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Serial assessment of corrected qt interval and its clinical correlates in patients receiving psychotropic medications

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Abstract---Background & Aims: Psychotropic medications vary in propensity to cause QT_C prolongation on electrocardiogram. It can be fatal sometimes. Prospective Indian studies in this area are lacking. Present study was conducted to prospectively assess the changes in QT_C in patients receiving psychotropic medications. Settings and Design: Hospital based prospective observational study. Methods: A total of 150 patients aged 18-60 years, diagnosed as having any psychiatric illness and receiving psychotropic medications formed the sample. Psychiatric diagnosis was made according to DSM-5. Baseline ECG was done and psychotropic medications as per the diagnosis of the patient were started. Serial ECGs were performed on them up to one month post treatment. Results: Females constituted 54.7% of the sample. Major Depressive Disorder was the most common diagnosis. The duration of illness was less than 6 months in 47.3% of the patients. The dose of all psychotropic medications prescribed were in the therapeutic range and none of them exceeded the recommended maximum dose. Psychotropic medication was associated with increase in QT_C from baseline. The prevalence of QT_C prolongation was 1.40% at first follow up and 15% at second follow up. It ranged between 1 ms to 21 ms. Males aged less than 30 years, polypharmacy and increase in dosage were associated with QT_C prolongation, more so between 1-2

weeks of treatment initiation. Conclusion: Psychotropic medications have propensity to prolong QT_C. Presence of potential risk factors needs ECG monitoring during early phases of treatment.

Keywords---Psychotropic medications, QT_C, ECG.

Introduction

The QT duration on Electrocardiogram (ECG) is a measure of the cardiac electrical cycle. It includes both ventricular depolarization and repolarization.[1] Ventricular depolarization results from rapid influx of sodium ions into the cardiomyocytes. Subsequent repolarization results from an outward flow of potassium through two delayed rectifying currents–rapid (IKr) and slow (IKs). Blockade of either current may prolong the action potential and thereby lengthen the QT interval.[2] The QT interval is measured on the ECG from the beginning of the QRS complex (Initial deflection or Q wave) to the end of the T wave.[2] The QT interval shortens at faster heart rates.[3] Hence it is typically corrected for heart rate (QT_C). The most commonly used formula to correct the QT interval is Bazett's square root formula (QT_C = QT/R-R interval$^{1/2}$).[2] The Fridericia cube root formula (QT_C = QT/$RR^{0.33}$) is suitable for higher heart rates.[1] Risk of arrhythmia increases if the QT interval increases >440ms for men and >470ms for women.[4] Beyond 500ms there is higher risk of arrhythmia and sudden deaths.[5] A malignant polymorphic ventricular tachycardia characterized by a twisting pattern of the QRS complex called Torsades de pointes has been described with QT_C prolongation.[6]

The risk factors for prolonged QT_C include : Female gender, Older age, Sleep, Congenital Long QT syndrome, Electrolyte abnormalities (Hypokalemia, Hypocalcemia, Hypomagnesemia), Anorexia nervosa, Diuretic use, Cardiac conditions (Bradycardia, Left ventricular dysfunction, Heart failure, Mitral valve prolapse, Myocardial infarction), Other medical conditions (Renal and Hepatic dysfunction, Hypoglycemia, Hypertension, Diabetes, Hypothyroidism, Pituitary insufficiency, Central nervous system injury (Stroke, Trauma, Tumor, Infection), Acquired Immunodeficiency Syndrome, Malnutrition, Obesity (Including acute weight gain).[2,7] Diurnal variation of the QT_C interval has been observed.[7,8] QT_C prolongation can also occur with non-psychotropic drugs like Antibiotics (Erythromycin, Cotrimoxazole, Pentamidine, Ampicillin, Clarithromycin), Antimalarials (Chloroquine, Mefloquine, Quinine), Antiarrythmics (Quinidine, Disopyramide, Procainamide, Sotalol, Amiodarone, Bretylium), Others (Amantadine, Cyclosporin, Diphenydramine, Hydroxyzine, Methadone, Nicardipin, Tamoxifen).[4,5]

Psychiatric patients are a population at risk for cardiovascular problems. [9,10] Mortality rates are higher among them than in the general population.[11] Pharmacotherapy may produce side effects that affect mortality among psychiatric patients.[12] Commonly used psychotropic medications (Anti psychotics, Anti-depressants, Mood stabilizers, Anti-anxiety drugs, Anti epileptics, Anti cholinergics,) are associated with QT_C prolongation which can result in fatal arrhythmias. Psychotropic medications vary in their propensity to

cause QT_C prolongation on ECG. The risk of QT_C prolongation with Antipsychotics has been categorized into: No-effect (Drugs with which QT_C prolongation has not been reported either at therapeutic doses or in overdose), Low-effect (Drugs for which severe QT_C prolongation has been reported only following overdose or where only small average increases (<10 ms) have been observed at clinical doses), Moderate-effect (Drugs which have been observed to prolong QT_C by >10 ms on average when given at therapeutic doses or where ECG monitoring is officially recommended in some circumstances), and High-effect (Drugs for which there is extensive average QT_C prolongation, usually >20 ms at therapeutic doses). The drugs known to have No effect are Brexpiprazole, Cariprazine& Lurasidone. Drugs known to have mild effect are Aripiprazole, Asenapine, Clozapine, Flupenthixol, Fluphenazine, Loxapine, Perphenazine, Prochlorperazine, Olanzapine, Paliperidone, Risperidone &Sulpiride. Drugs known to have moderate effect are Amisulpride, Chlorpromazine, Haloperidol, Iloperidone, Levomepromazine, Melperone, Quetiapine & Ziprasidone. Drugs known to have high effect are any intravenous antipsychotic, Pimozide, Sertindole& any drug or combination of drugs used in doses exceeding recommended maximum. Drugs known to have unknown effect are Pipotiazine, Trifluoperazine & Zuclopenthixol.[4]

Among Antidepressants Mono amine oxidase inhibitors & Mirtazapine have least risk of QT_C prolongation. Bupropion, Desvenlafaxine, Levomilnacipran, Mianserin, Sertraline, Vilazodone and Reboxetine are reported to be safe with a low risk of QT_C prolongation at therapeutic doses. Amitriptyline, Clomipramine, Doxepin, Imipramine, Moclobemide, Nortriptyline, Fluoxetine, Venlafaxine, Paroxetine, Citalopram, Duloxetine and Escitalopram are reported to be at a moderate risk of QT_C prolongation. Among the mood stabilizers, Lithium has a moderate risk of QT_C prolongation while the Antiepileptics used for this purpose such as Carbamazepine, Oxcarbazepine, Topiramate, Sodium valproate, Pregabalin, Gabapentin, and Lamotrigine are reported to be safe with a low risk of QT_C prolongation. Most of the benzodiazepines are reported to be safe with a low risk of inducing QT_C prolongation. Among the anticholinergic drugs, Biperiden, Orphenadrine, and Trihexyphenidyl are relatively safe with a low risk.[13]

Most of the earlier studies conducted in this area are retrospective and cross sectional. Very few studies have prospective design. There is lack of published Indian literature on psychotropic drugs and QT_C prolongation. Therefore, the present study was planned to determine the prevalence of QT_C prolongation in patients receiving psychotropic medications and study the relationship between QT_C on ECG and various psychotropic medications (Anti psychotics, Anti-depressants, Mood stabilizers, Anxiolytics, Anticholinergica) with respect to type & dose of drug and clinical variables, prospectively.

Materials and Methods

This was a hospital based prospective study. Patients diagnosed as having psychiatric syndromes and receiving treatment (Outpatient / Inpatient) from a tertiary care hospital who were aged between 18-60 years belonging to both genders formed the sample of the study. Patients having any physical illness detected based on history and physical examination and those taking medicines other than those being prescribed by the psychiatrist during study period were

excluded from the study. 150 consecutive patients who met the inclusion criteria and did not get excluded were recruited. Ethical clearance was obtained from the institutional ethics committee.

All patients and caregivers were explained about the possible cardiovascular side effects of psychotropic medications and the need to monitor it by ECG. After obtaining written informed consent and socio demographic data, psychiatric diagnosis according to DSM-5 criteria was made. A baseline ECG was recorded using RMS Vesta 301i ECG machine. Those patients having abnormal baseline ECG were excluded from the study and referred to physician. Psychotropic medications as per the diagnosis of the patient were started. The type, dosage, duration of psychotropic medications received by the patient was documented in each visit. First repeat ECG was done 4 to 7 days after the initial visit and then during subsequent follow-ups up to one month. QT_C interval was calculated automatically by the ECG machine and displayed on the ECG record. Physician's opinion about interpretation was obtained as and when needed. QT_C values were considered prolonged if it was more than 440ms in males and more than 470ms in females. Patients having prolonged QT_C interval were referred to physician for appropriate interventions.

Statistical analysis

Qualitative variables were represented in the form of frequencies and percentages. Association between qualitative variables was studied using Chi square test. If the cell value was less than 5 in the 2x2 table, Fisher's Exact test was used. Quantitative variables were represented in the form of mean and standard deviation. Intergroup comparison of the mean was done using Unpaired t test. Intragroup comparison was done using Paired t test. Comparison of more than 2 groups was done using Analysis of variance (ANOVA). p value of <0.05 was considered as significant. IBM SPSS (Statistical Package for the Social Sciences) version 22 for Windows was used for statistical analysis.

Results

Sociodemographic and clinical details

150 patients were recruited for the study. 71 patients attended first follow up, 20 patients attended second follow up, 8 patients attended third follow up and 2 patients attended fourth follow up. The mean duration between baseline and first follow up was 5.62 days; between baseline and second follow up was 14.3 days; between baseline and third follow up was 22 days and between baseline and fourth follow up was 28.5 days. The socio demographic details and clinical details are summarized in Table 1.

Details about psychotropic drugs

During first follow up 38 patients (53.5%) were on 1-2 psychotropic medication, 29 patients (40.8%) were on 3-4 psychotropic medications and 4 patients (5.63%) were on 5-6 psychotropic medications. During second follow up 11 patients (55%) were on 1-2 psychotropic medications and 9 patients (45%) were on 3-4

medications. During third follow up 3 patients (37.5%) were on 1-2 psychotropic medications and 5 patients (62.5%) were on 3-4 psychotropic medications. During fourth follow up 2 patients were on 3-4 psychotropic medications.

Escitalopram was the most commonly prescribed antidepressant (25 patients in first follow up and 7 patients in second follow up) followed by Fluoxetine (20 patients in first follow up and 5 patients in second follow up). Risperidone was the most commonly prescribed antipsychotic in first follow up (13 patients) followed by Olanzapine (10 patients) whereas Olanzapine was the most commonly prescribed antipsychotic in second follow up (4 patients) followed by Risperidone (3 patients). Clonazepam was the most commonly prescribed anxiolytic (21 patients in first follow up and 7 patients in second follow up) followed by Chlordiazepoxide (5 patients in first follow up and 2 patients in second follow up). Sodium valproate was prescribed in 3 patients in first follow up and 2 patients in second follow up. Trihexyphenidyl was prescribed in 11 patients and Thiamine was prescribed in 6 patients in first follow up. All psychotropic medications prescribed were within the therapeutic range.

QT_C assessments

The mean QT_C at baseline was 411.72ms (n=150) and it increased to 416.66ms (n=71) at first follow up. It further increased to 421.3ms (n=20) at second follow up. At third follow up it decreased to 414.9ms (n=8) and further increased to 430ms (n=2) at fourth follow up. Table 2 summarizes the comparison of mean QT_C between follow ups. There was a significant difference between the mean QT_C at baseline and the mean QT_C at first follow up of the patients who attended first follow up (n=71). There was a significant difference between the mean QT_C at baseline and the mean QT_C at fourth follow up of the patients who attended four follow ups (n=2). There was no significant difference between QT_C values in rest of the follow ups. When clinical parameters were compared with baseline QT_C the mean QT_C of females was significantly more than males. (Table 3)

The prevalence of QT_C prolongation at various follow ups is depicted in Table 4. At first follow up among 71 patients 1 patient had QT_C prolongation. During second follow up 3 out of 20 patients had prolonged QT_C. There was no QT_C prolongation during third and fourth follow up. The prevalence of QT_C prolongation at first follow up was 1.40% and it was 15% at second follow up. QT_C was prolonged in 3 male patients. The first patient had a prolongation of 1ms in first follow up, 5 days after starting medications and 2ms prolongation in second follow up, 14 days after starting medications. The second patient had a prolongation of 3ms in second follow up, 14 days after starting medications. The third patient had a prolongation of 21ms in second follow up, 13 days after starting medications. The comparison of various clinical correlates with QT_C prolongation is shown in Table 5. The patients aged less than 30 years were significantly more likely to have QT_C prolongation than patients aged more than 30 years. There was no prolongation of the QT_C in any female patient. Males were significantly more likely to have QT_C prolongation than females.

Table 1
Sociodemographic and Clinical details

Sociodemographic and Clinical details		Frequency (N=150)	Percent
Age (years)	<20	9	6.0
	21-30	47	31.3
	31-40	57	38.0
	41-50	31	20.7
	51-60	6	4.0
Gender	Male	68	45.3
	Female	82	54.7
Education	Nil	34	22.7
	Up to 9th	32	21.3
	SSLC	27	18.0
	PUC	25	16.7
	Degree	29	19.3
	Diploma	3	2.0
Marital Status	Married	119	79.3
	Unmarried	31	20.7
Diagnosis	Major depressive disorder	68	45.3
	Schizophrenia	13	8.7
	Others	69	46.0
Duration of illness (Months)	≤6	71	47.3
	7-29	39	26.0
	≥30	40	26.7

Table 2
Comparison of Mean QT_C between follow ups

Pairs	QT_C	N	Mean	Std. Deviation	Paired t test	p value
Pair 1	Baseline	71	410.41	29.83	-1.957	p<0.05, Sig
	First	71	416.66	24.77		
Pair 2	Baseline	20	418.70	26.93	-.442	0.664, NS
	Second	20	421.30	29.51		
Pair 3	Baseline	8	417.25	29.93	.309	0.766, NS
	Third	8	414.88	21.06		
Pair 4	Baseline	2	402.50	4.95	-11.000	p<0.05, Sig
	Fourth	2	430.00	8.49		
Pair 5	First	20	421.45	27.55	.026	0.98, NS
	Second	20	421.30	29.51		
Pair 6	First	8	419.25	33.23	.731	0.489, NS
	Third	8	414.88	21.06		
Pair 7	First	2	419.00	15.56	-2.200	0.272, NS
	Fourth	2	430.00	8.49		
	Second	8	415.25	34.98	.055	0.958, NS

Pair 8	Third	8	414.88	21.06		
Pair 9	Second	2	422.00	4.24	-2.667	0.228, NS
	Fourth	2	430.00	8.49		
Pair 10	Third	2	417.00	1.41	-2.600	0.234, NS
	Fourth	2	430.00	8.49		

Table 3
Comparison of clinical correlates with Baseline QT_C

Age in Years	N=150	Mean QT_C (ms)	Std. Deviation	ANOVA
≤ 20	9	409.8	25.4	F= 0.547, p<0.702, NS
21-30	47	413.0	28.5	
31-40	57	407.8	28.6	
41-50	31	416.4	33.1	
51-60	6	417.7	24.7	
Gender and QT_C				
Gender	N=150	Mean QT_C (ms)	Std. Deviation	Unpaired t test
Male	68	401.32	24.45	t = 4.205, p<0.000. Sig
Female	82	420.35	29.94	
Duration of illness and QT_C				
Duration of illness (Months)	N=150	Mean QT_C (ms)	Std. Deviation	ANOVA
≤ 6	71	412.27	31.43	F= 0.281, p<0.890, NS
7-12	21	415.33	24.85	
13-18	3	421.00	38.94	
19-24	0	-	-	
24 - 29	15	410.73	24.99	
≥ 30	40	408.55	28.61	

Table 4
QT_C prolongation at follow ups

QT_C	Assessment				
	Base line (n=150)	First Follow up (n=71)	Second Follow up (n=20)	Third Follow up (n=8)	Fourth Follow up (n=2)
Normal	150	70	17	8	2
Prolonged	0	1	3	0	0

Table 5
Comparison of clinical correlates with QT_C prolongation

Age (years)	QT_C Prolonged	QT_C Normal	Total
≤ 20	1	8	9
21-30	1	18	19
31-40	0	28	28
41-50	0	13	13
51-60	1	1	2
Total	3	68	71
Chi Square Test p<0.01			
Gender and QT_C prolongation			
Gender	QT_C Prolonged	QT_C Normal	Total
Male	3	29	32
Female	0	39	39
Total	3	68	71

Discussion

Socio demographic variables

In this study age of the sample was between 18-60 years. Some of the earlier studies also had similar inclusion criteria.[14] Other researchers have included younger patients (12-17 years) and older patients (65 years and above). [15,16] Females constituted 54.7% of the sample in the present study. Mario Miniati et al, included only male patients with psychotic disorders.[17] Few researchers have included only female patients. [18,19,20]

Diagnosis

In the present study patients having any type of psychiatric syndromes were included. Earlier studies differ with respect to the diagnostic category of the patients. They consisted of Psychotic disorders; [17,21,22] Schizophrenia, bipolar disorder, schizoaffective disorder;[19] Schizophrenia, Schizoaffective disorder, Delusional disorder, Mood disorders;[20] Only Schizophrenia. [14,23,24,25,26] Other researchers have included patients diagnosed as having all types of psychiatric illnesses. [21,27,28] In the present study patients were not on any psychotropic medications at baseline assessment. However, some patients who had previous episodes of psychiatric syndromes which had remitted after treatment and then recurred or those who had discontinued medication for more than 6 months during the present episode were also included. Johnsen et al, included patients who were drug naive.[22] Previous researchers have included patients who were not on any psychotropic medications for 2 weeks and 48 hours. [14,19,20] The duration of being medication free has not been mentioned in few studies. [15,23,29]

Duration of illness

In the present study patients having any duration of illness were included. One of the earlier studies included patients having a duration of illness of at least 2 years.[17] Other researchers have included patients having any duration of illness. [15,17,19,20]

Psychotropic medications

In the present study the effects of all psychotropic medications which the patients were given for their psychiatric syndromes (Anti-depressants, Antipsychotics, Mood stabilizers, Anti cholinergics, Anxiolytics, Miscellaneous drugs) on the QT_C interval was assessed. The number of psychotropic medications prescribed ranged from 1-6. Few researchers have compared monotherapy versus polytherapy. Sumic et al, compared the effect of monotherapy (Antidepressant or antipsychotic) and polytherapy (Antidepressant and antipsychotic).[20] Sala et al, compared QT_C interval prolongation between antipsychotic monotherapy and polytherapy (Antipsychotic with an additional antidepressant or Lithium).[19]

QT_C related outcomes
Baseline QT_C interval

In the present study QT_C was assessed at baseline before starting medication. There was no significant difference in the mean QT_C at baseline between different age groups. This has not been addressed by previous researchers. In the present study the mean QT_C of females at baseline was significantly more than males. Similar findings have been reported earlier. [15,20,30] However, no gender difference at baseline QT_C interval has also been reported.[22] The sex difference appears to be androgen driven and not determined by female hormones: At birth, QT_C interval measurements are the same for male and female infants. At puberty, the QT_C interval in males shortens and remains shorter than in females by about 20 ms until ages 50 to 55 years, coincident with a decline in testosterone levels. Moreover, baseline QT_C interval doesn't show significant fluctuations during the menstrual cycle and Hormone Replacement Therapy in postmenopausal age doesn't affect QT_C interval.[31]

In the present study the baseline mean QT_C of patients having Major depressive disorder was 412.66ms while it was 418.69ms in patients having Schizophrenia. QT variability was increased in unmedicated patients having Schizophrenia and it correlated with severity of positive symptoms. This indicates abnormal cardiac repolarization lability and high sympathetic cardiac activity which can result in increased cardiovascular mortality.[25]Baseline prolongation of QTc interval along with longer duration of illness (>10 years) has been observed.[20] Schizophrenia may carry a higher risk for other illnesses (e.g. Atherosclerosis and cardiac abnormalities).[32,33]Emotional distress due to agitation in acute psychosis can cause QT_C prolongation.[22]Higher risk of sudden death in schizophrenia independent of drug treatment could be due to illness, smoking, habits or both.[34]

QT_C interval during follow ups after medications

In this study the mean QT_C at baseline was 411.72ms (n=150) and it increased to 416.66ms (n=71) at first follow up. It further increased to 421.3ms (n=20) at second follow up. At third follow up it decreased to 414.9ms (n=8) and further increased to 430ms (n=2) at fourth follow up. The mean QT_C at first follow up (n=71) and fourth follow up (n=2) was significantly more than mean QT_C at baseline. Increase in mean QT_C after initiation of treatment has been reported.[14] According to Jensen et al, the mean QT_C increased from baseline to 12 weeks after treatment with Quetiapine. The change between baseline and week 4 was significant whereas the change from week 4 to week 12 was not significant. The authors have explained this finding on the basis that QT_C change occurs primarily as a direct blockade of a potassium channel and any effect will occur shortly after dose change.[15] However contradictory findings in the form of significant reduction of abnormally prolonged or borderline prolonged QT_C at baseline, 6 weeks after treatment with second generation antipsychotics has also been documented.[22]

QT_C prolongation

The prevalence of QT_C prolongation at first follow up was 1.40% and 15% at second follow up. There was no QT_C prolongation at third follow up (n=8) and fourth follow up (n=2). The patients at second follow up were significantly more likely to have QT_C prolongation than the patients at first follow up. Previous studies have reported prevalence of QT_C prolongation ranging from 0.9% to 88.37%. Higher prevalence has been attributed to long term use of psychotropic medications.[14] Most of the earlier studies have used a cross sectional approach in the assessment of QT_C interval.

Age and QT_C prolongation

In this study younger patients (<30 years) were significantly more likely to have QT_C prolongation than those aged more than 30 years. Older age has been associated with QTc lengthening. [14,26,30]

Gender and QT_C prolongation

In the present study QT_C prolongation was significantly more in males than females. In a study by Nizamie et al, males had statistically significant difference in the QT_C interval between 1st & 2nd and between 1st & 3rd ECG. Such difference was not observed in women.[14] According to previous studies QT_C interval is longer in female gender and females are more likely to have QT_C prolongation. [15,18,26,28] In comparison to men, women are at higher risk of developing Torsades de pointes [18]. This could probably be due to genetic predisposition, higher plasma concentrations of medications or greater sensitivity for QT prolonging effects. [35]

Psychotropic medications and QT_C prolongation

In the present study at first follow up 1 patient had QT_C prolongation. He was on three medications. At second follow up out of 3 patients who had prolonged QT_C, 2 patients were on two medications and 1 patient was on three medications. The patients who were on two medications were significantly more likely to have prolonged QT_C than patients who were on one or three medications. In all the 8 patients who came for third follow up QT_C was within normal limits. Few researchers have compared the QT_C interval between patients on monotherapy and polytherapy. Polytherapy was found to have significant QT_C prolongation as compared to Antipsychotic monotherapy.[22]Polypharmacy was positively associated with QT_C prolongation in patients exposed to antipsychotic drugs.[35] However the QT_C interval length did not differ significantly in the monotherapy and the polytherapy group.[20].Currently available evidence does not confirm that antipsychotic polypharmacy worsens QT_C prolongation.[36]The mechanisms implicated are synergic blockade of the HERG potassium channels and increase in drug levels (With subsequent augmented risk of cardiotoxicity) due to metabolic interactions between drugs that share the same metabolic pathway.[37] This could be relevant in those having genetic impairment of enzymes metabolizing the concerned medications.[38

In the present study 3 patients had QT_C prolongation. One patient was on Fluoxetine (20mg/day) & Etizolam (0.5mg/day) and he was followed up for 2 weeks. One patient was on Olanzapine (Started with 5mg/day and increased to 20mg/day), Sertraline (Started with 50 mg/day and increased to 150mg/day) & Nitrazepam (5mg/day for 1 week then advised to take if necessary) and he was followed up for 15 days. The third patient was on Fluoxetine (20mg/day), Escitalopram (10mg/day) & Amitryptaline (75mg/day added at second follow up). He was followed up for 2 weeks. First 2 patients did not turn up for further follow up and third patient was referred to Physician. QT_C prolongation is more likely in patients receiving doses above 2000mg Chlorpromazine equivalents daily.[39] Use of Aripiprazole decreased the risk of QT_C prolongation.[28] The mean QT_C interval is not significantly influenced by antipsychotic dose, type of antipsychotic treatment, use of depot antipsychotics or the number of different antipsychotics prescribed.[26] Almost all drugs causing significant QT prolongation are known to interact with repolarizing potassium channels, particularly with the IKr, encoded by the HERG channels.[40]

Limitations

Our study include high dropout rate, ruling out comorbid physical illness only on the basis of history & physical examination and non-assessment of risk of individual psychotropic medications.

Conclusion

The mean QT_C increased from baseline to second follow up, decreased in third follow up and increased in fourth follow up, but it was above baseline in all the follow ups. The prevalence of QT_C prolongation was 1.40% at first follow up and 15% at second follow up. It ranged between 1 ms to 21 ms. Prolongation occurred

1-2 weeks after starting treatment, more so around 2 weeks. Males aged less than 30 years, polypharmacy and increase in dosage were associated with QT_C prolongation. Fatal outcome from QT_C prolongation in these patients cannot be commented as they were lost for follow up.

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