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SYSTEMS-LEVEL QUALITY IMPROVEMENT

Providers' Response to Clinical Decision Support for QT Prolonging Drugs

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Abstract Commonly used drugs in hospital setting can cause QT prolongation and trigger life-threatening arrhythmias. We evaluate changes in prescribing behavior after the implementation of a clinical decision support system to prevent the use of QT prolonging medications in the hospital setting. We conducted a quasi-experimental study, before and after the implementation of a clinical decision support system integrated in the electronic medical record (QT-alert system). This system detects patients at risk of significant QT prolongation (QTc>500ms) and alerts providers ordering QT prolonging drugs. We reviewed the electronic health record to assess the provider's responses which were classified as "action taken" (QT drug avoided, QT drug changed, other QT drug(s) avoided, ECG monitoring, electrolytes monitoring, QT issue acknowledged, other actions) or "no action taken". Approximately, 15.5% (95/612) of the alerts were followed by a provider's action in the pre-intervention phase compared with 21% (228/1085) in the post-intervention phase (p=0.006). The most common type of actions taken during pre-intervention phase compared to post-intervention phase were ECG monitoring (8% vs. 13%, p=0.002) and QT issue acknowledgment (2.1% vs. 4.1%, p=0.03). Notably, there was no significant difference for other actions including QT drug avoided (p=0.8), QT drug changed (p=0.06) and other QT drug(s) avoided (p=0.3). Our study demonstrated that the QT alert system prompted a higher proportion of providers to take action on patients at risk of complications. However, the overall impact was modest underscoring the need for educating providers and optimizing clinical decision support to further reduce drug-induced QT prolongation.

Keywords Clinical decision support systems · Medical order entry systems · Electrocardiogram · Prolonged QT interval · Torsades de pointes · Medical informatics

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Introduction

Prolongation of the QT interval can trigger a potentially fatal ventricular arrhythmia known as torsade de pointes (TdP). Currently, more than 100 FDA-approved drugs can cause QT prolongation, and a subset of these drugs have torsadogenic potential [1]. Considering all possible drug interactions, it can be challenging for physicians to recognize all drugs with QT prolonging potential as well as identifying specific patients at risk for this potentially serious side-effect. In 2010 a joint scientific statement was published by American Heart Association and American College of

Cardiology to increase awareness among providers in hospital settings about the risk of QT prolongation, the need for monitoring (by obtaining a surveillance ECG before and after initiation of QT-prolonging drugs and/or additional monitoring of electrolytes), and management of drug-induced QT prolongation [2]. In this statement, a QTc of >500 ms was set as an actionable threshold because of its significant increased pro-arrhythmic potential for TdP [3, 4].

Prevalence of QT prolongation in patients admitted to the hospital ranges from 25 to 35% [5–8]. Hospitalized patients especially are at an increased risk, because of advanced age, multiple co-morbidities, electrolyte disturbances, renal dysfunction, and polypharmacy [2]. Previous studies have shown that, despite showing a history of QT prolongation, QT prolonging medications are still prescribed in 35–51% of patients. In fact, 40% of patients with a QTc > 500 ms were still exposed to such drugs [9].

Computer-based clinical decision support systems (CDSS) are important tools for promoting patient's safety in clinical practice [10–12]. A systematic review of these systems demonstrated that overall most alerts had a positive impact in improving prescribing behavior and/or reducing error rates [13]. Furthermore, the majority of hospitals now use electronic health records (EHR) with computerized provider order entry (CPOE) systems for medication orders, and CDSS can be easily integrated in the provider's workflow to help providers to identify and manage patients at risk.

Mayo Clinic has implemented a customized CDSS (QT alert system) to deliver several clinical decision support interventions to identify patients with high risk prolonged QT (QTc > 500 ms) and enhance awareness among the healthcare team by sending notifications and documenting this problem [14, 15]. In this study, we describe and systematically evaluate the CPOE component of the QT alert system. Specifically, we assess the provider's responses to the QT alert when they attempt to order a QT prolonging drug in a patient with evidence of QT prolongation at risk for complications.

Methods

Setting

Mayo Clinic, a tertiary academic medical center in Rochester, Minnesota, has a comprehensive EHR (Centricity Enterprise, GE Healthcare) with integrated CPOE and CDSS (Blaze Advisor ®, Fair Isaac Corporation). The study was approved by the Mayo Clinic Institutional Review Board. Subjects who had not provided authorization for use of their medical records in research were not included.

QT alert system

This system was described in previous publications [14, 15]. Briefly, all the ECGs were automatically screened by the Mayo Clinic QT alert system and those with significant QT prolongation (QTc ≥ 500 ms for adults, ≥ 470 ms for pediatric patients) generated a notification to the ordering provider and documented "Prolonged QT" in the problem list. The CPOE component was later added, which provided a "QT alert" to providers attempting to order a QT prolonging drug in a patient previously identified to have significant QT prolongation. The pop-up alert presented the name of the drug, level of the risk (risk of or possible risk of TdP), any QT prolonging drug already in the medication list, and a link to online educational resources with more information on how to manage QT prolongation. In this study, we aimed to evaluate the provider's actions upon receiving a CPOE QT alert.

Study design

This was a quasi-experimental study in the hospital setting with a pre-intervention phase and a post-intervention phase. The pre-intervention phase was between November 19, 2010 and February 8, 2011, during which the system was fully operational, but did not generate CPOE QT alerts. This "silent mode" allowed us to collect all the necessary baseline data. The post-intervention phase was between February 11, 2011 to June 29, 2011, and during this time the system generated CPOE QT alerts to providers who were ordering QT prolonging drugs to patients at risk. Each attempt for individual drug was logged and classified as an "alert". There were multiple alerts on multiple medications but only the first alert for each unique medication was included for data analysis, as it was assumed that responses to subsequent alerts for the same drug on same patient would not be independent of the initial exposure. Alerts generated by verbal orders, and orders entered by proxies, after discharge or after medication administration were not included. Of the total number of patients included in the study, 109 patients were hospitalized during both, pre-intervention and post-intervention, phases of the study. As providers would not have been aware of the alert during the pre-intervention phase (silent mode), these visits were considered separate events and the alerts were evaluated during both phases. A total of 1697 CPOE QT alerts to providers in 1004 patients were accumulated in the final study cohort.

Data collection

Clinical data was collected by searching and reviewing the EHR including patient demographics, provider characteristics, clinical setting, clinical notes, medications, ECG, orders,

and dismissal summary. The data was organized and attributed to specific events based on the time of the alerts. The QT alert system log provided the exact time of the alert and additional information related to the patient, provider and drug ordered. The drugs included in the study were based on the list of QT prolonging drugs defined by the Crediblemeds website. Only drugs with "known TdP risk" and "possible TdP risk" were included [1].

Outcome measures

The main outcome measure was defined as "any action taken" by the provider after receiving the QT alert and that could prevent potential worsening of QT prolongation or a complication like TdP. "An "action" was defined as one or more of the clearly defined expected behavior by the provider in response to a prolonged QT alert triggered by prescription one or more QT prolonging medications. We reviewed all clinical notes surrounding the date of the alert (emergency room notes, admission notes, progress notes by primary and consult team, and discharge summary) for documentation of any action taken in response to the alert. For example, if the provider mentioned a "prolonged QT interval" as one of the assessment without any change in the plans it was considered as "QT issue acknowledged". However, if a repeat ECG or electrolyte panel were ordered as a part of plan for prolonged QT interval, these actions were noted as such. Herein, the actual mention of the action rather than just the order of any additional tests were critical to our review."

The actions were classified as follows:

1. QT drug avoided: the drug triggering the alert was discontinued or placed on hold.
2. QT drug changed: the drug triggering the alert was substituted with a different drug with same therapeutic effect, but not present on the QT drug list.
3. Other QT drug(s) avoided: the provider acknowledged the potential for drug-induced QT prolongation and suggested avoidance of additional QT drugs.
4. ECG monitoring: the provider ordered additional ECG monitoring after the alert.
5. Electrolytes monitoring: the provider ordered monitoring of electrolytes or management of abnormal levels.
6. QT issue acknowledged: no specific action was taken, but the alert and associated QT prolongation was clearly noted by the provider in the EHR, (i.e. clinical notes).
7. Other actions: Action not classifiable in the above categories (i.e. recommendation for monitored bed, cardiology consultation, review of additional risks for QT prolongation, documentation of risk/benefit).

Additional outcome measures evaluated were length of hospital stay and 30-day all-cause mortality.

Statistical analysis

Demographic data was expressed as categorical data for gender and ethnicity, and mean and standard deviation for age. Other characteristics and the action taken were expressed as number and percentage. Descriptive analysis included frequencies and distributions of study variables. Chi-square test or Fisher Exact test was used to compare categorical variables. Student's t-test was used to compare means for normally distributed data.

A logistic regression model was built to predict action taken/no-action taken using a forward stepwise method, which added one variable at a time as long as all variables in the model were significant. The only two statistically significant variables were the most recent QTc and the cohort (pre/post-intervention). The QTc interval was analyzed as continuous variable and, in two additional models, as a categorical variable dichotomized at 500 ms and at 470/480 ms in male/female. All three models provided similar results. Only the results for the two models using the dichotomous variables are reported.

All statistical analyses were performed with GraphPad Prism statistical software. All statistical tests were two-sided, and $p < 0.05$ was considered significant.

Results

Overall, there were 612 QT alerts in 358 patients during the pre-intervention phase and 1085 QT alerts in 646 patients during the post-intervention phase. Approximately, 15.5% (95/612) of the alerts were followed by a provider's action in the pre-intervention phase compared with 21% (228/1085) in the post-intervention phase ($p = 0.006$). At the same time, the proportion of actions per patient in the pre-intervention phase compared with the post-intervention phase was 18% (65/358) vs. 24% (156/646), $p = 0.03$.

The characteristics of the patients were similar in both groups, pre-intervention and post-intervention, including age (mean ± SD, 64.1 ± 18.7 vs. 63.7± 19.1, $p = 0.5$), gender (female, 45.8% vs. 47.7%, $p = 0.6$) and ethnicity (Caucasian, 92.4% vs. 92.1%, $p = 0.8$). The characteristics of the providers were also similar in both groups including clinical specialty (medical 59.6% vs. 60.7%, $p = 0.65$; surgery 26.0% vs. 26.9%, $p = 0.67$; pediatrics, 1.8% vs. 2.3%, $p = 0.48$; other specialties 12.6% vs. 10.1%, $p = 0.10$) and provider class except for the group "other providers" that included pharmacists and registered nurses (consultant 5% vs. 4%, $p = 0.26$; nurse practitioner/physician assistant, 32% vs. 33%, $p = 0.59$; resident/fellow, 60% vs. 62%, $p = 0.60$; other providers 2.29% vs. 0.92%, $p = 0.02$).

Table 1 shows the proportion of action taken in the pre-intervention phase vs. the post-intervention phase based on class of providers and specialty of the provider. Only the class "resident/fellow" showed a trend to increase the proportion of

Table 1 Proportion of actions taken in the pre-intervention phase vs. the post-intervention phase based on class and specialty of provider

	Pre-intervention phase		Post-intervention phase		
	n = 612	Action(s) taken n (%)	*n* = 1085	Action(s) taken n (%)	*p*-value
Class of provider					
Consultant	32	5 (15.6)	44	12 (27.3)	0.3
Nurse practitioner/ physician assistant	197	27 (13.7)	363	69 (19.0)	0.1
Resident/fellow	369	61 (16.5)	668	143 (21.4)	0.06
Other providers*	14	1 (7.1)	10	2 (20.0)	0.6
Specialty of provider					
Medicine	365	74 (20.3)	659	183 (27.8)	0.008
Surgery	159	13(8.2)	292	25 (8.6)	0.9
Pediatrics	11	1 (9.1)	25	6 (24.0)	0.3
Other specialties**	77	7 (9.1)	109	14 (12.8)	0.4

*Other providers = pharmacists and registered nurses

** Other specialties = family medicine, emergency medicine, psychiatry, neurology, anesthesiology, pharmacology and physical medicine

action taken in the post-intervention phase but was not statistically significant (16.5% vs. 21.4%, $p = 0.06$). In addition, only providers in the "medical specialty" showed a significant increase in the proportion of actions taken in the post-intervention phase (20.3% vs. 27.8%, $p = 0.008$).

Figure 1 shows the frequency of specific actions taken by the providers. ECG monitoring was the most common action taken during both phases of the study. Only two actions were statistically significantly more frequent in the post-intervention phase compared with the pre-intervention phase, ECG monitoring (13% vs. 8%, $p = 0.002$) and QT issue acknowledged (4.1% vs. 2.1%, $p = 0.03$).

The 10 most frequently alerted medications during the study period and their associated number of alerts and action taken are listed in Table 2. In general, the most common drugs that triggered an alert were ondansetron (43%), levofloxacin

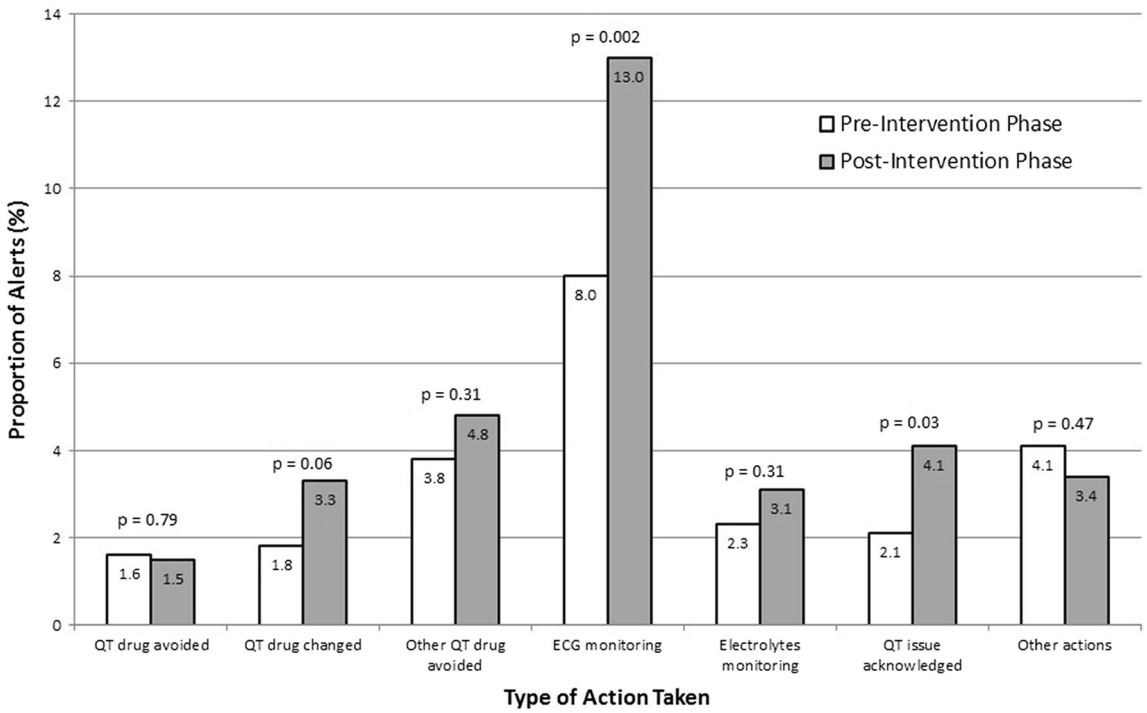

Fig. 1 Actions taken by the providers following a CPOE QT alert in the pre-intervention phase compared to the post-intervention phase of the study

Table 2 The ten most commonly alerted drugs, their associated number of alerts and the most common type of action taken. Proportion of action(s) taken in the pre-intervention phase vs. the post-intervention phase based on the drug

	Pre-intervention phase			Post-intervention phase			
Drug name	Number of alerts, n	Most common type of action, n (%)	Action(s) taken n (%)	Number of alerts, n	Most common type of action, n (%)	Action(s) taken n (%)	Action(s) taken *p*-value*
Ondansetron	236	ECG monitoring 12 (5.1)	29 (12.3)	413	ECG monitoring 32 (7.7)	60 (14.5)	0.477
Levofloxacin	75	ECG monitoring QT drug avoided 6 (8.0)	15 (20.0)	151	ECG monitoring 23 (15.2)	40 (26.5)	0.325
Amiodarone	68	ECG monitoring 3 (4.4)	5 (7.4)	141	ECG monitoring 13 (9.2)	21 (14.9)	0.188
Haloperidol	36	ECG monitoring 5 (13.9)	8 (22.2)	68	ECG monitoring 11 (16.2)	16 (23.5)	1.0
Azithromycin	12	ECG monitoring QT drug changed 3 (25.0)	6 (50.0)	23	ECG monitoring 7 (30.4)	13 (56.5)	0.736
Sotalol	12	ECG monitoring 6 (50.0)	6 (50.0)	16	ECG monitoring 7 (43.8)	7 (43.8)	1.0
Quetiapine	41	ECG monitoring 5 (12.2)	11 (26.8)	81	ECG monitoring 16 (19.8)	23 (28.4)	1.0
Tacrolimus	25	0	0	44	ECG monitoring QT issue acknowledged 2 (4.5)	6 (13.6)	0.079
Venlafaxine	10	ECG monitoring 2(20.0)	2 (20.0)	14	Electrolytes monitoring 1 (7.1)	1 (7.1)	0.550
Voriconazole	9	ECG monitoring QT drug avoided 1 (11.1)	2 (22.2)	18	ECG monitoring 10 (55.6)	11 (61.1)	0.103

*Fisher's exact test comparing proportion of action taken in the pre-intervention phase vs. the post-intervention phase

(15%) and amiodarone (14%). For these 3 drugs, the most common action taken was ECG monitoring in both, pre- and post-intervention phases.

Table 3 shows a subgroup analysis to assess how additional conditions influenced the action taken by providers. During the post-intervention phase, providers were less likely to take a specific action for patients whose current or most recent QTc was found to be below the pro-arrhythmic threshold (<500 ms for adults or <470 ms for pediatric patients), for patients whose current or most recent current QTc within normal range (QTc <470/480 ms for adults or <460 ms for pediatric patients), or patients with an already present, standing order to obtain an ECG within 72 h. They were more likely to take an action for patient with cardiac monitoring (intensive care

Table 3 Action(s) taken vs. no action taken by providers based on specific clinical conditions in the pre-intervention phase and post-intervention phase

	Pre-intervention phase		*p*-value	Post-intervention phase		*p*-value
	Action taken (*n* = 95)	No action taken (*n* = 517)		Action taken (n228)	No action taken (*n* = 857)	
QTc < 500 in adults or <470 in pediatric patients, n (%)	52 (54.7)	329 (63.6)	0.10	117 (51.3)	514 (60.0)	0.02
QTc < 470/480 in adults or < 460 in pediatric patients, n (%)	30 (31.6)	236 (45.6)	0.01	78 (34.2)	385 (44.9)	0.003
Comfort care, n (%)	0	21 (4.06)	0.0455	1 (0.43)	18 (2.1)	0.09
ECG obtained within 72 h, n (%)	23 (24.2)	181 (35.0)	0.04	42 (18.4)	352 (41.1)	0.0001
Pacemaker/Defibrillator, n (%)	15 (15.8)	59 (18.0)	0.23	9 (4.0)	109 (12.7)	0.1
Cardiac monitoring (intensive care unit), n (%)	56 (58.9)	296 (57.2)	0.8	124 (54.4)	332 (38.7)	0.0001

QTc Corrected QT interval in milliseconds, *ECG* electrocardiogram

unit). There was no significant difference for patients with orders for comfort care or with a pacemaker/defibrillator.

Logistic regression analysis showed that the log odds of taking action in the post-intervention cohort (vs. the pre-intervention cohort) was1.439 (p-value 0.0069). Among the different variables, only QTc on the ECG prior to the alert was found to be a statistically significant predictor of "actions taken". When the QTc was >500 ms the log odds of taking action was 1.429 (p-value 0.008) and with QTc > 470/480 ms (male/female) the log odds of taking action was1.4469 (p-value 0.006).

Overall, there was no statistically significant difference between pre-intervention and post-intervention phases in either length of stay (11.0 ± 19.3 vs. 9.9 ± 16.3 days; $p = 0.3$) or 30-day all-cause mortality (45/358, 12.6% vs. 63/646, 9.7%, $p = 0.16$).

Discussion

In this study, we showed that the CPOE QT alert system significantly impacts providers' prescribing behavior when prescribing medications that can potentially prolong QT in hospitalized patients at risk, addressing a common concern in prescribing medicating. However, the overall impact was fairly modest (15.5% vs. 21.0%), and a large number of CPOE QT alerts were still overridden (79%). Limited by the retrospective nature of this evaluation, when clear alert-driven actions were identified, providers most commonly ordered additional ECGs without stopping the QT prolonging drug meant to monitor a possible QT effect. This, in fact, is reasonable when we consider that close to half of the patients (43%) demonstrated normalization of the QTc at the time of the drug order. Additionally, providers would acknowledge in the EHR the potential risk without changing the order based on clinical needs. In many of these cases, the provider weighs the short term risk of QT prolongation with the important benefits of the chosen drug treatment. Even though not statistically significant, changing the order, by discontinuing the drug or using a different drug, was observed at relatively high frequency. The alert system did change prescribing pattern as seen our previous study by Atsushi et al. [14] and is now evident in the current study. In terms of prescription changes (hold/change/discontinue a QT prolonging medication) our results are modest as compared to previous study. We believe the effect size is underestimated in the current study, because even if there was a prescription change based on the alert but provider did not document it in their note, it was not counted as an action taken. This is in contrast to the previous study where the main outcome measure was proportion of completed orders irrespective of any documentation in the chart. Interestingly, provider class (consultants, nurse practitioner/physician assistants, residents/fellows, and others) did not impact the frequency of actions after the alert; even though the residents/fellows showed a trend that was not statistically significant (16.5% vs. 21.4%, $p = 0.06$). On the other hand, the specialty of the provider showed a significant impact for medical specialties (20.3% vs. 27.8%, $p = 0.008$) but not the other specialties. There was no significant difference in the 30-day all-cause mortality and length of stay between pre-intervention vs. post-intervention phases.

The high number of alert-overrides observed in our study is not uncommon. In a study by Tisdale et al. the overriding rates were similar (82%) and those alerts that were not overridden resulted in additional monitoring including ECGs, more frequent lab monitoring or treatment of modifiable risk factors such as discontinuing other QT prolonging medications and replacing electrolytes [16]. However, this study was conducted exclusively in patients admitted to a cardiac care unit and the alert displayed for the pharmacist confirming the order, who could then consult the prescriber. In our study, the alert displayed for all providers in the hospital entering a valid order in the CPOE system.

In many cases, no clear action was taken as patients demonstrated QT normalization at the time of the alert with the alert being triggered by QT prolongation on an earlier ECG or presence 'QT prolongation' in the patient's problem. Although this was more evident in the post-intervention phase (34.2% vs. 44.9%, $p = 0.003$), it was observed in the pre-intervention phase as well (31.6% vs. 45.6%, $p = 0.01$). This, however, is not the recommended management for patient at risk of significant QT prolongation. These patients should be monitored closely if they are exposed to factors that could increase the QT interval including QT prolonging drugs, electrolyte abnormalities and some comorbidities [2]. Our findings indicate the lack of knowledge related to current clinical practice guidelines and the need for more education in this area.

Overall, the most common drugs for which the CPOE QT alert was overridden were ondansetron and amiodarone. It seems reasonable to assume that the continued use of ondansetron is based on its relatively low QT prolonging risk as well its usually short term use in hospitalized patients [17]. Antiarrhythmic drugs like amiodarone are used for atrial fibrillation or for code-related cardiopulmonary resuscitation during which the QT alert and possible long term risk is appropriately ignored for the short-term benefit of the drug. The antibiotics (azithromycin and levofloxacin), on the other hand, can frequently be substituted by suitable alternatives.

Haloperidol is a commonly used medication and it was surprising that only about 25% of the time an action was taken in response to the alert, with ECG monitoring as the most common alert related action. The low number of actions in our study could be due to the fact that this medication is generally used on an as needed basis for agitation/delirium in hospitalized patients and may not exceed the safe cumulative dose of 2 mg in 24 h period [18]. In addition, haloperidol

is often prescribed as a part of comfort care order set at the time of end of life care, when prescribers appropriately ignore the alert. The lack of response to tacrolimus-triggered alerts is understandable considering its critical role in the management of patient with organ transplant where prevention of rejection outweighs the low risk of drug induced TdP.

In general, we observed that withholding or changing the QT prolonging drug depends on severity of disease, importance of the drug for treatment of the disease while weighing this against the risk of TdP, and the availability of a suitable alternative. However, actions to protect patients exposed to these drugs and at high risk of TdP can always be taken by the healthcare team including ECG monitoring, transfer to a monitor bed, electrolyte monitoring and correction, avoid other QT prolonging medications, etc.

One of the major strengths of our study is the large sample of patient and the hospital wide implementation of the QT alert system which helps to assess the impact on a variety of hospital services and staff. The results of this study therefore may be generalizable to similar, academic tertiary centers. Likewise, the CDSS was integrated into commercially available EHR which facilitate implementation. The limitations of the study include data from a single institution with a predominantly Caucasian population. Determination of some of the actions was based on data abstracted based on physician's documentation in EHR and may underestimate the providers response to QT alert. Given the complexity of patient situation, it is possible that in some patient's prolonged QTc may not be considered as the most important clinical problem and therefore not documented even if appropriate clinical decision was made at the time of CPOE alert. Another limitation inherent to the CDSS that must be acknowledged is "alert fatigue". This is a well-known phenomenon that significantly affects the desired impact of the alert system [19, 20]. Physicians are exposed to multiple alerts of varying degree of clinical relevance interrupting their workflow throughout the day, and this may result in bypassing or ignoring the alert. This may suggest that the system needs to refined or made more specific increase its desired effectiveness. For example, in our study, we found there were a significant number of cases when alert was overridden due most recent QTc being in normal range. One way we aim to address this in future, is to change the alert algorithm to alert only when recent QTc is prolonged in a patient with known history of prolonged QTc. Finally, it was not part of the study design to assess the immediate clinical impact of actions taken or not taken by providers.

Conclusions

CDSS integrated in the EHR has the potential to positively impact the management of patient at risk of significant QT prolongation by increasing awareness and prompting appropriate actions by providers at the time of ordering QT prolonging medications in the hospital setting. However, the current impact is modest and CDSS alone is not enough and unlikely able to fully cover the complex management of this condition. Our results underscores the need for additional education and dissemination of current clinical practice guidelines to better care for patient at risk for QT prolongation and related complications including TdP.

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Compliance with Ethical Standards

Conflicts of Interest Dr. Ackerman is a consultant for Boston Scientific, Gilead Sciences, Invitae, Myokardia, Medtronic, and St. Jude Medical. Dr. Ackerman and Mayo Clinic receive sales based royalties from Transgenomic for their FAMILION-LQTS and FAMILION-CPVT genetic tests. The other authors have no conflicts of interest to disclose. None of the disclosures pertain to this paper and none of the companies provided financial support for this paper.

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