ORIGINAL RESEARCH

Assessment of risk factors for QTc prolongation

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ABSTRACT

Background: Various risk factors have been recorded which prolong the QTc interval, like an increasing age, female gender, genetic variants, cardiovascular diseases and electrolyte disturbances. The present study was conducted to assess risk factors that causeQTc prolongation.**Material & methods:**Patient's relevant data required for this study was obtainedfrom the patient's medical record. The QTc was calculated, measured and analysed. The various Biochemical test were observed to find out any comorbidity/acquired cause of QTc prolongation in the patients. All the collected data was analysed statistically using SPSS version 21 software.**Results:**QTc prolonged among 9 subjects. Total 10 subjects observed with QTc prologation out of them 3 subjects with Bipolar affective disorder, 4 subjects with Pneumonia, 1 Generalised anxiety disorder, one with panic attack and 1 with panic disorder observed with QTc prologation.Comparison of distribution of study subjects having prolonged QTc of different levels after medication results revealed that not significant (p=0.16) association with different gender group. **Conclusion:**The study concluded thatprolonged QTc of different levels after medication had not significant association with different gender group.Current guidelines by the American Heart Association recommend monitoring a baseline QTc before initiating any agent that may prolong the QTc interval.

Keywords:QTc prolongation, ECG, Risk factors.

INTRODUCTION

The QT interval on the surface electrocardiogram (ECG) indicates the duration from the beginning of ventricular depolarization to the end of ventricular repolarization. Prolonged heart rate-corrected QT (QTc) interval has been correlated with many adverse cardiovascular outcomes including arrhythmia[1], coronary heart disease[2,3], sudden death[4] and mortality.[5] There are numerous risk factors have been recorded which proved the evidence that prolong the QTc interval, which comprised of an increasing age, female gender, genetic variants, cardiovascular diseases and electrolyte disturbances.[6,7] Other than these risk factors, there are various drugs that could possibly prolong the QTc interval which might include antimicrobial drugs, psychotropic drugs and cardiovascular drugs.[8] A plethora of patient-specific risk factors for drug-induced QTc-prolongation have been mentioned in the literature (e.g. female gender, age ≥65 years, cardiovascular history, familial history of SCD, liver/kidney failure, electrolyte disturbances), and the risk is stated to increase with the number of risk factors.[8-10]Agents that are known to contribute to QTc prolongation via pharmacokinetic interactions mostly include macrolide antibiotics, antifungal agents, the antiretroviral agent ritonavir, and grapefruit juice.[11]. It is currently not clear how risk factors should be weighted in a risk index. In 2013, Haugaa et al. introduced a pro-QTc score to predict mortality, but all risk factors were counting for one point and no distinction was made between the different risk factors.[12]The present study was conducted to asses risk factors that causes QTc prolongation.

MATERIAL & METHODS

This study was adopted as a prospective observational study and was planned to be conducted at L.N. Medical College & Research centre and associated J.K Hospital Bhopal. After obtaining the ethical approval from the institutional ethical committee, written consent was obtained from all the study subjects prior to the start of the study. All inpatient and outpatient of age 18 years and above giving consent, taking predefined subset of drugs, patient treated exclusively at the participating institution

were included in the study. Patient with QTc prolongation in baseline ECG, patient on antiarrhythmic medications, patient who did not gave consent were excluded from the study. Patient's relevant data required for this study was obtained from the medical profile of individual patient.After recording the observations in ECG, the following data were collectedfrom the patient's medical record; gender, age, maindiagnosis, comorbidities other than psychiatric disorders, and prescribed medications. The study group was formed based on the fulfillment of the inclusion and exclusion criteria. There are certain biochemical tests to be done in order to exclude the acquired cause. The primary test to be followed is ECG in which the QTc was calculated, measured and analysed. Baseline ECG was recorded at the time of inclusion then follow up ECG was recorded within 24 hours of completion of antibiotic treatment, and 7 days of antidepressant and antipsychotic treatment.In order to reduce thechances of bias from patients who were admitted multiple times in a year, the data obtained at the time of first encounter has been taken into account in the analysis. Moreover, in order to avoid bias from patients receiving several ECGs in an individual stay, the ECG that showed the longest QTc interval was identified and only this ECG and medications administered within 24 hours prior to it were considered in our analysis.The QTc intervals were promptly measured from the start of Q to the end of T wave. The U wave was not considered in the measurement of QTc interval in our study.Heart rate directly affects the QT intervaland various correction formulas are being employed to normalize it.*Bazett's* formula is the most common ones used by physicians for correction of QT interval. But overestimation is under debate as the heart rate deviates from60 beats/minute. It has been discussed that *Hodges* formula is the seemed to be the best choice for correction of QT interval. Therefore, the formula used for calculating the corrected QTc interval was *Hodges* [QTc = QT + 1.75 (HR − 60)]. The QTc intervals>440 ms in male and >460 ms in female and individual-level QTc >500 ms or change in QTc >60 ms above baseline were considered QTc prolongation.The Fridericia's formula (QTc = QT / RR1/3) on the other hand is described as a superior formula in order to compensate for the heart rate and proved the better predict mortality.

The various Biochemical test were observed at the time of inclusion to find out any comorbidity/acquired cause of QTc prolongation in the patients were-

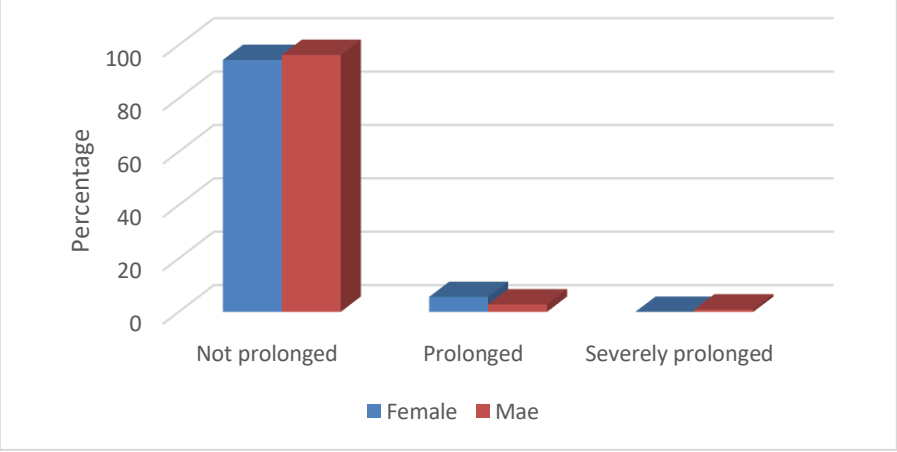
A) Serum electrolyte
B) Liver function test
C) Renal function test
D) ECG
E) Serum calcium and magnesium only to be done in patients who are clinically suggestive of hypocalcaemia and hypomagnesaemia.

All the collected data was analysed statistically using SPSS version 21 software in the form of percentages, proportions and are mostly represented as tables, charts, graphs wherever mandatory. Appropriate tests of significance was applied wherever necessary.

RESULTS

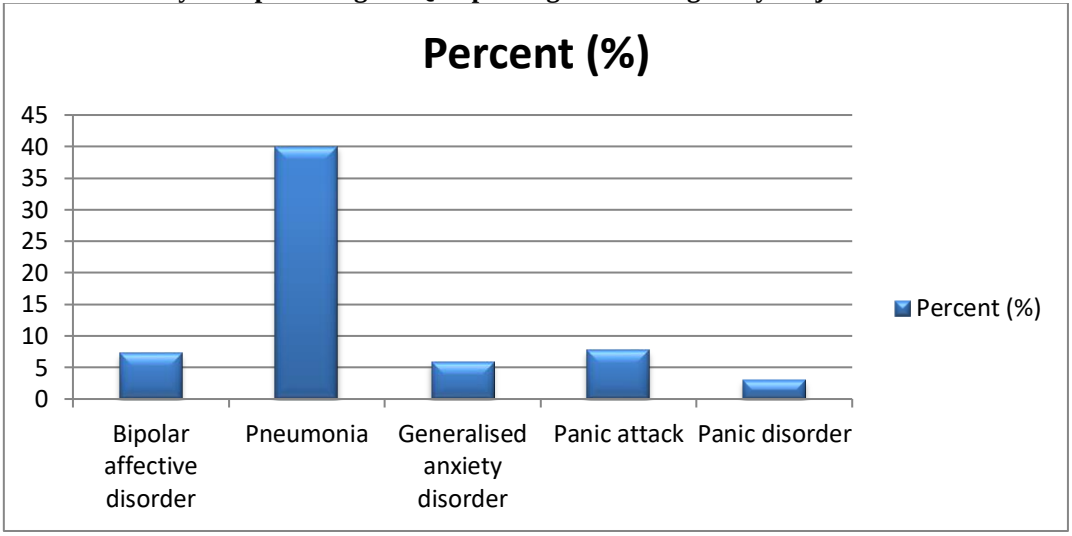
43 males, 40 female subjects treated with antibiotics (Azithromycin, Clindamycin),21 male and 38 female subjects treated with antidepressants (Escitalopram, Fluoxetine) treated with antidepresssnts and 43 male and 30 female subjects were on antipsychotic drugs (Olanzapine, Risperidone).Azithromycin prescribed among 29 male subjects and 19 female subjects, Clindamycin prescribed among 35 subjects those were 14 male and 21 female, Escitalopram prescribed among 36 subjects 17 were male and 19 were female, Fluoxetine prescribed among 23 subjects out of them 4 were male and 19 were female, Olanzapine prescribed among 41 subjects out of them 14 were male and 27 were female and Risperidone prescribed among 32 study subjects out of them 29 were male and 3 were female subjects which was showing statistically significant ($p<0.01$*) association among male and female prescribed drugs.

Graph 1: Gender wise prevalence of QTc prolongation among study subjects



QTc prolonged among 6 male and 3 female , severely prolonged in one female and no prologation found among 102 male and 103 female subjectsit was showing statstically non significant (P=0.367).

Graph 2: Comorbidity wise percentage of QTc prolongation among study subjects



Total 10 subjects observed with QTc prolongation out of them 3 subjects with Bipolar affective disorder, 4 subjects with Pneumonia, 1 Generalised anxiety disorder, one with panic attack and 1 with panic disorder observed with QTc prolongation.

Table 1: Mean QTc level at baseline, after treatment and change among study subjects with prolonged QTc according to drug

Drug name	Baseline		After treatment		Change	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
Azithromycin	435.50	3.54	448.00	7.07	12.50	3.54
Clindamycin	447.00	9.90	453.00	11.31	6.00	1.41
Escitalopram	437.00	1.41	441.50	0.71	4.50	2.12
Olanzapine	426.50	34.65	451.50	14.85	25.00	19.80
Risperidone	417.00	38.18	466.50	7.78	49.50	45.96

The subjects on Azithromycin drug, after treatment mean change 12.50 was found, subjects on Clindamycin drug after treatment mean difference 6.00 was found, subjects on Escitalopram drug after treatment mean difference 4.50 was found, subjects on Olanzapine drug after treatment mean difference 25.00 was found, subjects on Risperidone drug after treatment mean difference 49.50 was found.

Table 2: Mean QTc level at baseline, after treatment and change among study subjects according to comorbidity

Comorbidity	Baseline		After treatment		Change	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
Bipolar affective disorder	411.48	15.41	418.55	17.94	7.4	13.3
Pneumonia	422.44	12.73	424.31	12.87	1.86	1.26
Generalised anxiety disorder	411.71	15.21	415.59	15.67	3.94	2.11
Major anxiety disorder	410.33	21.75	413.33	22.17	3	1.41
Major depressive disorder	400	0	407	0	7	0
None	412.42	17.53	414.18	17.73	1.73	1.51
Obsessive compulsive disorder	407.56	22.62	410.22	21.88	3.11	0.78
Panic attack	421	13.62	424	13.47	3.77	1.01
Panic disorder	418.44	13.42	422.56	12.87	4.11	2.03
Phobia	412	24.66	416.5	24.53	4.5	2.65
Schizophrenia	416.52	16.05	421.88	16.41	6.25	3.65

The subjects those had Bipolar affective disorder as comorbidity, after treatment mean change 7.40 was found, Subjects withpneumonia as comorbidity, after treatment mean change 1.50 was found, Subjects with

generalized anxiety disorder as comorbidity, after treatment mean change 3.94 was found ,Subjects with hypothyroidism as comorbidity, after treatment mean change 1.29 was found , Subjects with Major anxiety disorder as comorbidity, after treatment mean change 3.0 was found, Subjects with Major depressive disorder as comorbidity, after treatment mean change 7.0 was found , Subjects with Obsessive compulsive disorder as comorbidity, after treatment mean change 3.11 was found , Subjects with Panic attack as comorbidity, after treatment mean change 3.77 was found, Subjects with Panic disorder as comorbidity, after treatment mean change 4.11was found , Subjects with phobia as comorbidityafter treatment mean change 4.50 was found, Subjects with Schizophrenia as comorbidity, after treatment mean change 6.25 was found.

Table 3:Gender wise distribution of study subjects according to level of QTc change according to drug

Drug name	Gender	QTc change level	Frequency	Percent (%)
Azithromycin	**Female**	**No change**	6	31.6
		1-5ms	12	63.2
		11-60ms	1	5.3
	Male	**No change**	5	17.2
		1-5ms	22	75.9
		6-10ms	2	6.9
Clindamycin	**Female**	**1-5ms**	18	85.7
		6-10ms	3	14.3
	Male	**1-5ms**	12	85.7
		6-10ms	2	14.3
Escitalopram	**Female**	**1-5ms**	15	78.9
		6-10ms	4	21.1
	Male	**1-5ms**	15	88.2
		6-10ms	2	11.8
Fluoxetine	**Female**	**1-5ms**	15	78.9
		6-10ms	4	21.1
	Male	**1-5ms**	4	100
Olanzapine	**Female**	**No change**	1	3.7
		1-5ms	19	70.4
		6-10ms	4	14.8
		11-60ms	3	11.1
	Male	**1-5ms**	8	57.1
		6-10ms	6	42.9
Risperidone	**Female**	**1-5ms**	1	33.3
		11-60ms	2	66.7
	Male	**1-5ms**	12	41.4
		6-10ms	12	41.4
		11-60ms	4	13.8
		>60ms	1	3.4

The QTc level change 1-5 ms among maximum 12 female and 22 male among all subjects who were on Azithromycin drug,18 female and 12 male among all subjects who were on Clindamycin drug,maximum 15 female and 15 among all subjects who were on Escitalopram drug, maximum 15 female and 15 among all subjects who were on Escitalopram drug, maximum 15 female and 4 among all subjects who were on Fluoxetine drug, maximum 19 female and 4 among all subjects who were on Olanzapine drug. and the QTc level change 11-60 ms among maximum 2 female and QTc level change 1-5 ms and 6-10ms each 12 male among all subjects who were on Risperidone drug.

Table 4: Comparison of distribution of study subjects having prolonged QTc of different levels after medication

	0-5ms		**6-10ms**		**11-60ms**		**>60ms**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Male	1	25.0	2	50.0	0	0.0	1	25.0
Female	1	16.7	1	16.7	4	66.7	0	0.0
Chi square value	5.13							
p value	0.16							

Comparison of distribution of study subjects having prolonged QTc of different levels after medication results revealed that not significant (p=0.16) association with different gender group.

Table 5: Gender wise distribution of study subjects according to level of QTc change according to comorbidity and drug

Comorbidity	Drug	Gender	QTc change	Frequency
Bipolar affective disorder	Olanzapine	Female	11-60ms	2
	Risperidone	Male	>60ms	1
Generalised anxiety disorder	Escitalopram	Male	6-10ms	1
Pneumonia	Azithromycin	Female	11-60ms	1
		Male	6-10ms	1
	Clindamycin	Female	6-10ms	1
		Male	0-5ms	1
Panic attack	Escitalopram	Female	0-5ms	1
Schizophrenia	Risperidone	Female	11-60ms	1

Gender wise distribution of study subjects according to level of QTc change according to comorbidity and drug results revealed that subjects those who had comorbidity of bipolar affective disorder 2 femalehad QTc level change 11-60 ms in female subjects those who were taking Olanzapine, and one male>60 ms were taking Risperidone, subjects those who had comorbidity of pneumonia 1 malehad QTc level change 0-5ms in female subjects those who were taking Clindamycin, subjects those who had comorbidity of generalised anxiety disorder 1 male had QTc level change 6-10ms in female subjects those who were taking Escitalopram, subjects those who had comorbidity of painic atack in 1 subject had QTc level change 0-5ms in female subjects those who were taking Escitalopram, subjects those who hadcomorbidity of schizophrenia in 1 subject had QTc level change 11-60ms in female subjects those who were taking Risperidone.

Table 6:Drug and comorbodies wise QTc prolongation amongstudy subjects

Drug Name	Frequency	Comorbodity	QTc Prolongation	Percent (%)
Azithromycin	48	Pneumonia	2	4.16
Clindamycin	35	Pneumonia	2	5.71
Escitalopram	36	General anxiety disorder	1	2.77
		Painic attack	1	2,77
Fluoxetine	23	-	-	-
Olanzapine	41	Bipolar affective disorder	2	4.87
Risperidone	32	Bipolar affective disorder	1	3.12
		Schizophrenia	1	3.12

There were 48 subjects of Pneumonia on Azithromycin out of them QTc prologation observed in 2 subjects , 35 subjects of Pneumonia on Clindamycin out of them QTc prologation observed in 2 subjects, 36 subjects of general anxiety disorder and painic attack which on Escitaloparam out them QTc prolongation was observed in 1-1 each,41 subjects of Bipolar affective disorder on Olanzapine out of them QTc prologation observed in 2 subjects 32 subjects of Bipolar affective disorder and schizopherenia which on Escitaloparam out them QTc prolongation was observed in 1-1 each.

DISCUSSION

Prolongation of the QTc interval on the ECG is associated with Torsade de Pointes (TdP), potentially fatal ventricular arrhythmias.[4]Schaffer D (2002)[13] et al observed in their case reports on macrolides and Torsades De Pointes in a clinical setting reported that there was a difference in pro-arrhythmic potential of macrolide antibiotics in a total number of 156 patients; 53% was associated with erythromycin, 36% with clarithromycin, and 11% occurred in azithromycin-treated patients. When gender wise distribution was taken into account, this present study showed that 43 males and 40 female subjects treated with antibiotics (azithromycin, clindamycin), 21 male and 38 female subjects treated with antidepressants (escitalopram, flouxetine) and 43 male and 30 female subjects were on antipsychotic drugs (olanzapine, risperidone).*Farzanegan* Bet al (2020)[14]evaluated the incidence and predictors of QTc prolongation in medical (M), surgical (S), and emergency (E) ICUs. The results of the study reported that the incidence of QTc prolongation was 6.5, 9.8, and 15.7% on day 1, 3, and 5 of ICU admission, respectively. In this study QTc was prolonged among 9 subjects, severely prolonged in one subjects and there were no prolongation found among 205 subjects after 24 hours of antibiotic treatment and 7 days of antidepressant and antipsychotic treatment. It has been observed that the QTc prolonged among 6 male and 3 female,

severely prolonged in one female and no prolongation found among 102 male and 103 female.There are certain comorbidities and drugs used to manage them that can cause QT prolongation.[15] Inour study, it has been observed thatamong 41 subjects which had bipolar affective disorder had not QTc prolongation among 39 subjects, prolonged in 2 subjects and severely prolongation observed in one subject. Total 36 subjects had Pneumonia out of them 4 had QTc prolongation, 17 subjects had generalised anxiety disorder from all of them 1 had QTc prolonged and 16 did not had QTc prolongation, 13 subjects had panic attacks out of them prolonged QTc was found in 1 subject, 33 had Schizophrenia out of them prolonged QTc was found in 1 subject, co morbidity was not observed among 45 study subjects which did had any QTc prolongation,subjects those had, Major anxiety disorder, Major depressive disorder , Obsessive compulsive disorder and Phobia had no QTc prolongation.In the present study, total 10 subjects were found to have QTc prolongation out of them 3 subjects with Bipolar affective disorder, 4 subjects with Pneumonia, 1 generalised anxiety disorder, one with panic attack and 1 with panic disorder observed with QTc prolongation. The study subjects on azithromycin drug mean QTc 413.13 was noted at baseline and 414.83 after treatment mean change 1.69 was found, subjects on clindamycin drug mean QTc 418.66 was noted at baseline and 421.97 after treatment mean change 3.26 was found, subjects on escitalopram drug mean QTc 416.47 was noted at baseline and 419.83 after treatment mean change 3.78 was found, subjects on fluoxetine drug mean QTc 409.05 was noted at baseline and 413.52 after treatment mean change 3.83 was found, subjects on olanzapine drug mean QTc 415.05 was noted at baseline and 419.41 after treatment mean change 5.40 was found, subjects on risperidone drug mean QTc 413 was noted at baseline and 422.13 after treatment mean change 3.83 was found. Another study conducted by *Dela cruz* et al (2021)[16] revealed that out of 642 patients, 142 had available pre- and post-ECG results available; 100 were included in Group 1 (1 dose) and 42 in Group 2 (2 doses). Mean QTc interval differences after 1 dose of azithromycin exhibited an increase compared to baseline values (424 vs 477 ms). A Wilcoxon signed-rank test indicated a significant QTc prolongation after 1 dose of azithromycin (mean rank, 43.76; $Z=-4.921$; $P<.001$). QTc interval differences after 2 doses of azithromycin did not reach statistical significance when compared to baseline values (422 vs 444 ms). A total of 10 patients (10%) in Group 1 and 4 patients (9.5%) in Group 2 had a QTc interval >500 ms after azithromycin.[16]Considering the overall distribution of the study subjects based on the level of QTc change according to the drug in the present study, it has been revealed that there were no change found among 11 subjects (22.9%) those were treated with azithromycin, QTc change 1-5ms was observed among 34 subjects (70.8%), 1-10 ms among 2 subjects (2.1%) and 11-60 ms in 1 subject those who were being treated with Azithromycin.QTc change 1-5ms was observed among 30 subjects (85.7%), 1-10ms among 5 subjects (14.3%) those who were being treated Clindamycin.QTc change 1-5ms was observed among 30 subjects (83.3%), 1-10 ms among 6 subjects (16.7%) those who were being treated with Escitalopram. QTc change 1-5ms was observed among 19 subjects (82.6%), 1-10 ms among 4 subjects (17.4%) those who were being treated with Fluoxetine. There were no change in 1 subject (2.4%) which was treated with Olanzapine, QTc change 1-5ms was observed among 27 subjects, 1-10 msamong 10 subjects (24.4%) and 11-60 ms in 3 subject (7.3%) those who were being treated with Olanzapine. QTc change 1-5ms was observed among 23 subjects, 1-10 ms among 12 subjects , 11-60 ms in 6 subjects and >60ms in one subject those who were being treated with Risperidone overall distribution of study subjects according to level of QTc change according to drug showing *statistically* significant ($P<0.01$). In this study gender wise distribution revealed that 108 subjects were female and 107 subjectswere male. QTc was prolonged among 9 subjects out of which 6 were male and 3 were female and severly prolonged in 1 subjects. Those who had bipolar affective disorder 2 femalehad prolonged QTc who were taking olanzapine,1 male had severly prolonged QTc who were taking Risperidone. Subjects those who had Pneumonia 2 male and 2 female had prolonged QTc who were taking clindamycin and Azithromycin. Subjects those who had generalised anxiety disorder 1 male had prolonged QTc who were taking Escitalopram.Subjects those who had schizophrenia 1 female had prolonged QTc who were taking Risperidone. In this study it is found that QTc level was prolonged in 4 subjects (4.8%) who were on antibiotics, 2 subjects (3.4%) those were antipsychotics and 3 subjects (4.1%) were on antipsychotics. All patients with prolonged QTc interval ($n = 23$) were receiving QT prolonging drugs. Of which, the most frequently prescribed drug classes were antidepressants ($n = 13$), and antipsychotics ($n = 5$). Among antidepressants, 30.4% of the drugs were carrying conditional risk of Torsades De Pointes, and 17.4% were having known risk of Torsades De Pointes. Among antipsychotics, 8.6% of the drugs were having known and possible risk of Torsades De Pointes, respectively.[15]Maximum 64 subjects those were on antibiotics, 49 subjects were on antidepressants and 40 subjects were on anti psychotics. There were significant ($p<0.01$) association of various drugs class with according to level of QTc change.

CONCLUSION

The study concluded thatprolonged QTc of different levels after medication had not significant association with different gender group.Risk factors for QT prolongation include hypomagnesemia, hypokalemia and concomitant administration of QT-prolonging drugs. Current guidelines by the American Heart Association recommend monitoring a baseline QTc before initiating any agent that may prolong the QTc interval, at the onset of any new bradyarrhythmias, severe hypokalemia or hypomagnesemia, or over dosages of known proarrhythmic pharmacotherapy agents. Caution should be exercised in case of usage of cardiac drugs as they are increasingly associated with fatal arrhythmias. More detailed randomized controlled studies with accurate description of baseline QTc, change in QTc interval and appropriate report of any significant ventricular arrhythmias with usage of multiple QTc prolonging drugs should be performed in future.Current guidelines by the American Heart Association recommend monitoring a baseline QTc before initiating any agent that may prolong the QTc interval.

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