ORIGINAL RESEARCH

ECG abnormalities (QTc interval and other related variables) in patients on psychotropics medications: A crossectional Study

[1]Dr. Aman Bharti, [2]Dr. Tanishq Gupta, [3]Dr. Poonam Bharti, [4]Dr. Jasmeen Chahal, [5]Dr. Arashdeep Kaur

[1,4]Assistant Professor, [5]Senior Resident, Department of Medicine, GGSMCH, Faridkot, Punjab, India
[2]PG 2year Resident, [3]Professor and Head, Department of Psychiatry, MM Institute of Medical Sciences & Research, Ambala, Haryana, India

Corresponding author
Dr. Arashdeep Kaur
Senior Resident, Department of Medicine, GGSMCH, Faridkot, Punjab, India
Email: sranarash1408@gmail.com

Received: 03 May, 2023 Accepted: 06 June, 2023

INTRODUCTION

Patients with mental illness are identified as a subject pool with increased chances of Cardiovascular changes [(1,2)]. When compared with general population [(3)] they are even at an increased risk of mortality due to adverse effect of psychotropics. [(4)] Consequently, there has been a rise in the concern over cardiac safety of psychotropic medications.

Psychotropics drugs(including typical, atypical antipsychotics, tricyclic antidepressants, non-selective monoamine oxidase and all anti parkinsonian anticholinergics) have anticholinergic as well as antimuscarinic effects and can lead to sinus tachycardia. [(5.6)]. Whereas SSRI causes mild degree of bradycardia. Tricyclic antidepressants also prolong QRS interval and causes conduction defects, these effects are dose dependent [(7,8)]. This finding is in particularly harmful for those with preexisting cardiac conduction delay and can lead to heart block in varying degrees. [(9)]

There is variation in the capacity of antipsychotic to cause QTc prolongation [(10)]. Low potency typical antipsychotics are implicated for the same whereas high potency typical as well as atypical antipsychoticscause torsade's de pointes less often with the exception of ziprasidone leading to debate in FDA leading to delay in their approval. The greatest concern is due to immediate use haloperidol and long-term use of olanzapine and clozapine [(11)]

Patients with psychiatric illness are subjected to polypharmacy [(12,13)], illicit drug use, high drug dosage which increases the risk of QTc prolonging drugs and QT drug-drug interaction [(14,15)]. In addition, QTIP is due to combined use of antipsychotic and antidepressants in most clinical settings [(16,13)]. The increased use of polypharmacy, increased doses, combination drugs with poor health care increased risk of QTIP related mortality and morbidity[(17,18,19)]

Secondary TCA affect children and elderly more whereas tertiary TCA affect entire general population. Mirtazapine is the only antidepressants that has been reported to have caused torsade's de pointes among other antidepressants. SSRI have no effects on QTc. Similarly, benzodiazepine have little effect on QTc but they can have effects on other cardiovascular parameters. [(11)]

Other risk factors for QT prolongation and torsade's de pointes in psychiatric population include, substance use, accidental or deliberate overdose and restrain that leads to high sympathetic arousal.

The aim of this study was to determine varied ECG changes, including QTc prolongation and other variables on outpatient who have been on long term use of psychotropic medications and its association with factors like sociodemographic profile, comorbidities and vitals.

METHODOLOGY

DESIGN AND SETTING

A prospective observational study was conducted at the psychiatry OPD of a tertiary care hospital. The convenience sampling was used to include patients diagnosed with psychiatric disorder, who had been on

psychotropics for >1 year, aged above 18 years or more, of either gender.

An ethical clearance was taken for starting the study. Prior to participation a written consent was taken from all the patients.

INCLUSION CRITERIA

1. Patients on psychotropics for more than one-year.
2. Both genders included.

EXCLUSION CRITERIA

1. Patients who were already on treatment for cardiac illness.
2. Patients who were unwilling/ did not consent.
3. Patients with prior history of abnormal ECG record before starting psychotropics.

DATA COLLECTION AND ANALYSIS

Patient's relevant data for the study was procured from medical profile of patients. After recording ECG, the following data were collected: age, gender, diagnosis, comorbities and prescribed medications.

STATISTICAL ANALYSIS

Mean values for continuous variables were compared using Patients *t* test for independent samples or the paired *t* test for dependent samples. To test for independence among the categorical variables, we used the Pearson Chi-square test. Differences in proportion of prolonged QTc were assessed using a generalized linear mixed model (logistic regression), fit by maximum likelihood to detect potential differences among the two groups, without adjusting these models for any covariates except for repeated measurements per admission. A linear mixed-effects model fit by restricted maximum likelihood was used to assess the influence of the covariates on QTc interval simultaneously.[20] Two nested random effects (one at the admission level nested in another random effect at the individual level) were used to take into account the repeated measurements of QTc per admission and for each individual. We used graphic tools to assess the fit and results were satisfactory. A *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata software version 15.0 (StataCorp, College Station, TX, USA), and R language and environment for statistical computing 3.3.1.[21]

RESULTS

Socio-Demographic on the Subjects of ECG Changes

Profiling	Set	N (%)	Normal ECG (%)	Abnormal ECG (%)
Gender	Male	67 (53.60%)	59 (88.05%)	08 (11.95%)
	Female	58 (46.40%)	50 (86.20%)	08 (13.80%)
Age-Group	18-30 Years	42 (33.60%)	36 (85.71%)	07 (14.29%)
	31-45 Years	49 (39.20%)	41 (83.67%)	08 (16.33%)
	46-60 Years	26 (20.80%)	22 (84.62%)	04 (15.38%)
	> 60 Years	08 (6.40%)	08 (100.00%)	00 (0.00%)
Education	Illiterate or Primary School	11 (8.80%)	09 (81.81%)	02 (18.18%)
	Secondary School	33 (26.40%)	29 (87.88%)	04 (12.12%)
	High School	57 (45.60%)	48 (84.21%)	09 (15.79%)
	College	24 (19.20%)	20 (83.33%)	04 (17.67%)
Occupation	Government Job	18 (14.40%)	15 (83.33%)	03 (16.67%)
	Non- Government Job	55 (44.00%)	48 (87.27%)	07 (12.73%)
	Retired	18 (14.40%)	18 (100.00%)	00 (0.00%)
	Housewife/Unemployed	34 (27.20%)	26 (76.47%)	08 (23.53%)
Marital Status	Single	20 (16.00%)	16 (80.00%)	04 (20.00%)
	Married	100 (80.00%)	85 (85.00%)	15 (15.00%)
	Divorced/Widow	5 (4.00%)	5 (100.00%)	00 (0.00%)
Location	Rural	82 (65.60%)	69 (84.15%)	13 (15.85)
	Urban	43 (34.40%)	38 (88.37%)	05 (11.63%)

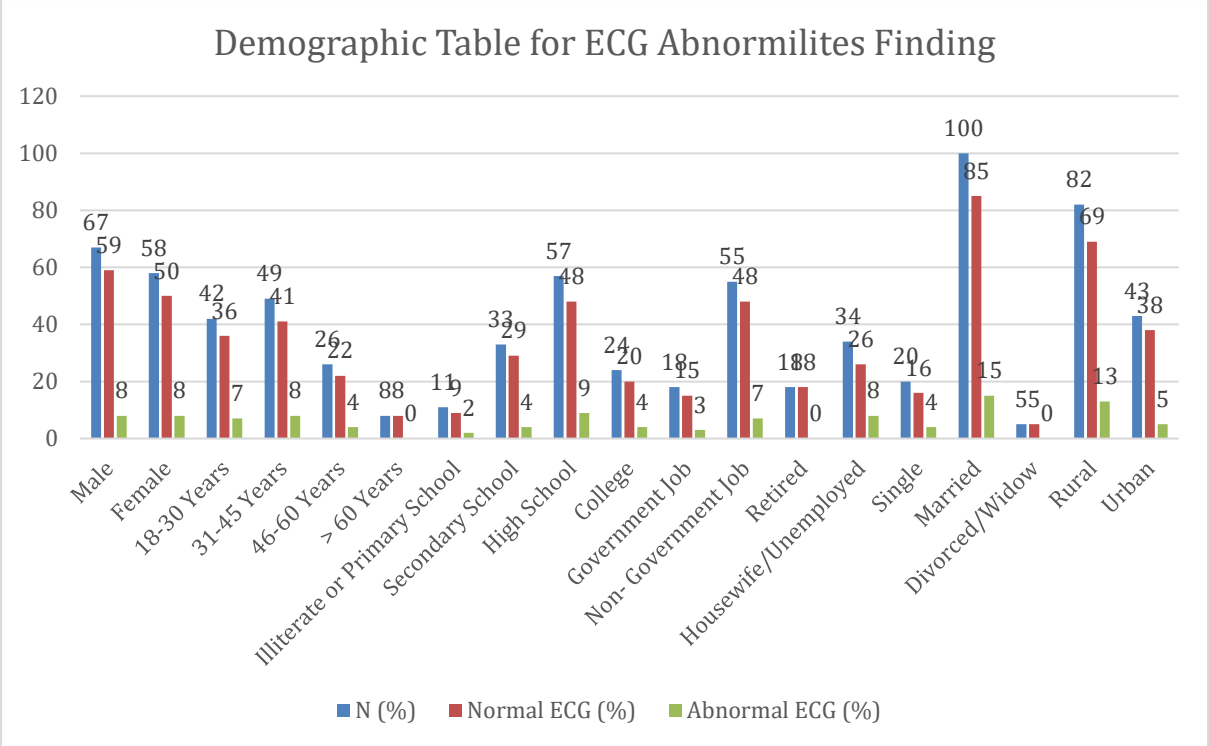

Table 1: This study included 125 psychiatric patients of which 53.60% (n=67) were males and 46.40% (n=58) were females. Abnormal ECG changes were almost same in both males and females which was 11.95% (n=08) and 13.80% (n=08) respectively. Majority of participants were from the age group 31 to 45 years constituting 39.20%(n=49) and abnormal ECG in them was seen in 16.33% (n=8) individuals. In education status majority of the participants were high school pass outs 45.60% (n=57) and ECG abnormalities were also seen majorly in them 1579% (n=9). Patients with non-government job constituted 44% (n=55) and had abnormal ECG of 12.73% (n=7). In this study majority of the participants were married 80% (n=100) among them abnormal ECG was in 15.00% (n=15). Patients from rural location constituted 65.20% (n=82) among which 15.82% (n=13) showed abnormal ECG.

Distribution of Subjects in ECG Changes on the Co-morbidities

Co-morbidities	ECG-Changes	
	Normal (%)	Abnormal (%)
Epilepsy	12 (100%)	0 (0%)
Substance Dependence	7 (100%)	0 (0%)
Obesity	1 (100%)	0 (0%)
COPD	1 (100%)	0 (0%)
Bronchial Asthma	1 (100%)	0 (0%)
Hypertension	15 (88.23%)	2 (11.77%)
Normal	70 (82.35%)	15 (17.65%)
Diabetes Mellitus	6 (75%)	2 (25%)
Arthritis	2 (66.67%)	1 (33.33%)
Hypothyroidism	6 (60.00%)	4 (40.00%)
Anaemia	0 (0%)	1 (100%)

Table 2: When the ECG changes were compared among various comorbidities including those without any comorbidity and it was seen that abnormal ECG changes were more in those with anemia 100% (n=1) followed by those with hypothyroidism 40% (n=4), arthritis 33.33%(n=3), diabetes mellitus 25% (n=2), whereas 20.00% (n=25) of abnormal ECG changes were also recorded among those with no co-morbid abnormalities.

Distribution of Psychotropic Drugs seen in ECG-Changes

Antipsychotic * ECG-Changes			ECG-Changes		Total
			Normal	Abnormal	
Antipsychotic	None	Count	57	5	62
		% within Antipsychotic	91.94%	8.06%	100.0%
		% within ECG-Changes	55.4%	30.0%	52.0%

	Use	Count	51	12	63
		% within Antipsychotic	80.95%	19.05%	100.0%
		% within ECG-Changes	44.6%	70.0%	48.0%
Antidepressant * ECG-Changes			ECG-Changes		Total
			Normal	Abnormal	
Antidepressant	None	Count	52	8	60
		% within Antidepressant	86.67%	13.33%	100.0%
		% within ECG-Changes	50.0%	45.0%	49.3%
	Use	Count	55	10	65
		% within Antidepressant	84.62%	15.38%	100.0%
		% within ECG-Changes	50.0%	55.0%	50.7%
Benzodiazepines * ECG-Changes			ECG-Changes		Total
			Normal	Abnormal	
Benzodiazepines	None	Count	5	0	5
		% within Benzodiazepines	100.0%	0.0%	100.0%
		% within ECG-Changes	3.8%	0.0%	3.3%
	Use	Count	100	20	120
		% within Benzodiazepines	83.33%	16.67%	100.0%
		% within ECG-Changes	96.2%	100.0%	96.7%
Others * ECG-Changes			ECG-Changes		Total
			Normal	Abnormal	
Others	None	Count	59	3	62
		% within Others	95.16%	4.84%	100.0%
		% within ECG-Changes	53.8%	20.0%	49.3%
	Use	Count	50	13	63
		% within Others	79.37%	20.63%	100.0%
		% within ECG-Changes	46.2%	80.0%	50.7%

Table 3: Of 65 participants on antipsychotics 15.38% had abnormal ECG whereas among 60 participants on antidepressants 13.33% showed abnormal ECG. It was also seen that of 120 patients on benzodiazepine 16.67% has ECG changes. Patients on psychotropics other than the above mentioned were 63 in number and constituted 20.63% of abnormal ECG changes.

Distribution of Sets on ECG-Changes

Set	**ECG-Changes**		
	Scales	**Normal (%)**	**Abnormal (%)**
Pulse	Low	2 (28.57%)	5 (71.43%)
	Normal	62 (95.38%)	3 (4.62%)
	High	41 (77.36%)	12 (22.64%)
BP	Hypotension	65 (92.86%)	5 (7.14%)
	Normal	4 (50.00%)	4 (50.00%)
	Hypertension	39 (82.98%)	8 (17.02%)
Height	Up to 155	10 (76.92%)	3 (23.07%)
	>155 – 165	59 (86.76%)	9 (13.24%)
	>165 – 175	25 (83.33%)	5 (16.67%)
	>175	13 (92.86%)	1 (7.14%)
Weight	Up to 55	14 (87.50%)	2 (12.50%)
	>55 – 65	40 (81.64%)	9 (18.36%)
	>65 – 80	41 (89.13%)	5 (10.87%)
	>80	13 (92.86%)	1 (7.14%)
BMI	Underweight	4 (100.00%)	0 (0.00%)
	Normal	80 (84.21%)	15 (15.79%)
	Overweight	20 (86.95%)	3 (13.05%)
	Obesity	2 (66.67%).	1 (33.33%)

Table 4: Abnormal ECG was seen in those with low pulse rate 71.43% (n=5) followed by those with high pulse rate 22.64%(n=12). Among blood pressure parameter abnormal ECG was seen in normotensives 50% (n=4) followed by those with hypertension 17.02% (n=8). Patients with height ranging from 165 to 175 cm had abnormal ECG 16.67% (n=5) followed by those with height with 155 to 165cm 13.24% (n=9). Those patients

with weight between 55 to 65 kgs had abnormal ECG 18.36% (n=9). It was also seen that patients with obesity had abnormal ECG 33.3% (n=1) followed by those patients with normal ECG 15.79% (n=15).

Distribution of Variables with its Overall Prevalence

Variables	Prevalence
Sinus Rhythm	87%
Sinus Tachycardia	8%
Sinus Bradycardia	3%
Prolonged PR Interval	1%
Sinus Arrhythmia	1%
QTC	353.95 (Average)
QT	322.37 (Average)
P	103.45 (Average)
QRS	95.75 (Average)

Table 5: Among the ECG changes, sinus tachycardia had a prevalence of 8%, that of sinus bradycardia was 3%. Prevalence of prolonged PR interval was 1% and that of sinus arrhythmia was 1%.

Model Summary				
Model	R	R Square	Adjusted R Square	Durbin-Watson
	.39	0.15	0.12	1.94
Dependent Variable: ECG-Changes				
Predictors: (Constant), QTC, P, HR, QRS, PR, QT				

Table 6: As per the Model Summary Table the R column represents the value of 0.39, the multiple correlation coefficients. R can be considered to be one measure of the quality of the prediction of the dependent variable i.e. ECG-Changes on the independent variables i.e. QTC, P, HR, QRS, PR, QT. R Square column also called the coefficient of determination is the proportion of variance in the dependent variable that can be explained by the independent variables, value of independent variables explains 15% of the variability of dependent variable. The Durbin-Watson value of 1.94 reveals the fitness of the Model.

ANOVA		Sum of Squares	df	Mean Square	F	Sig.
Model	Regression	2.62	6.00	0.44	4.24	.001*
	Residual	14.72	143.00	0.10		
	Total	17.33	149.00			
*Significant at the 0.05 level						
Dependent Variable: ECG-Changes						
Predictors: (Constant), QTC, P, HR, QRS, PR, QT						

Table 7: The F-ratio in the ANOVA Table determines F (6,143) =4.24 and further shows that the independent variables i.e. QTC, P, HR, QRS, PR, QT are statistically significantly at 0.001 with the dependent variable i.e. ECG-Changes and is an implication for its success.

DISCUSSION

The study conducted to find ECG abnormalities (QTc interval and other related variables) in patients on psychotropics medications for finding is in particularly harmful for those with preexisting cardiac conduction delay and can lead to heart block in varying degrees. There is 125 patients came under this study a prospective observational study was conducted at the psychiatry OPD of a tertiary care hospital. The convenience sampling was used to include patients diagnosed with psychiatric disorder, who had been on psychotropics for >1 year, aged above 18 years or more, of either gender from 20th September 2020 to 20th March 2020.

Previous Study showed limitations include its cross-sectional observational nature, which does not allow to the drawing of the causation of ECG abnormalities (e.g., mental disease vs. psychotropic medications). We did not consider medication adherence, duration of mental disease or pharmacological treatment. Future large prospective studies are recommended that will address all the above issues, as well as the relation of ECG changes to SCD in patients on antipsychotics and other psychotropic medications. [22]

Buprenorphine In general, QTc interval prolongation is not considered a consequence of the use of other narcotics. Buprenorphine has been found to be less likely to cause QTc interval prolongation than methadone.[23] However, some studies have shown that induction with buprenorphine was still followed by an increase in QTc interval.[24] Special Population: Children and Adolescents Our workgroup has chosen to limit our review to studies involving adults over the age of 18. While psychotropic medications can cause QTc interval prolongation in children and adolescents, there are few studies evaluating these effects. Importantly, additional research is necessary within this population to guide clinical decision-making and avoid "overcautious interpretation" of ECGs among children and adolescents, which may lead to non-

treatment.[25] Further, extrapolation of adult data is not appropriate. One example includes data surrounding the use of methadone among pediatric patients and young adults, which suggest methadone may be safe, though additional prospective data are needed.[26,27] Antipsychotic medications have received the greatest attention in the pediatric population, where a systematic review found ziprasidone to be linked to the greatest degree of QTc interval prolongation and aripiprazole to lead to a significant reduction in QTc interval, consistent with studies in adults.[28] Use of antipsychotic medications or other medications that may prolong the QTc interval in the context of eating disorders within this population requires specific consideration. One article highlights the importance of additive risk in the context of anorexia related to bradycardia and/or electrolyte abnormalities and the impact correction equations may have on normalizing the QTc interval, thereby underestimating the true severity of the repolarization abnormality.[29] Additional monitoring is recommended in this population as well as those with bulimia who may purge and be predisposed to electrolyte abnormalities. Caution and repeat ECGs are advised as medications posing risk for QTc interval prolongation are added or doses are adjusted, or additional risk factors for QTc interval prolongation arise over the course of treatment.

In this study data collection process is account to repeated measurement of QTc at time of admission, this classified in Socio-Demographic where we find that abnormal ECG in Gender wise came from female patients, Age wise year between 31-45 year and educational background there are Graduates or Post graduates find abnormalities in ECG, Occupation wise high abnormalities find in Housewife or unemployed person. As per material status there is Single person came under abnormalities observation and last is location where we found that rural area patients find more abnormalities than Urban.

Anaemia, Hypothyroidism the two Co-morbidities is major factor to change in ECG, after this Arthritis, Diabetes Mellitus and Hypertension is a diseases to change the level of ECG.

After using of Psychotropic Drugs seen in ECG-Changes, drug Antipsychotic shown 19.05% ECG Changes, were Antidepressant uses shown 15.30% ECG Changes, Benzodiazepines uses shows that 16.67% patients have ECG changes Whatever other Drugs uses shown that 20.63% patients ECG Changes this high than all.

For many years, SSRI antidepressants were considered safe from a QTc interval prolongation perspective, despite occasional case reports of QTc interval prolongation for all agents in this class. To date, studies examining QTc interval prolongation effect for fluoxetine, fluvoxamine, and paroxetine have provided no compelling evidence of QTc interval prolongation.[30] Sertraline remains the agent with the best-established track record in cardiac populations.[31, 32] As previously stated, on August 2011, the FDA issued a warning for QTc interval prolongation with citalopram based on a thorough QTc interval study demonstrating prolongation of 8.5ms at doses of 20mg and 18.5ms at doses of 60mg.[33] Subsequent studies, including a meta-analysis, a large retrospective study of an ECG database, and a randomized placebo-controlled study, have suggested that citalopram may be more likely than other SSRIs to cause QTc interval prolongation, and may prolong the QTc interval at a similar magnitude to that demonstrated in the FDA study.[34-37] The FDA currently advises practitioners to not utilize doses of citalopram greater than 40mg in all patients, and to use doses of 20mg or lower in patients over the age of 60 years or with liver dysfunction. Though most studies suggest that the risk of QTc interval prolongation and TdP increases with higher doses, at least one large study found higher doses to be associated with fewer adverse outcomes, though QTc interval was not specifically examined and the authors did not control for other known risk factors.[38]

As per previous study our study on 65 participants on antipsychotics 15.38% had abnormal ECG whereas among 60 participants on antidepressants 13.33% showed abnormal ECG. It was also seen that of 120 patients on benzodiazepine 16.67% has ECG changes. Patients on psychotropics other than the above mentioned were 63 in number and constituted 20.63% of abnormal ECG changes, the compression of both study we find that antidepressants are in same results than otherpsychotropics medications.

A study about Thyroid dysfunction and electrocardiographic changes in subjects without arrhythmias: a cross-sectional study of primary healthcare subjects from Copenhagen where they found Changes in P-wave, PR interval and QRS duration according to thyroid dysfunction. Regression plots showing the changes in the P-wave duration (ms), PR interval (ms) and QRS duration (ms) with thyroid disorder in comparison to the euthyroid reference group adjusted for age and gender.[39]

Whatever in our study ECG changes were compared among various comorbidities including those without any comorbidity and it was seen that abnormal ECG changes were more in those with anemia 100% (n=1) followed by those with hypothyroidism 40% ECG abnormalities.

REFERENCES

1. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia – antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. Br J Psychiatry1998; 173:325–329.
2. Ruschena D, Mullen PE, Burgess P, et al Sudden death in psychiatric patients. Br J Psychiatry1998; 172:331-336.
3. Politi P, Piccinelli M, Klersy C, et al. Mortality in psychiatric patients 5 to 21 years after hospital admission in Italy. Psychol Med 2002; 32:227-237.

4. Hannerz H, Borga P. Mortality among persons with a history as psychiatric inpatients with functional psychosis. Soc Psychiatry Psychiatr Epidemiol2000; 35: 380-387.
5. Kilian JG, Kerr K, Lawrence C, et al Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999; 354: 1841-1845.
6. Agelink MW, Majewski T, Wurthmann C, et al. Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine. J Clin Psychopharmacol 2001; 21: 8-3.
7. Schwalb H, Eckmann F, van Eimeren W. ECG changes in psychiatric patients under long-term therapy with psychopharmacology. Fortschr Neurol Psychiatr1978; 46: 484-490.
8. Burrows GD, Vohra J, Hunt D, et al. Cardiac effects of different tricyclic antidepressant drugs. Br J Psychiatry 1976; 129: 335–341.
9. Roose SP, Glassman AH, Giardina EGV, et al. Tricyclic antidepressants in depressed patients with cardiac conduction disease. Arch Gen Psychiatry1987; 44:273–27
10. Reilly JG, Ayis SA, Jones SJ, et al QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000; 355:1048-1052.
11. Goodnick PJ, Jerry J, Parra F. Psychotropic drugs and the ECG: focus on the QTc interval. Expert Opin Pharmacother 2002; 3: 479-498.
12. Mojtabai R, Olfson M. National Trends in Psychotropic Medications Polyphramacy in office based psychiatry. Arch Gen Psychiatry: 2010; 67(1): 26-36
13. Moller HJ, Seemuller F, Schennach-Wolff R, Stubner S, Ruther E, Grohman R, History,background, concepts and current use of comedication and polypharmacy in psychiatry. Int J Neuropsyvchopharmacol. 2014; 17(7); 17 (7): 983-96.
14. Zemrak WR, Kenna GA, Association of antipsychotics, Association of antipsychotics and antidepressant drugs with QT interval prolongation. Am J Health Syst Pharm, 2008; 65 (11); 1029-38
15. Khan Q, Ismail M, Haider I, Khan F. Prevalence of QT interval prolonging drug-drug interactions (QT-DDIS) in psychiatry wards of tertiary care hospitals in Pakistan: a multicentre cross sectional study. Int J Clin Pharm. 2017; 39(6): 1256-64
16. Vandael E, Marynissen T, Reytens J, Spriet I, Vandenberghe J, Willems R, et al. Frequency of use of QT- interval prolonging drugs in psychiatry in Belgium. Int J Clin Pharm. 2014;36(4); 757-65.
17. Kukreja S, Kalra G, Shah N, Shrivastava A. Polypharmacy in psychiatry: a review. Mens Sana Monogr. 2013; 11 (1) : 82-99
18. Chastang A, Renet S, Corny J, Beaussier H et al Impact of hospital Pharmacist Interventions on combination of citalopram or escitalopram with other QT- prolonging drugs. Int J Clin Pharm. 2019; 41 (1); 42-8
19. Berling I, Gupta R, Bjorksten C, Prior F, Whyte IM. A review of ECH and QT interval measurement use in a public psychiatric inpatient setting. Australas Psychiatry. 2018; 26(1): 50-5
20. Pinheiro J, Bates D, DebRoy S, Sarkar D. and R Core Team (2018). nlme: linear and nonlinear mixed effects models. R package version 3.1-137, https://CRAN.R-project.org/package=nlme.
21. R Core Team R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org/ (2018).
22. Nailya Bulatova, Noor Altaher: The Effect of Antipsychotics and Their Combinations with Other Psychotropic Drugs on Electrocardiogram Intervals Other Than QTc among Jordanian Adult Outpatients, Published in Department of Biopharmaceutics and Clinical Pharmacy, School of Pharmacy, The University of Jordan, Amman 11942, Jordan.
23. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007;167:2469-2475.
24. Krantz MJ, Garcia JA, Mehler PS. Effects of buprenorphine on cardiac repolarization in a patient with methadone-related torsade de pointes. Pharmacotherapy. 2005;25:611-614.
25. Roessner V, Wolff N, Ehrlich S, Waltereit R. Need for a more developmental perspective: QTc prolongation under psychotropic medication. European child & adolescent psychiatry. 2017;26:871-873.
26. Anghelescu DL, Patel RM, Mahoney DP, Trujillo L, Faughnan LG, Steen BD, Baker JN, Pei D. Methadone prolongs cardiac conduction in young patients with cancer-related pain. Journal of opioid management. 2016;12:131-138.
27. Madden K, Park M, Liu D, Bruera E. The frequency of QTc prolongation among pediatric and young adult patients receiving methadone for cancer pain. Pediatric blood & cancer. 2017;64.
28. Jensen KG, Juul K, Fink-Jensen A, Correll CU, Pagsberg AK. Corrected QT changes during antipsychotic treatment of children and adolescents: a systematic review and meta-analysis of clinical trials. Journal of the American Academy of Child and Adolescent Psychiatry. 2015;54:25-36.
29. Ritchie B, Norris ML. QTc prolongation associated with atypical antipsychotic use in the treatment © Copyright, American Psychiatric Association, all rights reserved. 41 of adolescent-onset anorexia nervosa. Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent. 2009;18:60- 63.
30. Funk KA, Bostwick JR. A comparison of the risk of QT prolongation among SSRIs. The Annals of pharmacotherapy. 2013;47:1330-1341.
31. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA, Huffman JC. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. The Journal of clinical psychiatry. 2014;75:e441-449.
32. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT, Jr., Krishnan KR, van Zyl LT, Swenson JR, Finkel MS, Landau C, Shapiro PA, Pepine CJ, Mardekian J, Harrison WM, Barton D, McLvor M. Sertraline treatment of major depression in patients with acute MI or unstable angina. Jama. 2002;288:701-709.
33. Administration: UFaD: FDA safety communication: abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). 2011.
34. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, Erb JL, Churchill SE, Kohane IS, Iosifescu DV, Smoller JW, Perlis RH. QT interval

and antidepressant use: a cross sectional study of electronic health records. BMJ (Clinical research ed). 2013;346:f288.
35. Drye LT, Spragg D, Devanand DP, Frangakis C, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Pollock BG, Porsteinsson AP, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG. Changes in QTc interval in the citalopram for agitation in Alzheimer's disease (CitAD) randomized trial. PloS one. 2014;9:e98426.
36. Kogut C, Crouse EB, Vieweg WV, Hasnain M, Baranchuk A, Digby GC, Koneru JN, Fernandez A, Deshmukh A, Hancox JC, Pandurangi AK. Selective serotonin reuptake inhibitors and torsade de pointes: new concepts and new directions derived from a systematic review of case reports. Therapeutic advances in drug safety. 2013;4:189-198.
37. Zhang Y, Baranchuk A, Hancox JC. Towards limiting QT interval prolongation and arrhythmia risk in citalopram use. Cardiology journal. 2014;21:454-457.
38. Zivin K, Pfeiffer PN, Bohnert AS, Ganoczy D, Blow FC, Nallamothu BK, Kales HC. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. American Journal of Psychiatry. 2013.
39. Bhupendar, Tayal,Claus Graff:Thyroid dysfunction and electrocardiographic changes in subjects without arrhythmias: a cross-sectional study of primary healthcare subjects from Copenhagen.Published online 2019 Jun 21. doi: 10.1136/bmjopen-2018-023854.