

ORIGINAL ARTICLE

## ANTIPSYCHOTICS AND ELECTROCARDIOGRAPHIC MONITORING IN PATIENTS WITH SCHIZOPHRENIA

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### Abstract

**Objectives:** Patients with schizophrenia are more likely to die prematurely than the general population. They have a higher risk of cardiovascular related morbidity and mortality. Antipsychotic medications are also known to be associated with the prolongation of the rate-corrected QT (QTc) interval, which is linked to dangerous arrhythmias. The primary objective of our study is to investigate the practice of electrocardiogram (ECG) monitoring for patients with schizophrenia who were hospitalised. The secondary objective is to evaluate the prevalence of QTc prolongation in this group of patients. **Methods:** We included patients with schizophrenia who were discharged from the acute general adult psychiatric wards of the Institute of Mental Health in Singapore from 1 July 2014 to 21 July 2014. A retrospective analysis of the medical records was carried out to assess if they had received ECG during their hospitalisation. We also analysed their risk of developing QTc prolongation. **Results:** We had a sample size of 107 patients. There were 31 patients (29.0%) who received ECG during their hospitalisation. Of the 95 patients who had moderate-to-high risk of developing QTc prolongation, 29 of them received ECG. Of the 31 patients who received ECG, 10 of them (32.3%) had QTc prolongation. **Conclusion:** The ECG monitoring in the study patients was inadequate, and as a result, we were unable to evaluate the prevalence of prolonged QTc interval with confidence. We recommend performing baseline ECGs for these patients and conducting ECG teachings for clinicians who work in the psychiatric service settings. *ASEAN Journal of Psychiatry, Vol. 17 (2): July – December 2016: XX XX.*

**Keywords:** Antipsychotic, Electrocardiogram, QTc, Schizophrenia

### Introduction

Patients with schizophrenia have an increased risk of sudden death and a decreased life expectancy by 10 to 25 years [1]. Multiple factors likely contribute to this and cardiac problems have been identified as a major contributor [2]. The increased risk for cardiovascular issues in these patients may be attributed to factors such as medical comorbidities, poor access to or poor adherence with medical care, and iatrogenic causes, e.g. psychotropic medications. Patients with schizophrenia may have cardiovascular risk factors such as cigarette smoking,

sedentary lifestyle, obesity, diabetes mellitus, hypertension, hyperlipidemia and family history of cardiovascular disease. In Singapore, the prevalence of metabolic syndrome in patients with schizophrenia was 46%, which was almost a 3-fold increase compared to the general population [3].

Prolongation of QTc interval that is associated with antipsychotic medications is a major concern, as it can lead to potentially life-threatening ventricular arrhythmias, especially Torsades de Pointes (TdP). The 2009 American Heart Association/American College of Cardiology Foundation/Heart

Rhythm Society Recommendations for the Standardization and Interpretation of the Electrocardiogram stated that a QTc interval of 450 ms or more (for males) and 460 ms or more (for females) be considered a prolonged QTc interval [4]. Most experts agree that a QTc interval over 500 ms is considered to be a major risk factor for cardiac arrhythmias [5]. TdP is often asymptomatic, but it can cause a sudden drop in the blood pressure, leading to dizziness and syncope. It most often reverts to normal sinus rhythm. However, TdP can recur, and in some cases. It can lead to ventricular fibrillation and sudden cardiac death, especially in the absence of prompt medical intervention.

There are many antipsychotic medications that have been shown to be associated with QTc prolongation. The first report of sudden cardiac death in the setting of antipsychotic treatment appeared in the 1960s, when thioridazine was found to prolong the QTc interval [6]. As a result, thioridazine was withdrawn from the market in 2005 [7]. Other antipsychotic medications with moderate-to-high effect on QTc prolongation include chlorpromazine, quetiapine, ziprasidone and haloperidol. Single or combination of antipsychotic medications used in doses that exceed the recommended maximum also has a high effect on QTc prolongation [8].

Clinicians often prescribe high doses of antipsychotic medications to patients who do not respond well to the standard treatment. A major factor contributing to high-dose prescribing is antipsychotic polypharmacy. The evidence from randomised controlled trials to support the use of antipsychotic polypharmacy in schizophrenia remains scarce [9,10], and there are concerns over the potential of increased adverse events and healthcare cost. Clinicians commonly prescribe more than one antipsychotic medication, hoping to expedite or increase effectiveness, to reduce the dosage and the side effects of the first antipsychotic medication or as an attempt after a failed trial of clozapine and/or electroconvulsive treatment [11]. A national audit of the prescribing patterns of antipsychotic medications in 47 mental health services in the United Kingdom reported that of the 3132 patients, 48% of patients were prescribed more

than one antipsychotic medication, and 20% were prescribed a total dose of antipsychotic medication above that recommended by the British National Formulary [12]. Drug interactions, which may affect the levels of antipsychotic medications, also need to be considered.

There is no clear consensus detailing precisely how and when ECG should be done on patients with schizophrenia. The National Institute for Health and Clinical Excellence guidelines recommended that before starting antipsychotic medication, a patient with schizophrenia should be offered an ECG if (1) it is specified in the summary of product characteristics, or (2) the physical exam has identified specific cardiovascular risk, or (3) there is personal history of cardiovascular disease, or (4) the service user is being admitted as an inpatient [13]. The Maudsley Prescribing Guidelines in Psychiatry recommended measuring the QTc interval in all patients prescribed antipsychotic medications (1) on admission, and (2) at yearly check-up if previous abnormality or additional risk factors [8]. A few studies reported inadequate ECG monitoring in patients with schizophrenia. One study reported that only 8% of patients prescribed high dose of antipsychotic medications had undergone an ECG [12]. Another study reported that half of the high-risk patients who required an ECG were not given one [14].

To the best of our knowledge, there has been no previous study in Singapore that investigates the practice of QTc monitoring in patients with schizophrenia receiving antipsychotic medications. The primary objective of our study is to investigate the practice of ECG monitoring for this group of patients while they were hospitalised in the acute general adult psychiatric wards at the Institute of Mental Health (IMH) in Singapore. The secondary objective is to evaluate the prevalence of QTc prolongation in these patients.

## **Methods**

Our study involved retrospective data collection from medical records. All patients who were discharged from the acute general adult psychiatric wards in the IMH from 1 to

21 July 2014 were screened from the hospital electronic health records. To be included in the study, the patients must have the diagnosis of schizophrenia and have received at least one antipsychotic medication. Patients aged less than 21 or more than 64 years old were excluded from the study.

For all the study patients, we analysed their admission case notes to investigate if an ECG had been done during the admission. We also investigated the patients' risk of developing QTc prolongation. The patients were considered to have moderate-to-high risk of developing QTc prolongation if they had at least one of the following risk factors: (1) high-dose antipsychotic medication (above the usual dosages as recommended by the Department of Pharmacy of the IMH), (2) more than one antipsychotic medication, (3) use of other psychotropic medication that is associated with QTc prolongation, (4) use of non-psychotropic medication that is associated with QTc prolongation, (5) cardiovascular risk factors: body mass index (BMI) of 27.5 kg/m<sup>2</sup> or above, diabetes mellitus, hypertension, hyperlipidemia, heart disease, (6) other physiological conditions that are associated with QTc prolongation.

The data collected included (1) patient's demographic characteristics (age, gender, ethnicity), (2) ECG monitoring (whether an ECG had been done; the reason for ordering an ECG, the QTc interval and the action taken if there was a prolonged QTc interval, which was based on the ECG machine interpretation), (3) medications and their dosages (antipsychotic, other psychotropic and non-psychotropic medications that are known to prolong the QTc interval, according to The Maudsley Prescribing Guidelines in Psychiatry, 11<sup>th</sup> edition), (4) cardiovascular risk factors and diseases, and (5) other physiological risk factors that are known to prolong the QTc interval. We considered a QTc interval of 450 ms or more (for males) and 460 ms or more (for females) a prolonged QTc interval.

Our study was approved by the National Healthcare Group Domain Specific Review Board, Singapore (NHG DSRB Ref: 2014/00761).

## Results

We had 107 patients who fulfilled the criteria of the study. Patients' demographic characteristics were summarised in Table 1.

**Table 1. Demographic characteristics of all study patients**

Characteristic	Number (%) (N = 107)
Age (years)	
21-29	14 (13.1)
30-39	17 (15.9)
40-49	34 (31.8)
50-59	27 (25.2)
60-64	15 (14.0)
Gender	
Male	66 (61.7)
Female	41 (38.3)
Ethnicity	
Chinese	85 (79.4)
Malay	15 (14.0)
Indian	5 (4.7)
Others	2 (1.9)

The pharmacological and medical risk factors for QTc prolongation in the study patients were summarised in Table 2.

**Table 2. Prevalence of pharmacological and medical risk factors in all study patients**

<b>Pharmacological risk factor</b>	<b>Number (%) (N = 107)</b>
High-dose antipsychotic medication	22 (20.6)
More than one antipsychotic medication	67 (62.6)
Other significant psychotropic medication	3 (2.8)
Significant non-psychotropic medication	28 (26.2)
More than one pharmacological risk factor	52 (48.6%)
<b>Medical risk factor</b>	<b>Number (%) (N = 107)</b>
Obesity	33 (31.1)*
Diabetes mellitus	22 (20.6)
Hypertension	26 (24.3)
Hyperlipidemia	41 (38.3)
Heart disease	6 (5.6)
Other physiological risk factor	4 (3.7)

\*This was calculated using a total number of 106 patients, as one patient was uncooperative to have his height and weight measured.

Of the 107 patients, 22 patients (20.6%) were receiving high-dose antipsychotic medications, and 67 patients (62.6%) were receiving antipsychotic polypharmacy (more than one antipsychotic medication, and the maximum number of antipsychotic medications per patient in our study was three). Patients who had cross-titration of antipsychotic medications during their hospitalisation were also considered to have received antipsychotic polypharmacy. In addition to the antipsychotic medications, 3 of 107 patients (2.8%) received other significant psychotropic medications which are known to prolong the QTc interval (these medications were dosulepin, venlafaxine and lithium), and 28 of 107 patients (26.2%) received significant non-psychotropic medications which are known to prolong the QTc interval (these medications were hydroxyzine, which is frequently prescribed to aid sleep). There were 52 of 107 patients (48.6%) who had more than one of the above-mentioned pharmacological risk factors.

As for medical risk factors, 33 patients (31.1%) were obese, 22 patients (20.6%) had diabetes mellitus, 26 patients (24.3%) had hypertension, and 41 patients (38.3%) had hyperlipidemia. Some of these patients were newly diagnosed to have these medical conditions during their hospitalisation. There were 6 of 107 patients

(5.6%) who had a history of heart disease, and this included coronary artery disease, cardiac arrhythmias and congenital heart disease. There were 4 of 107 patients (3.7%) who had other physiological conditions which could prolong the QTc interval, and these conditions were hypokalaemia and hypothyroidism. However, not all patients had blood tests done during their hospitalisation, and these patients might have undetected physiological conditions which could prolong the QTc interval.

In total, 31 of 107 patients (29.0%) received an ECG during their hospitalisation. We further analysed the practice of performing ECG according to patients' risk levels, and the reasons for ordering an ECG, as shown in Table 3. There were 29 of the 95 patients (30.5%) with moderate-to-high-risk of developing QTc prolongation who had received an ECG. Of the 31 patients who had received ECG, 10 of them (32.3%) had prolonged QTc intervals. Among these 10 patients, 2 of them (20.0%) had QTc intervals of more than 500 ms. We would also like to clarify that for patients who had received more than 1 ECG, they were considered to have prolonged QTc intervals if any of their ECGs showed a prolonged QTc interval.

**Table 3. ECG practice on acute general adult psychiatric wards**

<b>Number of patients who received an ECG</b>	<b>Number (%) (N = 107)</b>
Yes	31 (29.0)
No	76 (71.0)
<b>ECG practice according to patients' risk levels</b>	<b>Number (%) (N = 107)</b>
Low-risk patients who did not receive an ECG	10 (9.3)
Moderate-to-high-risk patients who did not receive an ECG	66 (61.7)
Low-risk patients who received an ECG	2 (1.9)
Moderate-to-high-risk patients who received an ECG	29 (27.1)
<b>Reason for ordering the first ECG</b>	<b>Number (%) (N = 31)</b>
Baseline ECG	10 (32.3)
Increase in dosage of antipsychotic medication	4 (12.9)
Pre-electroconvulsive therapy workup	3 (9.7)
Chest discomfort	3 (9.7)
Tachycardia or hypo/hypertension	5 (16.1)
Hypokalemia	1 (3.2)
Reason unclear	5 (16.1)

We further analysed the demographic characteristics and QTc-prolonging risk factors of the 10 patients with QTc

prolongation, as shown in Table 4. There was a patient who did not have any identifiable risk factor, while some had a few.

**Table 4. Demographic characteristics and QTc-prolonging risk factors in patients with prolonged QTc intervals**

<b>Demographic characteristics</b>	<b>Number (%) (N = 10)</b>
Age	
21-29	2 (20.0)
30-39	2 (20.0)
40-49	2 (20.0)
50-59	2 (20.0)
60-64	2 (20.0)
Gender	
Male	7 (70.0)
Female	3 (30.0)
Ethnicity	
Chinese	7 (70.0)
Malay	1 (10.0)
Indian	1 (10.0)
Others	1 (10.0)
<b>Pharmacological risk factor</b>	<b>Number (%) (N = 10)</b>
High-dose antipsychotic medication	1 (10.0)
More than 1 antipsychotic medication	2 (20.0)
More than one pharmacological risk factor	4 (40.0)
Nil identifiable	3 (30.0)
<b>Medical risk factor</b>	<b>Number (%) (N = 10)</b>
Cardiovascular risk factor (obesity, diabetes mellitus, hypertension, hyperlipidemia, or heart disease)	8 (80.0)
Other physiological risk factor	2 (20.0)
Nil identifiable	1 (10.0)

Table 5 shows the reasons for ordering the first ECG on these patients, and the actions taken by the doctors on them. Of these 10 patients who had prolonged QTc intervals, 1 patient (10·0%) received a repeat ECG, 2 patients (20·0%) had a repeat ECG with a non-urgent referral to cardiologist, and 1 patient

(10·0%) did not have a repeat ECG with the documentation of ‘to monitor’ in the case note. For the remaining 6 patients (60·0%), there was no documentation about follow-up on the ECG and we were unsure if the QTc prolongation had been identified.

**Table 5. Reasons for ordering the first ECG for patients with QTc prolongation and actions taken for prolonged QTc interval**

<b>Reason for ordering the first ECG</b>	<b>Number (%) (N = 10)</b>
Baseline ECG	2 (20·0)
Increase in dosage of antipsychotic medication	1 (10·0)
Pre-electroconvulsive therapy workup	1 (10·0)
Chest discomfort	1 (10·0)
Tachycardia or hypo/hypertension	4 (40·0)
Hypokalemia	1 (10·0)
<b>Action taken for prolonged QTc interval</b>	<b>Number (%) (N = 10)</b>
Repeat ECG	1 (10·0)
Repeat ECG and non-urgent referral to cardiologist	2 (20·0)
Documented ‘to monitor’ with no repeat ECG	1 (10·0)
Nil	6 (60·0)

## Discussion

Our study found that 29·0% of the inpatients with a diagnosis of schizophrenia received an ECG during their hospitalisation. We feel that the practice of ECG monitoring was inadequate. This is consistent with the results shown in other studies as mentioned above. Of those who had received ECGs, 32·3% of them had prolonged QTc intervals. It was also found that no action was taken for the 60·0% of patients with prolonged QTc intervals. We considered the possible reasons for insufficient ECG monitoring in this group of patients. Some of the reasons include (1) no clear consensus on ECG monitoring, (2) ‘slip one’s mind’ to monitor ECG, (3) lack of thorough assessment for QTc-prolonging risk factors, (4) lack of knowledge regarding QTc prolongation.

We believe that our study is the first in Singapore that had evaluated the practice of ECG monitoring in patients with schizophrenia in the acute general adult psychiatric wards. There are several limitations to our study. As there were very few ECGs being performed on these patients, we do not have sufficient number of patients to study the prevalence of QTc prolongation.

Another limitation is that we did not take into account medications which may have drug interaction with the antipsychotic medications, affecting the plasma concentration of antipsychotic medications. We were also unable to obtain information on patients’ other cardiovascular risk factors, such as smoking status, sedentary lifestyle and family history of cardiovascular diseases or sudden death, as this is a retrospective analysis of medical records and patients are not routinely screened for such information. Another issue to consider is the accuracy of our ECG machines in measuring the QTc intervals. The ECG machines used on the study patients were different and the QTc intervals provided by the different machines were likely to be different. Some patients had ‘QTc’ displayed on their ECG strips, while some had both ‘QTcB and QTcF’ shown on their strips (QTcB is the QTc interval corrected using Bazett’s formula, while QTcF is the QTc interval corrected using Fridericia’s formula). For patients who had both QTcB and QTcF displayed on their ECG strips, the QTcB reading was obtained as it is widely used in clinical practice. We also acknowledge that the ECGs were not read by a cardiologist, and that different clinicians may follow different guidelines and have different

thresholds to determine a prolonged QTc interval.

As clinicians become more specialised, they tend to be uncomfortable when managing health issues that are out of their specialties. This can happen in any specialty including psychiatry. We feel that psychiatrists should at least possess the basic medical knowledge, recognise their limitations and know when to refer to other specialists when required.

We are concerned as our study showed that no actions had been taken for some patients with QTc prolongation. We also did not evaluate our clinicians' knowledge on the QTc interval. In one study, it was found that 86% of the psychiatric trainees did not know what a QTc interval was, although the majority knew the significance of a prolonged QTc interval in relation to antipsychotic medications [14]. Another survey found that fewer than 20% of the psychiatric trainees were able to identify a prolonged QTc interval [15]. A different study showed that only 5% of psychiatric trainees and consultant psychiatrists could correctly indicate a QTc interval. This study also revealed that the performances on other measures, such as measuring the heart rate, were also poor, with senior house officers performing better than consultants. It was postulated that this could be because the senior house officers were preparing for their MRCPsych exam as they were expected to interpret an ECG in the examination [16]. Another study demonstrated that the QTc interval was calculated correctly by more than 80% of arrhythmia experts, but less than 50% of cardiologists and less than 40% of non-cardiologists [17].

Another concern is that clinicians have come to be more dependent on ECG machine interpretation. The British Heart Foundation advises that errors are common with ECG machines and interpretation should not be accepted without visual inspection [18]. Errors made by computerised ECG recording include dangerous underestimation of the QTc interval. Patients with complex T and U wave morphologies can also have inaccurate QTc intervals when measured by the computerised ECG recording that is fraught with errors [19,20]. The inconsistency between ECG manufacturers in terms of the methods used

for calculation of the QTc intervals is also a problem.

ECG is an inexpensive investigation with minimal burden on the patients. Taking into consideration the recommendations available and our humble opinion, we recommend the following for all inpatients with schizophrenia receiving antipsychotic medications:

(i) Perform thorough assessment. History taking should include cardiovascular risk factors/diseases, and family history of sudden death. Cardiovascular risk factors/diseases should be managed appropriately if identified. Check electrolytes especially in patients who are at higher risk of electrolyte abnormalities.

(ii) Prescribe minimal effective dosage of antipsychotic medications, avoid polypharmacy and bear in mind the potential drug interactions.

(iii) Pharmacists play an important role in reviewing the medications prescribed and recommending medication regimen for individual patients. They also help to remind the clinicians regarding monitoring of cardiovascular complications including ECG monitoring.

(iv) Perform a baseline ECG on admission. Repeat the ECG if dosage of antipsychotic medication is increased, if the previous ECG shows a prolonged QTc interval, or if the patient experiences symptom that is suggestive of a heart problem.

(v) If the QTc interval is prolonged but is less than 500 ms, consider reducing the dosage of the suspected medication or switching to another antipsychotic medication with less QTc-prolonging effects, while monitoring the QTc interval.

(vi) If the QTc interval is 500 ms or more, discontinue the suspected medication and refer the patient for urgent cardiologist review. Consider restarting antipsychotic medication with less QTc-prolonging effects when patient's QTc interval has improved.

(vii) Liaise with the information technology department to create reminders in the electronic medical records to remind the

clinicians to perform ECG. For example, a popup reminder on the electronic medical records is created upon the clinician's first access to the patient's medical record to remind him/her to perform a baseline ECG for that particular patient. If the clinician has increased the dosage of antipsychotic medication, another reminder is sent to the clinician to perform an ECG. If the patient's previous ECG shows a prolonged QTc interval, the medical record is able to capture this and a reminder will be sent to the clinician to follow up.

(viii) We suggest that the ECG manufacturers programme the ECG machines in such a way that they are able to capture a prolonged QTc interval and send an alert signal to the clinician who has ordered the ECG.

(ix) Recommendation for ECG refresher courses for clinicians from all levels of seniority who work in the psychiatric service settings. As the cardiologists lack the capacity to provide QTc validation service, we feel that clinicians who work in the psychiatric service settings need to be competent in their ECG reading.

We hope that this study has provided some understanding about the current ECG practice in the acute inpatient ward settings. It will be worthwhile to repeat similar study to monitor the trend of ECG monitoring. It is also interesting to evaluate the practice of ECG monitoring in the outpatient settings, as well as assessing clinicians' knowledge on interpretation of ECG. We also hope that there will be a clearer consensus on ECG monitoring for patients with schizophrenia who are on antipsychotic medications.

## **Conclusion**

Our study showed that the ECG monitoring in patients with schizophrenia in the acute general adult psychiatric wards was inadequate. As a result, we were unable to evaluate the prevalence of QTc prolongation with confidence. We recommend performing baseline ECGs for these patients when they are hospitalised, and conducting risk-benefit analysis on each patient when prescribing medications. We also feel that ECG refresher courses are necessary for clinicians who work

in the psychiatric service settings. We all have a responsibility to ensure that our patients receive the best healthcare. Remember, *primum non nocere!*

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## **Conflict of interest statements**

We declare no competing interests.

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