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Implementation of a QTc-interval monitoring protocol by pharmacists to decrease cardiac risk in at-risk patients in an acute care inpatient psychiatric facility

Nicole M. Daniel, PharmD[1]; Kim Walsh, RPh[2]; Henry Leach, PharmD[3]; Lauren Stummer, PharmD[4]

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Abstract

Introduction: Many medications commonly prescribed in psychiatric hospitals can cause QTc-interval prolongation, increasing a patient's risk for torsades de pointes and sudden cardiac death. There is little guidance in the literature to determine when an electrocardiogram (ECG) and QTc-interval monitoring should be performed. The primary end point was improvement of the appropriateness of ECGs and QTc-interval monitoring of at-risk psychiatric inpatients at Barnabas Health Behavioral Health Center (BHBH) and Monmouth Medical Center (MMC) following implementation of a standardized monitoring protocol. The secondary end point was the number of pharmacist-specific interventions at site BHBH only.

Methods: Patients who met the inclusion criteria were assessed using a standardized QTc-prolongation assessment algorithm for ECG appropriateness. A retrospective analysis of a control group (no protocol) from January 1, 2016, to July 17, 2017, was compared with a prospective analysis of the intervention group (with protocol) from December 11, 2017, to March 11, 2018.

Results: At BHBH, appropriate ECG utilization increased 25.5% after implementation of a standardized protocol ($P = .0172$) and appropriate omission of ECG utilization improved by 26% ($P < .00001$). At MMC, appropriate ECGs decreased by 5%, and appropriate ECG omissions increased by 28%, neither of which were statistically significant ($P = 1.0$ and $P = .3142$, respectively). There was an increase in overall pharmacist monitoring.

Discussion: The study demonstrated that pharmacist involvement in ECG and QTc-interval monitoring utilizing a uniform protocol may improve the appropriateness of ECG and QTc-interval monitoring in patients in an acute care inpatient psychiatric hospital.

Keywords: QTc prolongation, torsades de pointes, ECG monitoring, psychiatric hospital

[1] (Corresponding author) Pharmacy Resident, Barnabas Health Behavioral Health Center, Toms River, New Jersey; Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey, New Brunswick, New Jersey, nicole.daniel0189@gmail.com, ORCID: https://orcid.org/0000-0003-0111-3085; [2] Pharmacy Director, Barnabas Health Behavioral Health Center, Toms River, New Jersey, ORCID: https://orcid.org/0000-0002-7879-3720; [3] Pharmacy Clinical Coordinator, Barnabas Health Behavioral Health Center, Toms River, New Jersey, ORCID: https://orcid.org/0000-0003-1142-9868; [4] Pharmacy Resident, Barnabas Health Behavioral Health Center, Toms River, New Jersey; Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey, New Brunswick, New Jersey, ORCID: https://orcid.org/0000-0003-1241-713X

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Introduction

Many psychotropic medications as well as nonpsychotropic medications commonly prescribed in psychiatric hospitals can cause prolongation of the QTc interval, increasing a patient's risk for torsades de pointe (TdP) and sudden cardiac death. Genetics, sex, cardiovascular status,

pathological conditions, and electrolyte imbalances have also been associated with QTc prolongation. However, the current literature does not specifically recommend routine electrocardiograms (ECGs) for patients on antipsychotics.[1] The American Heart Association guideline for ECG monitoring in hospital settings was updated in 2017.[2] It provides recommendations on which patient populations are most likely to benefit from QTc monitoring while hospitalized but lacks specifics about patient selection and frequency of monitoring.[1] A previously validated risk-scoring tool was developed to identify patients at greatest risk of QTc prolongation, including factors such as age, sex, electrolytes, medications, and cardiac status, all of which are included in the protocol in this study.[3] Due to the lack of preexisting protocols or QTc-monitoring strategies associated with these medications, this study aimed to implement a protocol derived from this previously validated risk-scoring tool to enhance the delivery of patient care and safety in patients at risk for cardiac complications as a result of medications prescribed in an inpatient psychiatric hospital.

Methods

The primary facility was Barnabas Health Behavioral Health Center (BHBH), an acute care, 100-bed adult psychiatric hospital located in Toms River, New Jersey. The secondary site was Monmouth Medical Center (MMC), a 500-bed hospital with 44 dedicated adult inpatient psychiatric beds located in Long Branch, New Jersey. Patients who received 1 or more predetermined medication(s) while admitted to either facility between January 1, 2016, and July 17, 2018, and between December 11, 2017, and March 11, 2018, were included as the control and intervention groups, respectively. The medication(s) must have been scheduled, thus excluding all as-needed or 1-time medications. The medication(s) could have been given by any route of administration and must have been on the formulary for the health system. Patients were excluded if they were under 18 years of age. The control group was evaluated retrospectively, and the intervention group was evaluated prospectively.

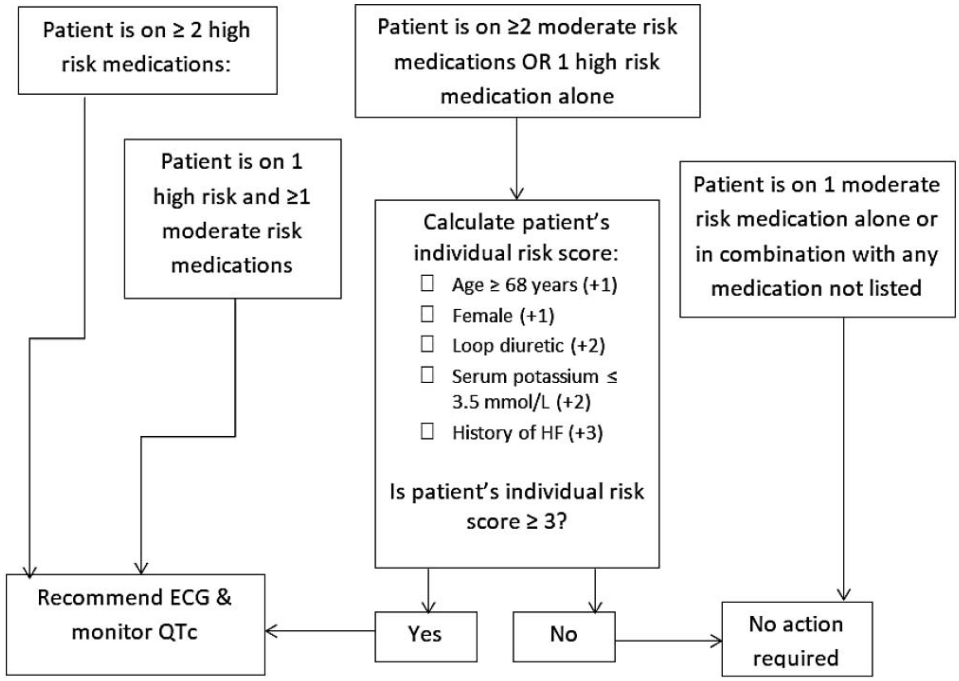
A retrospective analysis of both the primary and secondary end points was conducted to establish a baseline for QTc monitoring, labeled the control group. For the primary end point, patients who met the inclusion criteria were assessed using a standardized QTc prolongation monitoring algorithm (Figure) to determine which of those were appropriately monitored. We also analyzed the data for changes in missed-opportunity ECGs, which we define as patients who inappropriately lacked QTc-interval monitoring. The algorithm was created utilizing several resources based on known risk factors for QTc prolongation. CredibleMeds.org[4] provided the foundation for categorizing medications based on high or moderate risk. Several other studies[5-8] that examined the average QTc-interval increase of different medications and genetic and clinical predictors of QTc prolongation and TdP as well as medication monitoring parameters from package inserts were considered in including and categorizing high- and moderate-risk medications. For the secondary end point, pharmacist-specific interventions at site BHBH that were electronically documented were evaluated.

A prospective analysis was conducted from December 11, 2017, to March 11, 2018, to determine QTc-interval monitoring after protocol implementation, labeled the intervention group. Patients meeting criteria were identified in real time by a clinical decision support program based on active medications. If a patient was found to be an appropriate candidate for an ECG (Figure), a pharmacist would contact the prescriber with the recommendations and document the intervention using the QTc-interval monitoring form. Analysis of these 2 cohorts (preimplementation and postimplementation of the protocol) allowed a comparison to be made between our previous practice of ECG and QTc-interval monitoring and our practice after the implementation of a standardized protocol. For the secondary end point, the quantity, type, and outcome of pharmacist interventions at site BHBH only were evaluated.

The medications determined to be high or moderate risk are as follows. High-risk medications included citalopram, haloperidol, chlorpromazine, ziprasidone, quetiapine, clozapine, clomipramine, methadone, and amiodarone. Moderate-risk medications included fluoxetine, escitalopram, amitriptyline, doxepin, imipramine, nortriptyline, levofloxacin, azithromycin, fluconazole, ondansetron, donepezil, and atomoxetine. QTc prolongation for this study was defined as a QTc interval greater than 450 milliseconds for men and greater than 460 milliseconds for women. A QTc interval greater than 500 milliseconds was evaluated for all sexes as high risk for TdP. The diagnostic test utilized to evaluate the potential cardiac risk was the ECG. The ECGs performed for any reason during admission or those performed in the emergency department immediately leading up to admission and evaluated at the study site were included within the scope of this study. This study was approved by the appropriate institutional review boards at BHBH and MMC.

End Points

The primary end point was to improve the appropriateness of ECG and QTc-interval monitoring in at-risk psychiatric inpatients at BHBH and MMC. We performed a multisite comparison of the primary end point. Secondary outcomes included the quantity of pharmacist-specific interventions concerning ECG utilization and



Medication High Risk:

- Citalopram
- Standing Haloperidol
- Chlorpromazine
- Ziprasidone
- Quetiapine
- Clozapine
- Clomipramine
- Methadone
- Amiodarone

Medication Moderate Risk:

- Fluoxetine
- Escitalopram
- Amitriptyline
- Doxepin
- Imipramine
- Nortriptyline
- Levofloxacin
- Azithromycin
- Fluconazole
- Ondansetron
- Donepezil
- Atomoxetine

FIGURE: QTc-interval monitoring algorithm[5,6,8] (ECG = electrocardiogram; HF = heart failure)

QTc-interval monitoring, the types of interventions, and the resulting outcomes to medication management.

Statistical Analysis

Nominal data were analyzed using a Fisher exact test with an alpha of 0.05 and a *P* value of ≤.05. Results were compared across all groups.

Results

There were no statistically significant differences in the baseline characteristics of age, serum potassium level, loop diuretic use, or history of heart failure between the control and intervention groups at both locations (Table 1). The difference in number of female patients in each group was statistically significant. The BHBH had more patients on high- and moderate-risk medications than did MMC, resulting in a larger sample size. The mean QTc interval from both sites was similar and below the threshold for classification as prolonged.

The top 3 most commonly prescribed study medications stratified by study group were as follows: quetiapine (37.3%), citalopram (29.9%), and methadone (17%) for the BHBH control group; quetiapine (55.2%), escitalopram (24.4%), and methadone (7.4%) for the BHBH intervention group; citalopram (80%), quetiapine (18%), and haloperidol (12%) for the MMC control group; and citalopram (85.7%), quetiapine (9.5%), and fluoxetine (9.5%) for the MMC intervention group. The medication regimen most frequently associated with QTc-interval prolongation was

TABLE 1: Baseline characteristics

	Barnabas Health Behavioral Health Center		Monmouth Medical Center		
	Control (n = 311)	Intervention (n = 299)	Control (n = 100)	Intervention (n = 21)	*P* Value[a]
Age, y, mean ± SD	50.6 ± 19	49.9 ± 19.0	38.3 ± 13.8	33.6 ± 12.1	.8774
Female, No. (%)	183 (58.8)	129 (57)	41 (41)	11 (52.4)	.0055
Serum K^+ < 3.5 meq/L, No. (%)	16 (5.1)	12 (4)	7 (7)	1 (4.8)	.2125
Loop diuretic use, No. (%)	23 (7.4)	4 (1.3)	3 (3)	0 (0)	1
History of heart failure, No. (%)	10 (3.2)	3 (1)	0 (0)	0 (0)	1
QTc interval, ms, mean ± SD	434.3 ± 26	448.8 ± 36.4	430.5 ± 24.8	426.1 ± 18.5	.6661

[a]*P* value derived from Fisher exact test 2 × 2 site Barnabas Health Behavioral Health Center, control and intervention groups versus site Monmouth Medical Center, control and intervention groups.

the combination of 1 high-risk medication plus 1 or more moderate-risk medications (Table 2).

At BHBH, appropriate ECG monitoring per protocol increased by 25.5% after implementation of the protocol ($P = .0172$). Patients who did not receive an ECG and did not meet criteria to require an ECG also improved by 26% ($P < .00001$), which was statistically significant. Prior to protocol implementation, 31.3% of patients who met criteria for requiring an ECG and QTc-interval monitoring did not receive either. After implementation, the number of missed-opportunity patients decreased by 29% to 5.3% (Table 3).

At MMC, the number of appropriate ECGs remained lower than anticipated, going from 32% prior to protocol implementation to 27% afterward. In the missed-opportunity analysis, the percentage of patients who were inappropriately lacking an ECG and QTc-interval monitoring decreased from 28% to 0%. These results were not statistically significant.

We also evaluated a composite assessment of patients who met criteria and received an ECG with patients who did not meet criteria and did not receive an ECG to assess appropriateness across both groups. At site BHBH, 203/311 (65%) of patients were appropriately monitored prior

TABLE 2: Frequency of medication combinations, No. (%)

	Barnabas Health Behavioral Health Center				Monmouth Medical Center			
	Control (n = 311)	Control With Elevated QTc (n = 8)	Intervention (n = 299)	Intervention With Elevated QTc (n = 14)	Control (n = 100)	Control With Elevated QTc (n = 8)	Intervention (n = 21)	Intervention With Elevated QTc (n = 1)
Patients on ≥2 high-risk and 0 moderate-risk medications	43 (13.8)	2 (25)	10 (3.3)	2 (14.3)	19 (19)	2 (25)	2 (9.5)	0 (0)
Patients on 1 high-risk and ≥1 moderate-risk medication	52 (16.7)	4 (50)	22 (7.4)	7 (50)	10 (10)	3 (37.5)	2 (9.5)	1 (100)
Patients on 1 high-risk or ≥2 moderate-risk medications	180 (57.9)	2 (25)	204 (68.2)	3 (21.4)	70 (70)	3 (37.5)	15 (71.4)	0 (0)
Patients on 1 moderate-risk medication	36 (11.6)	0 (0)	62 (20.7)	2 (14.3)	1 (1)	0 (0)	2 (9.5)	0 (0)
Men with QTc interval >450 ms	3/128 (2.3)		6/170 (3.5)		6/59 (10.2)		1/10 (10)	
Women with QTc interval >460 ms	5/183 (2.7)		8/129 (6.2)		2/41 (4.9)		0/11 (0)	
Patients with QTc intervals >500 ms	0 (0)		3 (1)		1 (1)		0 (0)	

TABLE 3: Primary end point: appropriateness of electrocardiogram (ECG) monitoring

	Control (%)[a]	Intervention (%)[a]	*P* Value
Barnabas Health Behavioral Health Center			
Appropriate ECG[a]	32/62 (51.6)	27/35 (77.1)	.0172
Appropriate no ECG[a]	171/249 (68.7)	250/264 (94.7)	<.00001
Monmouth Medical Center			
Appropriate ECG[a]	18/57 (32)	4/15 (27)	1.0
Appropriate no ECG[a]	31/43 (72)	6/6 (100)	.3142

[a]As defined per protocol.

to protocol, and 277/299 (93%) of patients were appropriately monitored after protocol implementation. At site MMC, 49/100 (49%) of patients were appropriately monitored prior to protocol, and 10/21 (48%) of patients were appropriately monitored after protocol implementation.

In terms of secondary outcomes, despite the prospective analysis occurring over a 3-month period, as opposed to the retrospective analysis, which occurred over the course of 18 months, there was an increase in overall pharmacist involvement (Table 4).

Discussion

The study had several strengths. At both sites, there was no formal method of pharmacist monitoring of QTc intervals or ECG monitoring; this protocol provided a uniform method of doing so. It focused on medications commonly prescribed in psychiatric facilities. We acknowledge that some controversy may exist regarding our classification of medications, such as citalopram. The algorithm and monitoring form can be easily modified to reflect different hospital preferences and formularies. There was a focus on high- and moderate-risk medications and patients to avoid creating alert fatigue. As-needed medications were excluded. The protocol does not interfere with the prescribers' ability to utilize ECGs outside of the protocol. There was a statistically significant difference in women across groups. However, risk assessments for this group would have been accounted for because sex was incorporated into the protocol.

There were also some limitations. Retrospective data was limited by the number of interventions documented. Medications reviewed were limited to the hospital formulary. One limitation faced by the hospital was pharmacists being unable to order ECGs without prescriber consent. All ECGs ordered prior to protocol were at the discretion of the prescriber; medical consults were not required. Additionally, ECGs performed during psychiatric admission or in the emergency department prior to admission, were included. Both sites have an average length of stay of 5 to 7 days. Due to time constraints as well as occasional patient refusal, there was often time for only 1 ECG. However, patients were reassessed by the pharmacists after any medication or dose change of any of the predetermined medications. The limitation is that this method did not guarantee a repeat ECG when 1 may have been indicated. It also did not attempt to translate the findings into guidelines that could be consistently recommended.

At MMC, ECGs are performed as part of the initial patient workup, meaning they are ordered for the majority of

TABLE 4: Secondary end point: pharmacist interventions at Barnabas Health Behavioral Health Center

	Control	Intervention
No. drug dose decreased (%)	5 (4.7)	4 (1.4)
No. drug discontinued (%)	84 (79.2)	16 (5.4)
No. no change in therapy (%)	17 (16.1)	273 (93.2)
Total No. pharmacist-specific interventions[a]	106/18 mo	293/3 mo
Average No. documented interventions per mo	5.9	97.7
No. ECGs performed	22	35
No. ECGs recommended by a pharmacist/Total No. ECGs performed (%)	4/22 (18.2)	20/35 (57.1)

ECG = electrocardiogram.

[a]Includes any documented pharmacist activity in regards to any study patients' medications and monitoring.

patients regardless of indication. Additionally, an indication is not always documented, so it is possible ECGs ordered for reasons other than QTc-interval monitoring were included. More patients received ECGs at MMC than were deemed appropriate according to this algorithm, but anyone who did not receive an ECG did not meet criteria, and there were no missed-opportunity ECGs. It is also worth noting that site MMC had a smaller sample size in both groups. Therefore, the impact of this protocol in terms of streamlining ECGs to more appropriate patients was greater at BHBH.

For the secondary end points, there was an increase in overall pharmacist involvement, which was expected. There was also a decrease in medication dose reduction and discontinuation as well as an increase in medication regimens with no change. We believe a potential explanation for this is that, because patients were being better monitored and we had ECGs to support or oppose the concern for QTc-prolongation risk, patients required fewer changes in their medications based on cardiac risk alone. Not all of the medication discontinuations and dose decreases directly resulted from pharmacist intervention; in some cases, the prescribers made changes prior to pharmacist intervention. In addition, not all of these changes included a documented reason of QTc prolongation. Therefore, it is a limitation that we cannot attribute all of the appropriate QTc monitoring to the protocol implementation. We concluded there was a positive impact on both prescribers and pharmacy, which included the ability to maintain medication regimens without fear of harming the patient, increasing confidence in safe, long-term options, and a decrease in medication discontinuation based on theoretical risks. This study performed a short-term evaluation of each patient. Further studies examining long-term outcomes, especially the protocol's effectiveness in mitigating long-term cardiac risk, may be warranted.

As a result of this protocol, a greater number of at-risk patients were screened via ECG to determine the actuality of that risk, and lower-risk patients were not being monitored unnecessarily, which decreased the number of excess ECGs. This suggests a possible cost savings for the hospital. Further studies evaluating the financial impact may be warranted.

Overall, the study demonstrated that in an acute care inpatient psychiatric facility, implementation of a standardized QTc-interval monitoring protocol being performed routinely by pharmacists can greatly improve the appropriateness of ECGs and QTc-interval monitoring. Further studies to replicate results are warranted given only 1 site demonstrated a significant change.

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