

Evaluation of the use of electrocardiogram monitoring in patients on psychotropic medications that have a risk of QT prolongation

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Abstract

Introduction: Many psychotropic medications carry a risk of prolonging the QT interval and increasing the risk of developing Torsade de pointes (TdP). The goal of this study was to evaluate whether patients taking psychotropic agents with a known risk of TdP are being monitored at a community hospital through the use of electrocardiograms (EKGs).

Methods: This was a retrospective chart review of 100 adult patients—50 from general medicine floors and 50 from psychiatric units—who were taking at least one psychotropic agent with a known risk of TdP during hospitalization.

Results: The mean number of medications with QT-prolongation risk administered to the psychiatric and general medicine patients was 4.2 ± 1.7 and 3.9 ± 2.0 , respectively ($P = .7484$). Thirty-two of the psychiatric patients (64%) and 48 of the general medicine patients (96%) received EKGs during their hospitalization ($P < 0.0001$). Of those newly starting the target medications, 58% (18 of 31) of the psychiatric patients and 71% (5 of 7) of the general medicine patients received a baseline EKG. The difference was not statistically significant ($P = .6807$). Overall, 8 patients (8%) had corrected QT (QTc) intervals >500 ms. Four had repeat EKGs performed, and none had medication changes made to decrease TdP risk.

Discussion: Many inpatients on psychiatric medications received multiple medications with a risk of TdP, but not all received monitoring through baseline or repeat EKGs when warranted. Patients with QTc intervals >500 ms were not appropriately managed to lower their risk of TdP. Pharmacists thus can help improve the monitoring and management of QT prolongation.

Keywords: psychotropic medications, EKG monitoring, QTc prolongation, Torsade de pointes

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Introduction

A prolonged QT interval is a risk factor for the development of Torsade de pointes (TdP), a potentially fatal arrhythmia. The risk for TdP increases as the corrected QT (QTc) interval increases; a QTc interval >500 ms is associated with a 2- to 3-fold higher risk of TdP compared with a QTc interval <500 ms. However, there is no threshold of QTc prolongation above which TdP is certain to occur (or below which avoiding it is certain). The risk of TdP can increase if more than one QT-prolonging drug is used concurrently.¹ Patients with risk

factors such as age above 65 years, female sex, congenital QT syndrome, bradycardia, and electrolyte disturbances are more likely to develop QTc prolongation.² Many medications often used in the psychiatric setting—such as tricyclic antidepressants, certain selective serotonin reuptake inhibitors, lithium, antipsychotics, and methadone—carry a risk of prolonging the QT interval and increase the risk of developing TdP.³⁻⁵ Patients with psychiatric conditions are often on combinations of these medications, which may further increase their risk of developing TdP.

According to American Heart Association practice standards on electrocardiogram (EKG) monitoring in hospital settings, an EKG is indicated for patients who: begin to take a drug known to cause TdP, overdose from potentially proarrhythmic drugs, have new-onset bradyarrhythmias, or suffer from severe hypokalemia or severe hypomagnesemia. The QTc interval should be documented before and at least 8 to 12 hours after the initiation, increase in dose, or overdose of QT-prolonging drugs.¹ Patients with a QTc increase of at least 60 ms after medication initiation, or who have a QTc interval >500 ms, are at risk for TdP. A QTc of <450 ms in men or <470 ms in women is considered safe, with no need for additional intervention.⁶

The goal of this study was to evaluate whether EKGs were being used to appropriately monitor patients at this inpatient facility who were taking psychotropic medications that have a known risk of TdP. The study also looked at the frequency of use of concomitant medications with a risk of QT prolongation. We compared the monitoring received on medical floors to that on the psychiatric units to see whether these patient populations are being managed differently.

Methods

This was a retrospective chart review of patients admitted to Monmouth Medical Center, a community teaching hospital in Long Branch, New Jersey, between December 1, 2014, and January 31, 2015. Patients admitted to two general medicine and two psychiatric units were included if they were 18 years or older and had at least one standing order for a psychotropic medication classified by CredibleMeds® (AZCERT Inc, Oro Valley, AZ) as having a known risk for TdP (haloperidol, methadone, citalopram, escitalopram, droperidol, chlorpromazine, pimozide, or thioridazine). Although many psychiatric medications have a risk of causing QT prolongation, and subsequently TdP, these medications were chosen because they have the strongest data to support this risk. Medications in other risk categories (eg, possible or conditional risk) were included in the analysis of all medications the patient

received. Patients were excluded if they did not receive at least one dose of the studied medication. The first 50 chronologic patients from each service (medicine or psychiatry) who met these criteria were included. If patients were moved from a general medicine to a psychiatric unit, or vice versa, each transfer was considered a separate admission.

Data collection included patients' age, sex, admitting diagnosis, medical service, full medication list, medication administration times, EKG results, and serum electrolyte concentrations. For patients with multiple electrolyte lab values reported, only the first set of values obtained was used. The QTc intervals were automatically calculated by the EKG machine using Bazett formula.⁷ Heart rates were obtained from EKG reports to determine whether bradycardia was present. Other risk factors for TdP and QT prolongation were also monitored for, including serum potassium and magnesium concentrations, when available. The first EKG obtained was used in the analysis for baseline EKGs as long as it was performed prior to or within 24 hours after starting the studied medication. Additional medications administered that have a possible or conditional risk of TdP were also recorded, including both standing orders and medications ordered on an as-needed basis. Each medication's risk of TdP was classified as known, possible (if it prolongs the QT interval but there is no substantial evidence that it causes TdP), or conditional (if it carries a risk of TdP and/or QT prolongation only under certain conditions, such as congenital long QT syndrome, drug overdose, or when coadministered with other QT-prolonging drugs) based on the classification by crediblemeds.org as of December 2, 2014.³

Demographic characteristics and clinical parameters were compared by treatment group using the Fisher exact test for categorical variables and Student *t* test for continuous variables. Data were analyzed using GraphPad software (La Jolla, CA). This study was approved by the appropriate institutional review boards at Monmouth Medical Center and Rutgers University.

Results

A total of 764 patients were screened for inclusion: 212 from psychiatric units and 552 from general medicine units. Of the former, 54 met inclusion criteria, and the first 50 were included, along with the first 50 qualified patients reviewed from the general medicine units.

Of the patients in the psychiatric units, 31 were on citalopram, 10 on escitalopram, 10 on haloperidol, and 4 on methadone. Two patients received both escitalopram and citalopram at different times during their inpatient

TABLE 1: Mean maximum daily doses received

Inpatient Unit	Citalopram, mg	Escitalopram, mg	Haloperidol, mg	Methadone, mg
Psychiatry	23.2	14	17	104
General medicine	18.8	15.5	5.9	66.7

stay. One patient had standing orders for both haloperidol and methadone, and one received both haloperidol and escitalopram. Of the patients in the general medicine units, 16 were on citalopram, 28 on escitalopram, 4 on haloperidol, and 3 on methadone. One patient received escitalopram and citalopram at different times during his stay. The mean daily doses for the standing orders of these medications were calculated using the highest daily dose achieved during inpatient stay and are reflected in Table 1.

Baseline characteristics of all patients are listed in Table 2. Most of the patients from the psychiatric units (62%; $n=31$) were not on the studied medication prior to admission, whereas most patients from the general medicine units (86%; $n=43$) were continuing the medication ($P < .001$). The most common admitting diagnosis for the general medicine patients was shortness of breath (26%; $n=13$), followed by medical or psychiatric screening exams (10%; $n=5$). Other diagnoses included altered mental status, weakness, lethargy, chest pain, rectal bleeding, and a drug overdose. The drugs involved in overdose were not recorded as part of data collection.

Aside from the studied medications, patients received several other medications with a known, possible, or conditional risk of TdP, as summarized in Table 3. The most common were diphenhydramine, furosemide, hydroxyzine, ondansetron, pantoprazole, quetiapine, risperidone, and trazodone. Including pro re nata medications, the mean number of medications with known, possible, or conditional TdP risk ordered per patient was significantly higher in the psychiatric cohort, at 5.7 ± 1.6 (median, 6; range, 3-9) for psychiatry and 3.8 ± 2.3 (median, 4; range,

1-10) for general medicine ($P=.0002$). The average numbers actually administered to the psychiatric and general medicine patients, however, were not significantly different, at 4.2 ± 1.7 (median, 3; range, 1-8) and 3.9 ± 2.0 (median, 4; range, 1-9; $P=.7484$), respectively.

A total of 49 of the psychiatric patients (98%) and all of the general medicine patients had potassium levels checked during hospitalization ($P=1.000$). A total of 1 of the 49 psychiatric patients and 4 of the 50 general medicine patients had low potassium levels (<3.5 mEq/L) initially ($P=.3622$), 4 of whom (the general medicine patients) then received potassium supplementation. The psychiatric patient did not receive potassium for her potassium level of 3.4 mEq/L. Two general medicine patients with very low potassium levels of 2.9 and 2.8 mEq/L had prolonged QTc intervals: 465 and 550 ms, respectively. Both were treated with potassium supplementation and one was also treated with magnesium supplementation for a magnesium level of 1.5 mg/dL. Overall, magnesium monitoring was less frequent, particularly in psychiatric patients, with concentrations checked in 2 of the psychiatric patients (4%) and 19 of the general medicine patients (38%; $P < .0001$). Two patients, both from general medicine, had low magnesium concentrations (<1.5 mg/dL) and were treated with magnesium supplementation.

Results from baseline EKGs are shown in Table 4. Significantly more general medicine patients (96%; $n=48$) than psychiatric patients (64%; $n=32$) were monitored with EKGs during their stay ($P < .0001$). Of the psychiatric patients, 26 (52%) had an EKG done within 24 hours of admission or starting the medication. Another

TABLE 2: Baseline characteristics

Inpatient Unit	Mean Age, y (SD)	Female, No. (%)	Mean Length of Stay, d (SD)	Low K ⁺ , No. (%) ^a	Low Mg ²⁺ , No. (%) ^b	Low HR on EKG, No. (%) ^c	No. (%)
							Not on Studied Medication PTA
Psychiatry, $n = 50$	39.0 (13.4)	28 (56)	8.4 (3.8)	1/49 (2)	0/2	5/32 (15.6)	31 (62)
General medicine, $n = 50$	67.6 (15.6)	30 (60)	7.8 (5.3)	4/50 (8)	2/19 (10.5)	1/49 (2)	7 (14)
<i>P</i> value	$<.001$.8396	.3442	.3622	1.0000	.0352	$<.001$

EKG = electrocardiogram; HR = heart rate; PTA = prior to admission.

^aLow K⁺: <3.5 mEq/L.

^bLow Mg²⁺: <1.5 mEq/L.

^cLow HR: <60 bpm.

TABLE 3: Number of patients who received additional medications based on risk of Torsade de pointes

Classification	Medications	Psychiatric Floors	Medical Floors
Known risk	Amiodarone	...	1
	Azithromycin	...	2
	Dofetilide	...	1
	Levofloxacin	...	10
	Ondansetron	6	13
Possible risk	Aripiprazole	4	1
	Clozapine	1	...
	Famotidine	1	3
	Lithium	2	...
	Mirtazapine	1	1
	Olanzapine	4	4
	Promethazine	0	4
	Quetiapine	11	8
	Risperidone	8	3
	Venlafaxine	2	1
Conditional risk	Ziprasidone	4	...
	Amantadine	2	...
	Amitriptyline	...	1
	Ciprofloxacin	...	1
	Diphenhydramine	4	9
	Doxepin	3	...
	Fluconazole	...	2
	Fluoxetine	3	1
	Furosemide	...	20
	Hydrochlorothiazide	...	2
	Hydroxyzine	12	3
	Metoclopramide	...	2
	Metronidazole	...	4
	Nortriptyline	1	...
	Pantoprazole	13	17
	Paroxetine	2	...
	Sertraline	5	1
	Trazodone	32	10
	Trimethoprim-sulfamethoxazole	...	3

6 (12%) had their first EKG done within several days of admission. Of the general medicine patients, 47 (94%) received an EKG within 24 hours of admission or starting the medication. One patient (2%) underwent an EKG 3 days after starting the medication.

A total of 31 of the psychiatric patients (62%) and 7 general medicine patients (14%) started the medication during hospitalization ($P < .0001$). Of these, 58% (18 of 31) of the psychiatric patients and 71% (5 of 7) of the general medicine patients received an initial EKG prior to or within

24 hours of starting the medication ($P = .6807$). A total of 23% (7 of 31) of the psychiatric patients compared with 71% (5 of 7) of the general medicine patients who were started on the medication during hospitalization had a repeat EKG to monitor for changes in the QTc caused by the medication ($P = .0224$).

A total of 1 of 18 men (6%) and 7 of 18 men (39%) from the psychiatric units and general medicine units, respectively, had QTc intervals >450 ms ($P = .0408$). A total of 2 of 14 women (14%) and 14 of 30 women (46%) from the psychiatric units and general medicine units, respectively, had QTc intervals >470 ms at baseline ($P = .0487$). A total of 8% ($n = 8$) of patients had QTc intervals >500 ms (Table 5), all of them hospitalized in general medicine units. Only half of those with QTc intervals >500 ms had repeat EKGs performed, and none had medication changes made specifically to decrease TdP risk. One patient—a general medicine patient—with an initial QTc <500 ms had QTc prolongation to >500 ms on a repeat EKG. None of the patients had a change in their QTc of >60 ms from baseline. There were no documented episodes of TdP in any of the studied patients.

Discussion

Overall, patients received an average of 3 to 4 medications that pose a risk of QT prolongation during hospitalization. Some received as many as 8 or 9 such medications. When patients are acutely ill, they often receive more medications than in their typical regimen, which may also have a risk of causing QT prolongation. The prevalence of these interactions has been seen in other studies. One study of 592 hospitalized psychiatric patients found a total of 965 drug interactions in patient profiles, 11.7% ($n = 113$) of which carried a risk for QT prolongation.⁸ Our study shows that most patients who were already on a psychiatric medication associated with a known risk of TdP received multiple medications that carry an additional risk of QT prolongation. Some recent data suggest that polypharmacy with QT-prolonging agents may not significantly increase the risk of QT prolongation over monotherapy.^{9,10} Further studies on the impact of these interactions are warranted to fully understand their significance.

A total of 60% (23 of 38) of the patients who were newly started on one of the studied medications had an EKG. According to American Heart Association recommendations, they should receive both a baseline and a repeat EKG after starting the medication.¹ There was also a difference in the frequency of EKG monitoring between psychiatric and general medicine patients. This may be partly due to the fact that patients admitted to the general medicine floors likely received EKGs for medical

TABLE 4: Electrocardiogram (EKG) results

Inpatient Unit	Baseline EKG Done ^a	Baseline EKG Done if New Medication	Repeat EKG Done if New Medication	QTc Above Normal Range at Baseline ^b	Repeat EKG Done if >450 ms	QTc >500 ms at Baseline	Repeat EKG Done if QTc >500 ms	Medication Changes Done if QTc >500 ms
Psychiatry, No. (%), n = 50	26 (52)	18/31 (58)	7/31 (23)	3/28 (11)	1/3 (33)	0
General medicine, No. (%), n = 50	47 (94)	5/7 (71)	5/7 (71)	21/47 (45)	10/21 (48)	8/47 (17)	4/8 (50)	0/8
P value	<.001	.6807	.0224	.0023	.6043	.0443

QTc = corrected QT interval.

^aBaseline EKG is any EKG done within 24 hr of admission or starting the medication.

^bNormal ranges are considered to be ≤ 450 ms for males and ≤ 470 ms for females.

reasons related to the cause of their admission and not purely for the monitoring of QTc intervals.

The low use of EKGs may not be unique to our institution and likely extends to outpatient populations. In a study of 3420 outpatients in the United Kingdom who were prescribed haloperidol during the study period, only 1.8% (n=62) had an EKG at the start of treatment.¹¹ Given how often potentially QTc-prolonging medications are used, evaluating the need for EKG monitoring should be part of all psychiatric patients' care. An analysis conducted in Switzerland found that routine EKG monitoring on all admitted psychiatric patients was cost-effective at reducing sudden cardiac deaths, especially in cases of polypharmacy and illicit substance use.¹²

Although normal QTc intervals for patients vary depending on sex, we chose to focus on those patients who had a QTc >500 ms because this is generally accepted as the

cutoff above which the risk of TdP increases.¹ In our study, QTc prolongation above 500 ms was detected in 8% (8 of 100) of patients overall. There may have been more patients with QTc prolongation that were missed because of the low number of repeat EKGs performed on patients during their inpatient stay.

Except for correction of electrolyte abnormalities, no readily identifiable changes were made in the treatment of patients who had QTc intervals >500 ms. This presents an opportunity for improvement in patient care. All patients with prolonged QTc intervals should have, at a minimum, received repeat EKGs. In a population-based cohort study of 3484 patients 55 years and older who had records of multiple EKGs performed, those who had 2 consecutive EKGs with prolonged QTc intervals had an increased risk of sudden cardiac death compared with patients who had consistently normal QTc intervals (Bazett hazard ratio, 2.23; 95% confidence interval, 1.17-

TABLE 5: Results in patients with corrected QT interval (QTc) >500 ms on initial electrocardiogram (EKG)

Patient	Initial QTc, ms	Age, y/Sex	[K ⁺]	[Mg ²⁺]	HR, bpm	Medications With Any QTc Prolongation Risk	QTc on Repeat EKG	Medication Changes
1	550	81/F	2.8	2.3	74	CIT, furosemide, OLZ, ondansetron, pantoprazole	Not performed	None
2	516	73/F	4.1	...	82	ESC, pantoprazole, trazodone	Not performed	None
3	513	100/F	4.5	1.6	77	CIT, furosemide, pantoprazole	Not performed	Added risperidone
4	532	61/F	3.8	1.2	130	ESC, levofloxacin, metoclopramide, ondansetron, pantoprazole, TMP/SMZ	Not performed	Added metronidazole, promethazine-codeine Discontinued levofloxacin, pantoprazole, TMP/SMZ
5	536	81/M	4.7	2	100	CIT, furosemide	536 (2 d later)	None
6	504	72/M	4.5	1.6	77	ESC, amiodarone, furosemide	522 (1 d later)	None
7	513	53/F	3.5	...	88	CIT, famotidine	502 (9 d later)	None
8	502	89/F	4	...	105	ESC, furosemide, pantoprazole	490 (6 d later)	None

CIT = citalopram; ESC = escitalopram; F = female; HR = heart rate; M = male; OLZ = olanzapine; TMP/SMZ = trimethoprim/sulfamethoxazole.

4.24; Fridericia hazard ratio, 6.67; 95% confidence interval, 2.96-15.06).¹³ Patients with a prolonged QTc interval in one EKG reading but not the other did not have an increased risk of sudden cardiac death compared with patients with consistently normal QTc intervals.¹³ Although this study was not specifically in a psychiatric population and excluded patients on QTc-prolonging agents, it can be helpful in identifying patients who require an intervention based on repeat EKGs.

Patients with prolonged QTc intervals of >500 ms or with a change of >60 ms from baseline should have changes made to their medications in order to reduce the risk of TdP. Possible changes include switching to alternative agents with lower TdP risk, decreasing doses of the high-risk agents, identifying and rectifying drug interactions, or adjusting electrolyte imbalances. In our study, no changes were made to the studied medications in patients with prolonged QTc intervals. No history on how long patients were on these medications prior to admission was able to be obtained from the medical record, although most of the patients were on these medications prior to admission. Also, no earlier EKG results from prior to this hospitalization were checked for comparison.

Patients were also poorly monitored for electrolyte abnormalities. Most patients were monitored with baseline chemistry panels, which included potassium concentrations, but very few were checked for magnesium levels, especially in the psychiatric population. High-risk patients, including those with cardiac conditions, female patients, and older patients, should be assessed for all risk factors to ensure their safety when starting a medication with a relatively higher risk of TdP.

The present study has limitations. Because we focused our screening criteria on psychotropic medications, the results from our general medicine population may not be generalizable to all such patients. Another limitation is that we included EKGs that were performed within 24 hours of hospital admission. Ideally, these would have been done prior to initiating the medication; however, whether this is reasonable depends on EKG availability. Thus, the actual rate of EKGs performed prior to starting one of the studied medications may be even lower than reported here. The QTc intervals were only calculated using the Bazett formula, which works best when the heart rate is between 60 and 100 beats per minute, possibly overcorrecting at slower rates and undercorrecting at faster ones. The Fridericia formula for correction would have been another option: it has the same limitations at slow rates but is more accurate at faster ones.¹⁴ Moreover, risk factors for TdP were not comprehensively assessed. Only the initial electrolyte levels were recorded, even though many patients, especially those from the general medicine units, had repeat labs done.

Also, aside from admitting diagnoses, we did not assess medical histories, including TdP risk factors like cardiovascular conditions and renal or hepatic impairment.

Conclusions

This study assessed the appropriateness of EKG monitoring in patients taking psychotropic medications with a known risk for causing TdP. Improvements can be made in both the psychiatric and general medicine areas of the hospital: more frequent monitoring of EKGs at baseline when starting a medication that can prolong the QT interval; monitoring of electrolytes, such as potassium and magnesium, in patients at a higher risk for TdP; and, perhaps most importantly, mitigating the risk of TdP through medication changes in patients who develop QTc prolongation. Pharmacists can play an important role in monitoring for QTc prolongation in patients and recommending medication changes in those patients at higher risk for TdP.

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