ECG study in Patients on High Dose Antipsychotics.
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ORIGINAL ARTICLE

ECG STUDY IN PATIENTS ON HIGH DOSE ANTIPSYCHOTICS

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Abstract

***Objectives*: There are many antipsychotic medications that have been shown to be associated with the prolongation of the rate-corrected QT (QTc) interval on the electrocardiogram (ECG). Studies have shown that QTc prolongation is associated with increased risk of arrhythmias and sudden cardiac death. This study aims to identify and study the risk profile of patients on high-dose antipsychotic and to examine the prevalence of rate and rhythm abnormalities, in particular, QTc prolongation. We hope that this study could throw a light on current practice patterns and also could potentially guide us towards safe practice in the future. *Methods*: We recruited 37 adult outpatients who are on high-dose antipsychotic from the 3 outpatient clinics of the Institute of Mental Health in Singapore. Baseline characteristics risk profiling was performed to identify their pre-existing risk, including checks on Calcium, Potassium and Magnesium levels to rule out confounders. 12 lead ECG was done and reviewed manually by our resident physician. *Results*: It showed that rate abnormality was detected in 8 patients (22%) and QTc interval prolongation was detected in nearly 12 patients (32.4%) but of those only 3 patients had significantly prolonged QT interval needing the primary treating team to review their psychopharmacology regime. *Conclusion*: QTc Prolongation was positively linked with a number of cardiovascular risk factors.**

Keywords: ECG study, High-dose antipsychotics, Patients, Antipsychotic treatment

Introduction

The association between antipsychotics and cardiovascular events has been well known, in particular, the prolongation of the rate-corrected QT (QTc) interval, which is associated with potentially life-threatening cardiac arrhythmias, especially Torsades de Pointes (TdP). Harmful effects of antipsychotic were proven at therapeutic levels in a dose-dependent way as well as in patients with comorbid cardiovascular disease [1,2]. Newer atypical antipsychotics are thought to be relatively safe compared to typical medication with the exception of established risk with sertindole, ziprasidone, and clozapine. The association between prolongation of QTc interval and sudden cardiac death has been confirmed in a meta-analysis of 23 observational studies, showing a dose-related effect of antipsychotic medications on QTc interval and subsequent mortality [3].

In Singapore, a local study by Chong and colleagues reported that of the 163 in patients with schizophrenia who were prescribed any psychotropic medications, 110 patients (67.5%) received more than one medication, and 11 (6.7%) of them had a prolonged QTc interval [4]. This study however only looked at typical antipsychotics and the practice of use of typical versus atypical antipsychotics has since then changed dramatically. A more recent study by Ng and colleagues conducted in Singapore reported that of the 107 patients with the diagnosis of schizophrenia who were on antipsychotic medication, there were 31 patients (29.0%) who had ECG during their hospitalization [5]. Of this group, 20.6% were thought to be on a high dose and 62.6% were on combination antipsychotics. Of the 95 patients who had moderate-to-high risk of developing QTc prolongation, only 29 of them received ECG. Of the 31 patients who had ECG, 10 of them (32.3%) had QTc prolongation, with 2 patients had a QTc interval of over 500 ms. In this study, machine calculated QTcB was used and there was no manual reading of the ECGs. It did not differentiate patients being on typical, atypical or combinations antipsychotics. A few other studies also had reported inadequate ECG monitoring in patients on antipsychotic medications [6,7]. Although several publications have highlighted the importance of ECG monitoring in patients receiving antipsychotic medications, there is no clear consensus detailing precisely how and when this should be done.

High dose antipsychotic and antipsychotic polypharmacy is not uncommon in clinical practice despite scarce evidence for antipsychotic polypharmacy, concerns about increased adverse events and healthcare costs. Despite this,

antipsychotic polypharmacy continues to prevail. Risks associated with high doses and combination of antipsychotics are not that well studied.

This study aims to identify and study the risk profile of patients on high-dose antipsychotic and to study the prevalence of rate abnormality and QTc prolongation in these patients. We define high-dose antipsychotic either as monotherapy, with the individual antipsychotic above the maximum dosage recommended by the British National Formulary, or as polypharmacy, with a total antipsychotic daily dosage equivalent to 1 gram or more of chlorpromazine [8,9]. A normal QTc interval is generally defined as <450 ms for men and <460 ms for women [10]. The above reference point was used in Study by Ng et al., Some studies quoted 430-450 ms as a borderline rise for men and 450-470 ms as a borderline rise for women [11]. QTc interval over 500 ms is generally considered to be a major risk factor for cardiac arrhythmias [12]. Risk factors for QTc prolongation include increased age, female gender, congenital long QT syndrome, cardiovascular risk factors and disease, other medical conditions (commonly electrolyte abnormalities), psychotropic and non-psychotropic medications [13]. Prolonged QTc is considered a surrogate marker of polymorphic ventricular tachyarrhythmias such as TdP [14]. QTc prolongation is not an invariable precursor for TdP [15]. Risk is thought to be high when a person has a combination of factors as such genetic predisposition and also drugs that prolong QTc on top of that. This study has been approved by the IMH Clinical Research Committee and National Healthcare Group DSRB and supported by their seed funding.

We hope that the findings of this study could help us better understand the risk profile of patients needing high dose antipsychotics, the current level of ECG monitoring in such patient groups and the association between high-dose antipsychotic and QTc prolongation. We also hope that this study would remind clinicians to be more vigilant and could potentially guide clinicians towards safe practice in this group of patients.

Method

We included patients aged 21-65 years with any psychiatric diagnosis from the 3 outpatient clinics of the IMH of Singapore from June 2016 and Dec 2017. They are on high-dose antipsychotic that was defined either as 1) monotherapy, with the individual antipsychotic above the maximum dosage recommended by the Institute of Mental Health Pharmacy Department, references used include British National Formulary, MICROMEDEX (DRUGDEX) Healthcare Series, American Hospital Formulary System, Manufacturers Product Information and UpToDate, or 2) as polypharmacy, with a total antipsychotic daily dosage equivalent to 1 gram or more of chlorpromazine -CPZ). Informed consent was obtained. Exclusion criteria include intellectual disability, female patients who are pregnant or breastfeeding, patients taking drugs that are known to cause significant impact on QT prolongation (antiarrhythmic Class I and Class III drugs, imidazole antifungal agents, antibiotics of macrolide derivatives and fluoroquinolone group, certain non-sedating antihistamines such as terfenadine and astemizole) and tricyclic antidepressants. Pharmacists in the study team identified patients who are on high-dose antipsychotic via the Online Analytical Processing system and coordinated patients' study visits. They then tagged the recruited patients and those who refused consent to prevent duplication. The initial aim was to recruit a total of 80 patients from our 3 outpatient clinics.

Clinicians obtained the following information from the consenting patients and their electronic medical records, such as demography (age, race, gender), psychiatric diagnosis, cardiovascular risk factor/disease (smoking, lack of exercise, obesity, hyperlipidaemia, hypertension and diabetes mellitus and ischaemic heart disease, valvular heart disease and arrhythmia), family history of cardiovascular risk factor/disease or sudden death, other medical history (renal/liver dysfunction, hypothyroidism), antipsychotics details (name, dosage per day and chlorpromazine equivalent dose) other psychotropic and non-psychotropic medications, any ECG done in the past 12 months and the findings of such if it was done. Subsequently, the clinicians ordered an ECG and blood tests (potassium, calcium and magnesium levels) to reduce the confounding. Participants were given S$30 as an inconvenience fee. The ECG and blood results were uploaded onto their electronic documents for patients' primary physician to have access. All ECGs were done from Philip ECG machine (models 1. TC50 and Model 2. US90821237) throughout the study [16]. Resident physician (RI) manually read all the ECGs. Parameters such as Rate, PR interval, QRS duration and axis, QT interval and QTc, ST segment and T wave are studied in addition to physician's overall comment on the ECGs. Manual reading of QT done from lead II and compared with another best lead to double check QT calculations. Rate correction was done using Bazett's Formula (QT/RR). Bazett's formula is the most commonly used method to adjust for heart rate, unless there is severe Brady or tachyarrhythmias (below 60 and above 100Bpm) when Bazett's method tends to give an erroneous reading.

We also studied whether the frequency of rate and QTc interval abnormality was in anyway related to any other significant factors such as a number of cardiovascular risk factors (high risk was defined as the presence of 3 or more factors), having (3 or more) combination of antipsychotics and also very

high doses (up to CPZ 1500 mg equivalent vs more than CPZ 1500mgs equivalent).

Statistical Analyses

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 16.0 [17]. Mean and standard deviations were calculated for continuous variables, and frequencies and percentages were calculated for categorical variables. Significant associations between two categorical variables were tested using Chi-square test and Fisher exact test if the expected value in each cell is greater than 5. All significance tests were performed using two-sided tests evaluated at the 0.05 level of significance

Result

Only 37 patients consented out of 113 who have fulfilled a high dose category. We feel that it is the blood test that had deterred patients from participating despite the inconvenience fee. Baseline characteristics and risk profiling of consented patients on high dose antipsychotics are shown in the given data (Table 1).

Table 1. Baseline characteristics of patients on high dose antipsychotics.

Socio-demography	
Gender	Male 64.9%, Females 35.1%
Race	Chinese (73%), Malay (16.2%) and Indian (10.8%)
Age	Average 48 (Range 27-65)
Diagnosis	Schizophrenia 95%, Schizoaffective disorder 5%
Cardio-vascular risk factors	
Smoking	Yes (27%)
Lack of exercise (regular >1 in a week)	Yes (49%
Obesity	Yes (32.4%)
Hyperlipidaemia	Yes (62.2%)
Hypertension	Yes (37.8)
Diabetes Mellitus	Yes (29.7%)
Past h/o Ischaemic HD	Yes (0%)
Past h/o Valvular HD	Yes (0%)
Past h/o Arrhythmia	Yes (2.7%)
Family h/o IHD	Yes (37.8%)
Antipsychotics prescribing patterns	
Number of antipsychotics	2 (46%), 3 (46%), 4 (5.2%), 6 (2.7%)
Dose of antipsychotics (CPZ equivalent)	1000-1500 mgs (89.2%), 1500-2000 mgs (5.4%), >2000 mgs (5.4%)
Type of antipsychotics	Atypical and Typical combination (83.8%), Typicals only (10.8%) and Atypicals only (5.4%)
Use of depot antipsychotics	Yes (83.8%)
Other psychotropic medication usage	
Mood stabilisers	Yes (43%)
	Lithium use (8%)
Anticholinergics	Yes (65%)
Antihistamines	Yes (24%)
Benzodiazepine	Yes (51.4%)
Propranolol	Yes (13.5%)
SSRI antidepressants	Yes (32.4%)
Escitalopram	-3%
Non-Psychotropic Medication Usage	
Antihypertensive	Yes (27%)
Anti-hyperglycaemic	Yes (21.6%)
Anti-hyperlipidaemic	Yes (46%)
Thyroid supplements	Yes (3%)
Others	Yes (24.3%)
Pre-study ECG monitoring (6-12months earlier)	
Baseline ECG done	Yes (24.3%)
Presence of significant electrolyte abnormality	
Abnormal K/Ca/Mg	No (0%)

Of the 37 patients who had their ECG done, 64.9% of them are males, 73% are Chinese ethnic origin with a mean age of 48 (ranged between 27 and 65) and almost all of them had the diagnosis of Schizophrenia except 2 cases of Schizoaffective disorders. Amongst the cardiovascular risk factors studied 62.2% had hyperlipidemia, followed by Hypertension (37.8%) and then Diabetes (29.7%). A significant proportion of cases also had a family history of Ischaemic Heart Diseases too (37.8%) and nearly half of them do not engage in regular exercise (49%) and nearly a third (27%) are smokers. Looking at their antipsychotic prescription patterns all of them had combination antipsychotics, the majority had 2 and 3 antipsychotic combinations (46% each) whilst a small proportion were given a combination of 4 or more (8%). Amongst the use of antipsychotic, flupenthixol depot (57%) was the most commonly prescribed medication followed by oral risperidone (41%) and then quetiapine (35%). Oral haloperidol, chlorpromazine, and zuclopenthixol depot were prescribed in 22% of subjects each. The majority were given CPZ equivalent of between 1000 and 1500 mgs (89.2%), 2 cases were given CPZ equivalent of between 1500 and 2000 mgs and 2 cases were given CPZ equivalent dose over 2000 mgs. To assess the impact of CPZ equivalent above 1500 mg's defined as high dose and above 1500 mg's defined as ultra-high dose.

Looking at other psychotropic drugs prescription, the majority (65%) were also prescribed anticholinergic (benzhexol or benztropine). Nearly half were on a mood stabilizer (43%) of which lithium, is known to have cardiovascular side-effects and was given in 8% of the subjects only. Majority of them were prescribed concomitant antiepileptic mood stabilizer (sodium valproate). About a third were given SSRI (32%) and of that only one patient received escitalopram, which is also known to have dose-related effect on QT, particularly in the elderly population. Amongst the non-psychotropic drugs, anti-lipid drugs topped the list (46%) followed by antihypertensives (27%) and anti-hyperglycaemic (22%) drugs. Only a quarter had any ECG done in the preceding 12 months.

None of the 37 patients recruited for this study had single antipsychotic high dose i.e. above BNF recommended limits. All of them had a combination of least 2 antipsychotics of which 46 percent were on 2 and 3 antipsychotics combination respectively. None of them noted to have significant electrolyte abnormalities that warranted further intervention.

Rate abnormality was detected (below 60 and above 100 Bpm) in 8 patients (22%) and of that almost all, excepting one, had bradycardia (<60 Bpm). Of those with rate abnormality, 75% are Chinese representing closely the total cohort but males were slightly overrepresented (75%). Comparing to the total cohort their age range showed slightly older age group individuals between 48 and 65 with a mean age of 56. Other factors such as number of antipsychotics used, the total dose of antipsychotics (high/ultra-high doses), number of cardiovascular risk factors all did not show any significant impact on rate abnormality (Table 2).

Table 2. Relationship between rate abnormality, dosage, number of antipsychotic and cardiovascular risk factors.

Impact on Heart Rate	Rate of abnormality		
	Normal N (%)	**Abnormal N (%)**	**p-value**
	Dosage of antipsychotics		
High dose (1000-1500 mgs CPZ equivalent)	26 (78.8)	7 (21.2)	1.00[b]
Ultra-high dose (>1500 mgs)	3 (75.0)	1 (25)	
	Number of antipsychotics		
less than 3 (<3) antipsychotics	14 (87.5)	2 (12.5)	0.423[b]
3 or more antipsychotics	15 (71.4)	6 (28.6)	
	Cardiovascular risk factors		
less than 3	17 (81.0)	4 (19)	0.705[b]
3 or more	12 (75)	4 (25)	

Note: Fisher exact test[b]

PR interval abnormality identified in 2 patients (5.4%), shorter PR with sinus rhythm in one, whereas the other noted to be prolonged (1st Degree Heart Block) with bradycardia. QRS duration was noted to be normal in all and only 3 patients (8%) had axis deviation (2 left axis and 1 right axis deviation).

QTc Prolongation was identified in 15 patients (40%) by Machine reading but when manually corrected, QTc interval normalized in three patients, thereby reducing QTc abnormality frequency to 12 patients (32%). Of these, 67% are males and 75% are of Chinese origin. Their age ranged between 28 and 65 with a mean age of 47. Age, ethnicity, and gender closely represented the total cohort (Table 1). Slight QTc prolongation was detected in a male as young as 28 and female as young as 39. The 28 years old male was on Clozapine and risperidone combination with QTc reading of machine and manual as 458ms) and the 39 years old female was on sulpiride, olanzapine

and zuclopenthixol Combination with the machine reading of QTc was 498 whilst manually read it nearly normalized to only 461 ms). In 8 (22%) patients, there was more than the 20 seconds difference in QTc interval between machine reading and manual reading. ST segment abnormality and T wave abnormality was identified in only one patient each respectively. A number of antipsychotics used, the total dose of antipsychotics used did not show significant impact on QTc abnormality (Table 3). Whereas the number of cardiovascular risk factors made a difference. Those with 3 or more cardiovascular risk factors were significantly associated with risk of having prolonged QTc. 9 out of 16 (56%) with 3 or more cardio-vascular risk factor had QTc prolongation whereas only 3 out of 21 (14.2%) with less than 3 cardiovascular risk factors had QTc prolongation.

Table 3. Relationship between QTc Prolongation, dosage, number of antipsychotic and cardiovascular risk factors.

Impact on QTc	Normal QTc N (%)	Prolonged QTc N (%)	p-value
	Dosage of antipsychotics		
High dose (between 1000-1500 CPZ equivalent)	22 (66.7)	11 (33.3)	1.00[b]
Ultra-high dose	3 (75.0)	1 (25.0)	
	Number of antipsychotics		
less than 3 (<3) antipsychotics	9 (56.3)	7 (43.8)	0.199[a]
3 or more antipsychotics	16 (76.2)	5 (23.8)	
	Cardiovascular risk factors		
less than 3	18 (85.7)	3 (14.2)	0.007[a]
3 or more	7 (43.8)	9 (56.3)	

Note: Chi-square test[a], Fisher exact test[b]

Only one patient, 65 years old Chinese female is noted to have both QTc prolongation (485) and also tachycardia (102). Independent rate abnormality was noted in the other 7 subjects with bradycardia and Independent QTc prolongation abnormality was noted in the other 11 subjects.

Amongst the antipsychotic medications, being only on the typical or atypical or mixed group did not make any influence on QTc Prolongation (Table 4). Having said that the vast majority was on combinations of typicals and atypicals (83%). Only 2 patients had all high doses from atypical combinations and 4 had only typical combinations.

Table 4. Relationship between QT-Corrected interval and with individual antipsychotic or other co-prescribed medications.

	QT-Corrected interval (prolonged QTc interval Manual)		
	No	**Yes**	
	N (%)	**N (%)**	**p-value**
Flupenthixol deport			
Typical	2 (50)	2 (50)	0.069[a]
Atypical	0 (0)	2 (100)	
Flupenthixol deport			
No	8 (50%)	8 (50%)	0.046
Yes	17 (81%)	4 (19%)	
Risperidone			
No	15 (68.2%)	7 (31.8%)	0.599
Yes	10 (66.7%)	5 (33.3%)	
Quetiapine			
No	15 (62.5%)	9 (37.5%)	0.303
Yes	10 (76.9%)	3 (23.1%)	
Haloperidol			
No	16 (61.5%)	10 (38.5%)	0.209
Yes	9 (81.8%)	2 (18.2%)	
Chlorpromazine			
No	22 (75.9%)	7 (24.1%)	0.055
Yes	3 (37.5%)	5 (62.5%)	
Zuclopenthixol depot			
No	20 (69%)	9 (31%)	0.52
Yes	5 (62.5%)	3 (375%)	

Olanzapine			
No	22 (68.6)	10 (31.3)	1.00[b]
Yes	3 (60)	2 (40)	
Other Co-prescribed medications			
Mood stabilizer			
No	14 (66.7%)	7 (33.3%)	0.893
Yes	11 (68.8%)	5 (31.3%)	
Anticholinergics			
No	7 (53.8%)	6 (46.2%)	0.189
Yes	18 (75%)	6 (25%)	
Antihistamines			
No	17 (60.7%)	11 (39.3%)	0.121
Yes	8 (88.9%0	3 (11.1%)	
Beta blockers			
No	20 (62.5%)	12 (37.5%)	
Yes	5 (100.0%)	0 (0%)	0.122
Antihypertensive			
No	19 (70.4%)	8 (29.6%)	0.412
Yes	6 (60.0%)	4 (40%)	

Note: Chi-square test[a], Fisher exact test[b]

The most commonly dispensed antipsychotics (flupenthixol decanoate 57%, risperidone 41%, quetiapine 35%, haloperidol 22%, chlorpromazine22%, zuclopenthixol Decanoate 22% and olanzapine 13%) were individually compared against other antipsychotic as a group (Table 4). None of the above showed significant impact on QTc interval. Flupenthixol decanoate showed negative association compared to having other antipsychotics. Authors would like to remind that none of the patients were on Mono antipsychotic therapy.

Nearly half had also mood stabilizers prescribed and two third of them had anticholinergics. None of the co-prescribed medications, including others such as anticholinergics, antihistamines, mood stabilizers, beta-blockers, and antihypertensives had any significant impact on the QTc interval results (Table 4).

Discussion

Our study focused on high dose antipsychotics and also excluded potential confounders such as drugs with known QT prolongation effects (antiarrhythmics, tricyclics and certain antihistamines) and electrolyte abnormalities. In our study, only a quarter of the patients on high-dose antipsychotics received ECG in the last 12 months. This is consistent with previous studies that ECG monitoring was inadequate in patients receiving antipsychotics. Our study has been the first such study in Singapore with a focus on high-dose antipsychotic. Apart from looking into ECG abnormalities, this study looked at the polypharmacy of patients on high dose antipsychotics, whilst the majority of the individuals (92%) had combinations of 2 or 3 antipsychotics for treatment-resistant cases; combinations of more than 3 antipsychotics were required in a small proportion (8%) of study subjects. This finding is noteworthy too as sometimes clinicians erroneously argue that antipsychotic polypharmacy reduces the total amount of antipsychotic medication.

Our resident physician calculated QT interval manually and then used Bazett's Formula for rate correction and thereby reduced QTc abnormality from 40% in machine reading to 32% in manual reading. Clinicians are dependent on ECG machine interpretations, particularly in psychiatric specialist clinics. British Heart Foundation advises that errors are common with ECG machines and interpretation should not be accepted without Visual inspection [18]. The error in calculating QT interval could be explained by difficulties in determining the endpoint of T wave like the back slope of the T-wave can trail off and look rather inconclusive [19,20]. Experts usually use 2 best leads that can determine the most distinct end points of T wave to calculate QT interval and then apply Bazett's formula for rate correction. This has been applied by our resident physician in this study. Whenever the machine reading was off from the manual reading, the machine tended to overestimate the QT interval rather than the other way around. Whilst QTc prolongation is a risk factor, our patients possibly required such high dose medication due to lack of response to usual dose mono therapy approaches. Therefore, prudent risk-benefit analysis is essential before deciding to change the antipsychotic drug regime that has been keeping the individual well in terms of psychopathology. Manual checking of QT interval and rate correction plays a significant part in preventing unnecessary

medication changes which could cause a detrimental relapse of their psychiatric condition.

The main limitation of the study was the small sample size which effectively limits the comparison between antipsychotic medications and their QTc and rate abnormality. Nevertheless, the authors tried to study the risk profiling of this group of patients comprehensively including ruling out electrolyte's abnormality. The authors also tried to explore the impact of co-prescribed medication such as anticholinergics, antihistamines, mood stabilizers and also antihypertensives on QTc interval. Another limitation to this study has been the lack of control groups, such as comparing against similar patient profiles but maintained on normal doses.

This study whilst further confirming the previous findings such as elevated risk in those with pre-existing cardiovascular risk factors, also noted that males as young as 28 and females as young as 39 had QTc prolongation, necessitating the urgent need to ensure compliance with ECG monitoring in all those with high dose antipsychotics.

On manual reading of ECG, QTc prolongation was detected in 12 patients. Of which 9 patients had a slight increase in manual reading (<10 ms increase), 3 patients had more than 10 ms prolongation of which only one patient had more than 20 ms increase. If clinicians only take machine reading into account, the QTc prolongation is overestimated. The frequency of having more than 10 ms prolongation was noted in 8 patients by machine reading and it reduced to only 3 patients when manually read. Interestingly one female patient had QTcB as 530 ms in machine reading of QT interval but normalized to 426 ms when manual reading of QT interval was done along with the use of same Bazett's formula for rate correction. Another female patient had 473 ms in machine reading which normalized to 436 ms when manually red by our resident physician. This study highlighted that clinically significant ECG abnormalities frequency is reduced when the QTc interval was properly calculated manually by experts or trained personnel even in our high dose antipsychotic patients. We do acknowledge that the study sample size remains as a potentially limiting factor for our study. Authors would like to highlight a study done in a much bigger population of 725 patients pointed out that antipsychotic dose mediated the association between polypharmacy and corrected QT interval [20].

It is also important to highlight the role of the genetic variation as the modulating factor for QT interval prolongation in psychopharmacological treatment and therefore contribute valuable information towards personalized medicine in the future [21]. This study covered all psychotropic medications that are known to prolong QTc and identified in its secondary analysis some genes (ABCB1, NOS1AP, and KCNH2) may play a role in QTc duration/prolongation during treatment with psychotropic drugs.

Beyond QTc interval other related sub-parameters such as Peak to end of T Wave (Tp-e) and QT dispersion are also studied to understand the impact of Psychotropics and ventricular repolarisation [22]. The components of QTc such as Tp-e and Tp-e/QT ratio might be superior biomarkers because they better reflect increased transmural dispersion of ventricular myocyte repolarisation which can lead to TdP. One recent study highlighted that given the observed variability in QTc, Tpe, and Tpe/QT ratio, 24-hour ECG recordings warranted to provide an accurate assessment of the risk of TdP rather than just relying on rate corrected QT interval to capture the risk of TdP [23].

Recommended Guidelines for High Dose-Antipsychotics

1. Ensure high dose is clinically required and periodic review of such at least on annual basis during the already established Annual Review Clinic

2. Before Initiation:

   a. Cardio-Vascular risk profiling (Past history of CVS disease, Family History of CVS disease, DM, HTN, Lipids, Smoking, Absence of Exercise and Obesity)

   b. Screening for concurrent medication that enhances QT prolongation risk

   c. Baseline ECG

3. After initiation:

   a. Perform follow up ECG, repeating on an annual basis, early if further dose increase is required for clinical reasons

   b. Clinician involved in such prescribing to be taught to manually evaluate QTc interval alongside regular refresher training at the periodic interval to reduce false alarms and false negatives

4. Early intervention for QTc interval abnormality such as dose reduction and to seek cardiologist opinion where necessary

5. Periodic auditing of compliance to such recommendation could increase clinical utility

Conclusion

Our study found that ECG monitoring remains inadequate in patients with Schizophrenia, even in patients receiving a high dose of antipsychotics. Interestingly the frequency of significant QTc prolongation abnormality reduced drastically when manual reading and rate correction was done by experts and trained personnel. In our study, ECG manual reading picked up QTc prolongation in 12

patients (32%) of the total sample but that reduced to just only 3 if we were to only include patients with more than 10ms increase from recommended upper limit. Oftentimes, high doses of psychotropics are justified as a clinical necessity. The discrepancy between machine and manual reading of QTc highlighted that clinician-guided reading can avoid false alarms and prevent unnecessary dose down-titration that could potentially increase the risk of relapse. Therefore, the authors recommend clinical guidelines (as listed below) be enforced and overseen by a clinical pharmacist to ensure adequate and appropriate (clinician-guided QTc interval) monitoring for patients on antipsychotic medications and in particular for high dose prescriptions.

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