: low (scores <7), moderate (7–10), and high (≥11). A high-risk score of 11 or higher was associated with sensitivity of 0.74, specificity of 0.74, positive predictive value of 0.79, and negative predictive value of 0.76 for prolonged QTc. In our study, the incidence of QTc greater than 450 milliseconds for males and greater than 470 milliseconds for females significantly correlated with subject risk scores ($P = 0.001$) (Fig. 1).

Clinical Practice Recommendations/ECG Monitoring Protocol

Risk scores can be integrated with the CredibleMeds drug classification system to guide ECG monitoring and treatment. Figure 2 shows our protocol for ECG monitoring on psychotropics. We suggest first evaluating a patient's risk based on either the Mayo Clinic Pro-QTc Risk Score or the Tisdale Risk Score. Next, the CredibleMeds drug list is used to delineate based on the risk of individual medications (Table 2). CredibleMeds define medications with "known risk" as those drugs that can prolong QT interval and are clearly associated with TdP, even when taken as recommended. Medications with "conditional risk" are associated with TdP, but only under certain conditions of use or when creating a condition that facilitates TdP. "Possible risk" medications are associated with QT prolongation but currently lack evidence for risk of TdP when taken as recommended. A comprehensive list of QT prolonging medications can be found at the CredibleMeds website, which is continually updated. Following our protocol, a low-risk subject with Mayo Clinic Pro-QTc Risk Score of 3 or a Tisdale Risk Score of 5, taking fluoxetine (a "conditional risk" medication) at Food and Drug Administration–recommended dosages, may not require ECG monitoring. Alternatively, a subject with higher Mayo Clinic Risk Score equal to or greater than 4 or Tisdale Score greater than 7 taking fluoxetine may benefit from ECG monitoring. This protocol allows for a careful risk-benefit analysis, taking into account an individual's TdP risk factors and medication risks.

Study Limitations

This study had several limitations. First, the sample size was limited; however, this study did capture a heterogeneous subject population, with multiple risk factors on combination therapy at a major university hospital. Second, we were unable to establish a cause-effect relationship between drug and QTc prolongation due to the study's retrospective nature and the high incidents of polypharmacy. Third, we cannot completely rule out that the low incidence of QTc prolongation was uninfluenced by ECG monitoring that steered toward more conservative use of medications. However, our retrospective review found only 2 documented cases of medication changes during this period out of concern for QTc changes.

CONCLUSION

In summary, the subjects in our study were treated with a wide spectrum of psychotropics with 60.3% on combined medication therapy. The subjects also carried many risk factors, and risk scores ranged from 0 to 9, with a mean and median of 2.0. Despite this, the occurrence of QTc prolongation was quite low and there were no incidents of TdP within the study period. These findings are congruent with the overall low incidence of TdP.[17] Nevertheless, 2% to 3% of prescription medications carry a risk for TdP,[18] and the use of atypical antipsychotics is on the rise. Because of this and the catastrophic nature of TdP, some clinicians and hospitals, such as ours, obtain ECGs on all admissions regardless of patient risk factors or medications. Routine ECGs are not currently endorsed by the American Psychiatric Association, except for high-risk medications or for subjects with concerning risk factors.[17,19] We hope that a more balanced and evidence-based protocol for ECG monitoring, such as that proposed in our study, will be adopted in the future to improve appropriate ECG monitoring and quality of care.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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