Original Article

Top 20 drug – drug interactions, polypharmacy and analysis of the nature of risk factors due to QT interval prolonging drug use in elderly psychiatry outpatients

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Abstract

Introduction and Objectives: Psychotropic medications extend the corrected QT (QTc) period in the ECG. Psychiatric patients exposed to ≥ 1 psychotropic medication (s) represent a group with a marked probability of drug-activated QTc-prolongation. Prolonged QTc interval in elderly patients (age > 60 years) is connected to a greater risk of all-cause and coronary heart disease deaths. We investigated the pattern of utilization of QTc-interval prolonging medications, QT-extending interactions between drugs, and prevalence of QTc-interval prolonging risk factors in elderly patients. **Methods:** This was a cross-sectional, prospective study at the Psychiatry OPD at All India Institute of Medical Sciences (AIIMS), Rishikesh, Uttarakhand, India from October 1, 2017 to December 31, 2018 employing the pertinent prescriptions. **Results:** A total of 208 elderly patients (age 60 years or more) visiting the Psychiatry OPD during the aforementioned study period were investigated. 105 (50.5%) patients were males whereas 103 (49.5%) were females in our study. 147 out of 208 patients (70.7%) were using interacting agents with the capacity to produce TdP. 288 interacting torsadogenic medication pairs were unraveled. As per AzCERT/CredibleMeds Classification, 254 (48.8%), 181 (34.8%), and 62 (12%) interacting medications were identified with known, possible, and conditional risk of TdP, respectively. The common interacting medications belonged to antidepressant (144), proton pump inhibitor (91), antipsychotic (85), anti-nausea (46), antimicrobial (39), and H_2 receptor antagonist (15) therapeutic categories. **Conclusions:** Many geriatric patients were administered drugs and drug combinations with heightened proclivity towards QT-interval prolongation. Therefore, we need to exigently embrace precautionary safety interventions, to be vigilant, and forestall QT-prolongation and TdP in clinical settings. Online evidence-based drug information resources can aid clinicians in choosing drugs for psychiatric patients.

Keywords: Drug-induced QT prolongation, elderly patients, psychiatry OPD, psychotropic drugs, Torsade de pointes

Introduction

It has been estimated that the annual global mortality resulting from sudden cardiac death (SCD) due to ventricular tachyarrhythmias is about 6 million.[1,2] SCD accounts for 1 in 5 deaths in developed nations.[3-5] Approximately 10.3% of total deaths occur due to SCD in India.[6] QT interval prolongation is a confirmed risk factor for Torsade de Pointes (TdP) finally ending in ventricular tachycardia and fibrillation (VT/VF) and SCD.[5,7-9] A multitude of correction formulae (e.g., Bazett, Fridericia, Ashman, Hodges, Van de Water, Framingham (Sagie), etc.) have been advanced in order to estimate a heart rate corrected QT (QTc) interval. An inverse relation occurs between the heart rate and the QT interval.[10] As per the expert group guidelines

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of the American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF), a QTc-interval exceeding 470 ms for adult males and 480 ms for adult females is deemed to be abnormal.[7] There is an elevated risk toward TdP development when QTc interval ≥ 500 ms in patients.[7-8] It has also been documented that with each 10 ms extension of QTc interval, there is approximately a 5% exponential increase for cardiac event risk in subjects with long QT syndrome (LQTS).[11]

A sizable collection of >280 drugs (comprising of typical and atypical antipsychotics, typical and atypical antidepressants, antihistamines, prokinetics, proton pump inhibitors, anti-infectives, etc.) capable of leading to QT-prolongation based upon reliable clinical evidence is accessible at AzCERT.[12] A multitude of antipsychotic, gastrointestinal, antihistaminic, and chemotherapeutic agents (e.g., mesoridazine, thioridazine, sertindole, astemizole, terfenadine, cisapride, droperidol, gatifloxacin, grepafloxacin, sparfloxacin, terodiline) have witnessed removal from the market or have been placed under watchful scrutiny as they have been identified in delaying cardiac repolarization and TdP reporting in subjects.[13-15] Pharmacokinetic drug − drug interactions (inhibition of biotransformation of a QT-prolonging agent) and/or pharmacodynamic drug − drug interactions (cumulative or synergistic of two QT-prolonging agents) have the capability to escalate TdP risk.[16,17] Because of this risk, electrocardiograms (ECGs) are used during treatment for monitoring QTc; however, this practice varies greatly among clinicians and across hospitals. Whether or not QTc interval should be routinely monitored in patients receiving psychotropic and adjunctive medications in psychiatry is a controversial issue, given logistic and fiscal dilemmas.

An interplay between one or more risk factors affecting individual propensity towards QT-prolongation have been identified in the medical literature; some of these are QT-prolongation at baseline, elderly patients, female sex, electrolyte imbalances (hypokalemia, hypocalcemia, hypomagnesemia), bradycardia, and hereditary cardiac diseases (long QT syndrome, ion channel polymorphisms).[18] TdP usually is the result of multiple risk factors, such as advanced age, use of more than one TdP-classified hERG-blocking drug, cardiovascular disease, and possible electrolyte changes related to renal function compromise, use of diuretics, and/or acid-secretion inhibitors.[19,20] Elderly patients commonly possess many of these risk factors. To cite an example, about 10% of patients aged ≥75 years are known to be affected by congestive heart failure.[21] Moreover, elderly patients are more likely to be prescribed diuretics. Diuretic-induced hypokalemia and hypomagnesemia might accentuate drug-induced TdP risk.[22,23] Additionally, elderly patients are more at risk of high levels of offending drugs owing to reduced renal clearance, reduced hepatic biotransformation capacity, as well as polypharmacy-related drug-drug interactions.[24]

A host of antipsychotic and antidepressant medications have been documented in the medical literature to lead to remarkable QT-prolongation and therefore, patients with psychiatric illnesses make up a population at significantly high risk for drug-induced QT-prolongation.[18,25,26] In general, any modality to obviate or decrease the frequency of TdP must espouse an appraisal of such risk factors which could be patient-centric, drug-centric, and clinical scenario-centric, comprising of drug − drug interactions and comorbid illnesses. Integrated medical care for patients with chronic mental illness requires a close working relationship between the psychiatrist and primary care physician. In no area of medicine is this more important than when considering the subject of cardiovascular disease. The primary care physician is a key member of the team managing a patient who requires the administration of antipsychotic drugs. Evidence regarding the risk of TdP for each drug changes constantly; this makes it almost impossible for physicians and pharmacists to keep updated. Primary care physicians may facilitate the detection of additional risk factors; this can have positive impacts on the prescription of QT- prolonging drugs, such as drug selection, withdrawal, dose reduction, or electrocardio- gram monitoring. Not many epidemiological studies have investigated the interactive vital aspects of frequency of usage of QTc-interval extending medications, QT-prolonging drug − drug interactions, and prevalence of risk factors and comorbidities for QTc-interval prolongation in geriatric patients visiting the Psychiatry OPD, particularly in developing countries. To the best of our knowledge, no such analytical pharmaco-epidemiological exercise has been conducted in elderly patients in India.

Our present study was, therefore, performed in order to investigate the nature of utilization of QTc-interval prolonging agents, QT-prolonging drug-drug interactions, and prevalence of variables for QTc-interval prolongation risk in elderly patients visiting the Psychiatry OPD in a tertiary care hospital in India.

Materials and Methods

Our prospective cross-sectional hospital-based study was executed in the Psychiatry OPD at All India Institute of Medical Sciences (AIIMS), Rishikesh, Uttarakhand, India from October 1, 2017 to December 31, 2018. In this study, researchers (BD and SK) visited the Psychiatry OPD with the intent of prescription collection of psychiatric patients reporting to the Psychiatry OPD randomly thrice/week. The thrice/week survey for all weeks was conducted for period of more than 1 complete year. Randomization was applied for the days of the week on which such surveys were carried out.

Patient details were recorded into a tailored proforma particularly crafted for this study. The information from the applicable prescriptions (i.e., the OPD case record forms and treatment sheets) was culled, scored, scrutinized, and then subjected to deliberation with our clinical collaborators (VSR and BK). The tailored proforma had essentially 2 divisions, viz.

(i) An identification sheet (capturing the patient's name, registration no., age, sex, body weight, diagnosis, etc.), and
(ii) A detailed sheet with prescription drug use details for psychiatric afflictions (indicating name (s) of agents, their

dosage (es), frequency of administration, duration of treatment, etc.).

TdP-inducing medications were determined and typecasted into 4 groups according to the most current version of AzCERT/CredibleMeds QT Drug Lists (December 26, 2019).[12]

Anatomic therapeutic chemical (ATC) classification system codes of WHO Collaborating Centre for Drug Statistics Methodology have been utilized as deemed fit.[27,28]

We assessed the proportion of elderly patients (on psychotropic and other adjunctive medications with a propensity for QT prolongation) who were more likely to have an ECG advised during their initial and/or follow-up visits. Patients who received 1 or more ECGs during their initial and follow-up visits were documented, in addition to individual risk factors for TdP, and all agents (psychiatric or other) taken which have been documented to produce QTc prolongation potential. From available 12-lead ECGs, QTc morphology was deciphered initially by computer algorithm followed by cardiologist's verification (BK). The computed QTc (QT interval corrected for heart rate) was arrived at from Bazett Formula (QTcB = QTc/(RR) $^{0.5}$). QTcB between 450 and 500 milliseconds (ms) in males and QTcB between 470 and 500 ms in females were considered borderline prolonged. QTcB ≥500 ms or with >60 ms of change from baseline were deemed prolonged. These cutoffs were selected based on documentation in the scientific literature as evidenced by elevated risk of SCD or arrhythmias.

The 20 most frequently used QTc-prolonging drug − drug interactions were investigated using freely available online evidence-based medscape drug interaction checker,[29] Epocrates online[30], and Drugs.com drug − drug interactions checker.[31]

Risk factors present in the patients and capable of causing prolongation of the QTc interval and TdP (viz., cardiovascular disease,[32,33] prescription use of digoxin,[8] dyselectrolytemia,[34] thyroid dysfunction,[35,36] hypogonadism, and androgen deprivation therapy (ADT) (in men),[37] use of oral contraceptive pills (OCPs) containing drospirenone (in women),[38-40] polypharmacy,[41] and use of >1 agent with an elevated probability of TdP[7,42]) were detected and subjected to scrutiny on the basis of information gleaned from treatment sheets and OPD case-record forms.

Statistical analysis

We employed descriptive statistics on the data from this study. Presentation of categorical data has been done as frequencies and percentages, whereas continuous data are presented as median (IQR). Microsoft Excel and IBM SPSS statistics version 23 was used for all statistical analyses.

Results

A total of 208 elderly patients (age 60 years or more) attending the Psychiatry OPD during the study period were considered. 105 (50.5%) patients were males whereas 103 (49.5%) were females in our study [Table 1]. Many of the elderly patients belonged to 60 − 69 year age range (44.7%) followed by patients belonging to 70 − 79 year age category (35.6%) and the median age was 67 years (IQR = 62 − 75). Most of the patients were receiving 5 − 6 drugs and the median number of medications prescribed was 5 (IQR = 4-6). The majority of our elderly patients attending the Psychiatry OPD had diagnoses of major depression (40.9%), schizophrenia (11.1%), bipolar disorder (9.6%), conversion disorder (8.7%), anxiety (7.7%), mania (6.7%), and dissociative disorder (5.3%) [Table 1].

Of the 208 geriatric patients, 147 patients (70.7%) were prescribed interacting medications with the capability to usher in TdP [Table 2]. The interacting drug − drug pairs with torsadogenic risk were computed to be 288 in this analysis.

In accordance with the AzCERT Classification, 254 (48.8%) of the interacting medications were related with a known risk of TdP, 181 (34.8%) of interacting medications were related with a possible risk of TdP, and 62 (12%) of the interacting medications were related with a conditional risk of TdP [Table 3]. Interacting medications were commonly prescribed from antidepressant (144), proton pump inhibitor (91), antipsychotic (85), anti-nausea (46), antimicrobial (39), and H_2 receptor antagonist (15) therapeutic categories [Table 3]. Table 4 provides an analysis of the top 20 torsadogenic drug − drug interactions along with their AzCERT Classification (CredibleMeds Risk Stratification), and therapeutic categories/classes. A total of 27 interacting drug-drug pairs where both have AzCERT listing as torsadogenic agents with a known risk of TdP were recorded. A great many investigated drug − drug interactions linkable with TdP risk could interact pharmacodynamically rather than pharmacokinetically. The most frequent drug − drug interacting pairs with a pharmacodynamic basis were escitalopram-risperidone (33), escitalopram-olanzapine (32), fluoxetine-olanzapine (25), lithium-pantoprazole (21), and haloperidol-risperidone (12). A few torsadogenic interacting pairs with a pharmacokinetic basis were also identified, viz., omeprazole-sertraline (3), omeprazole-amitriptyline (3), ciprofloxacin-amitriptyline (1), ketoconazole-imipramine (1), and cimetidine-amitriptyline (1) [Table 4].

The most common medications with a capability of inducing QT-prolonging drug-drug interactions were escitalopram (96), olanzapine (71), risperidone (59), fluoxetine (47), haloperidol (39), pantoprazole (36), quetiapine (28), and domperidone (13) [Table 4].

The evidence-based identification and risk-stratification of QT interval prolonging drug-drug interactions in this study as gleaned from medscape drug interactions checker, epocrates online interactions checker, and Drugs.com drug interactions checker are available as supplementary data [Table 5].

In our study sample, 45 elderly patients were afflicted with cardiovascular diseases, 3 elderly patients were prescribed

Table 1: Basic socio-demographic and clinical characteristics (including comorbidities) of the elderly patients

Variable	Patients (*n*)	%[a]
Gender	208	100
Male	105	50.5
Female	103	49.5
Age Groups		
60-69	93	44.7
70-79	74	35.6
80-89	26	12.5
≥90	15	7.2
No. of drugs prescribed per patient[b]		
≤2	24	11.5
3-4	71	34.1
5-6	80	38.5
>6	33	15.9
Diagnosis		
Major depression	85	40.9
Schizophrenia	23	11.1
Bipolar affective disorder (BAD)	20	9.6
Conversion disorder	18	8.7
Anxiety	16	7.7
Mania	14	6.7
Dissociative disorder	11	5.3
Cannabis abuse	6	2.9
Acute psychosis	5	2.4
Psychosis	5	2.4
Obsessive compulsive disorder (OCD)	5	2.4
Coexisting Illness (es)		
Acid peptic disorders	11	5.3
Tuberculosis	9	4.3
Cancer/Metastatic carcinoma	9	4.3
Epilepsy	8	3.8
Diabetes mellitus	7	3.4
Ischemic Heart Disease (IHD)	6	2.9
Dementia	6	2.9
Rheumatic Disease	6	2.9
Congestive cardiac failure	5	2.4
Cardiac arrhythmias	5	2.4
Hypertension	5	2.4
Benign Prostatic Hypertrophy (BPH)	5	2.4
Dyslipidemias	4	1.9
Parkinson's Disease	4	1.9
Bronchial asthma	3	1.4
Cerebrovascular Disease	3	1.4
HIV/AIDS	3	1.4
Malaria	2	1
Mycoses (superficial)	2	1
Thyroid dysfunction	2	1
Hepatitis B	1	0.5
Hepatitis C	1	0.5
COPD	1	0.5
Paraplegia/Hemiplegia	1	0.5
Renal Disease	1	0.5

[a]Percentage calculated in total number of patients i.e., 208; [b]All prescribed medications mean QT prolonging medications as well as other medications;

Table 2: Prevalence of QT interval prolonging drug-drug interactions in elderly patients

Type of prevalence	Patients (*n*)	%[a]
Overall prevalence	147	70.7
QT-DDI per patient		
1-2	25	12.0
2-4	83	39.9
> 4	39	18.8
Gender-wise prevalence		
Male	84	40.4
Female	63	30.3
Age-wise prevalence		
60-69	62	29.8
70-79	56	26.9
80-89	16	7.7
>90	13	6.3

QT-DDI: QT prolonging drug-drug interactions; [a]Percentage computed from total number of elderly patients i.e., 208

digoxin for congestive cardiac failure, 21 were prescribed diuretics, whereas medications for thyroid disorders were used by 4 elderly patients. In our study, 2 elderly males were receiving antiandrogens (bicalutamide and cyproterone acetate) for prostatic cancer. Minor polypharmacy (use of 2 − 4 drugs) was the third most common risk factor observed in 101 patients. Major polypharmacy (use of ≥5 drugs) was the second most common risk factor observed in 98 patients. A total of 147 patients received >1 QT-interval prolonging agents [Table 6].

Of the 208 geriatric patients in our present study, 78 patients (37.5%) were advised ECG (s) by the attending psychiatrists in our institution. Of these 78 subjects, 15 (19.2%) subjects had QTcB > 450 ms for males (44; 56.4%) and 8 (10.3%) had QTcB > 470 ms for females (34; 43.6%). There was one incidence of TdP in an elderly female subject who was managed but failed to survive. Of these, 11 (14.1%) subjects had QTcB ≥ 500 ms or >60 ms of change from baseline [Table 7].

Discussion

Extent of prescription of psychotropics and QT-interval prolonging torsadogenic agents and their combinations in geriatric patients in Psychiatry OPD

Our results unravel frequent prescriptions of drug − drug combinations bearing documented hazards of TdP in geriatric psychiatry patients aged ≥ 60. Most of these drug − drug interactions could lead to QT-prolongation owing to pharmacodynamic reasons rather than pharmacokinetic underpinnings. Substantial chunk of elderly patients were exposed to minor and major polypharmacy involving high-risk TdP-inducing agents. Majority of medications used by elderly psychiatric patients are known to result in QT-interval prolongation.

Systematic characterization of prescribing frequency of torsadogenic medications and their combinations in real-life clinical therapeutic scenarios are scanty in the medical literature.

Table 3: AzCERT classification, and therapeutic classes of drugs involved in QT-interval prolonging drug-drug interactions in elderly patients

Classification scheme	*n* (interacting drugs)	%[a]
AzCERT classification		
Known risk of TdP (List 1)	254	48.8
Possible risk of TdP (List 2)	181	34.8
Conditional risk of TdP (List 3)	62	12.0
Not included in AzCERT QT drugs lists (List 4)[b]	23	4.4
Therapeutic categories		
Antidepressant (N06A)	144	27.7
Proton pump inhibitor (A02BC)	91	17.5
Antipsychotic (N05A)	85	16.3
Antinausea (A04AA)	46	8.8
Antimicrobial (J01MA/J01FA)	39	7.5
H2-Receptor Antagonist (A02BA01/02/03)	15	2.9
Antihistamine (R06AD)	12	2.3
Anticonvulsant (N03AX11)	10	1.9
Antidementia (N06D)	10	1.9
Diuretics (C03)	10	1.9
Antineoplastic & immunomodulating agents (L01/L02/L03)	8	1.5
Antimalarial (P01B)	6	1.2
Antifungal (D01AC)	5	1.0
Calcium channel blocker (C08CA01)	5	1.0
Antituberculars (J04A)	5	1.0
Antidiabetics (A10A/A10B)	5	1.0
Beta blocking agents (C07A)	4	0.8
Antiarrhythmics (C01B/C01E)	4	0.8
Drugs for airway obstructive diseases (R03)	3	0.6
Antivirals (J05A)	3	0.6
Platelet aggregation inhibitors (B01AC)	2	0.4
Lipid modifying agents (C10A/C10B)	2	0.4
Antithyroid(H03B)	1	0.2
Antiparkinsonian Drugs(N04)	1	0.2
Drugs for BPH(G04C)	1	0.2
Agents acting on Renin Angiotensin system (C09)	1	0.2

AzCERT=Arizona Center for Education and Research on Therapeutics (CredibleMeds); TdP=Torsades de Pointes; Total number of QT-interval prolonging drug-drug interactions i.e., 288; [a]Percentage calculated from number of all interacting drugs i.e., 520; [b]"Not included in AzCERT QT drugs lists (List 4)" = Total number of drugs to avoid in congenital long QT (List 4) = 18 (including 3 two-drug combinations); This list contains drugs exclusively from List 4; overlapping drugs from CredibleMeds Lists 1-3 have been excluded

Beuscart *et al.*[43] studied prescriptions for psychotropic agents to older patients aged ≥ 75 in a 222-bedded French general hospital setting. ≥ 3 psychotropic agent co-prescriptions for ≥3 days were found in 374 stays of total of 11,929 stays (3.1%). 89.2% of these 374 co-prescriptions contained unacceptable drug combinations (viz., concurrent prescription of ≥2 agents belonging to the same psychotropic class (duplication) and/or unjustifiable prescriptions without valid therapeutic indication).

In another Belgian cross-sectional study executed in a psychiatry setting, 7.3% of patients were using interacting drugs with an associated hazard of TdP.[44]

In a retrospective cohort study, Curtis *et al.*[45] determined that 2.2% of patients were exposed to interacting drugs with TdP risk. Khan *et al.*[46] from Pakistan determined that 51.7% of patients in their study were prescribed interacting drugs with TdP risk.

Moreno-Gutierrez *et al.*[42] determined 10.3% (n = 5786) patients had been prescribed > 1 QT-prolonging drug. Possibility of patients receiving > 1 QT-prolonging medication (i.e., polypharmacy) was maximum in those suffering from psychiatric and neurological illnesses. QT-prolonging drug use in psychiatric and neurological illnesses was higher among women than in men. A total of 46.6% (*n* = 4359) of such patients were prescribed > 1 QT-prolonging agent and 6.9% (*n* = 647) patients were using 3 − 5 such drugs.

In another recent North Jordan study, 58.5% (*n* = 3114) of elderly patients were using drugs with TdP risk. 62.3% (n = 1939), 29.8% (*n* = 929), 6.6% (*n* = 207), and 1.1% (*n* = 33) patients were taking 1, 2, 3, and 4 drugs (i.e., exposed to polypharmacy) with TdP risk, respectively.[47]

In our present work, we observed an exposure of 70.7% of Psychiatry OPD elderly outpatients ≥60 years old to drug-drug interactions with torsadogenic hazards [Table 2].

Many factors for the differences between other studies and our study results may be considered. Disease occurrence and medication utilization trends could be expected to be diverse across regions, nationalities, and continents which may explain variability in our study results when compared to few other studies.

Attributes of geriatric patients using medications with risk of QT prolongation and TdP

A total of 44.7% and 35.6% of elderly patients reporting to Psychiatry OPD were 60 − 69 years of age and 70 − 79 years of age, respectively. A total of 12.5% of patients were 80 − 89 years of age while 7.2% of patients were ≥ 90 years. When prescribing antipsychotic agents to elderly patients (especially with dementia), SCD has become a serious clinical worry. There is an almost two-fold increase inpatient mortality rates in patients over age 65, who are taking first- and second-generation antipsychotics (FGA & SGA) compared to people on a placebo.[48]

Elderly patients were commonly prescribed documented QTc prolonging FGAs and SGAs, as well as TCAs, which is a major cause of concern. Among antidepressants, TCAs and citalopram present highest risk for QT prolongation in older adults whereas other SSRIs and SNRIs do not appear to pose any significant risk on their own, as per the available data.

A rare but potentially serious complication of long-term proton-pump inhibitor (PPI) use is PPI-induced hypomagnesaemia. PPIs reduce intestinal magnesium absorption leading to hypomagnesaemia; a class-effect seen with all PPIs. Risk of PPI-induced hypomagnesaemia is elevated in geriatric age group,

Table 4: Top 20 QT-prolonging drug-drug interaction pairs in the elderly patients

QT-DDIs	TdP risk[a]		Therapeutic class		Frequency
	Drug 1	Drug 2	Drug 1	Drug 2	QT-prolonging drug-drug interactions: *n* (%)[b]
Escitalopram- Risperidone	Known risk of TdP	Conditional risk of TdP	Antidepressant	Antipsychotic	33 (11.5)
Escitalopram- Olanzapine	Known risk of TdP	Conditional risk of TdP	Antidepressant	Antipsychotic	32 (11.1)
Fluoxetine- Olanzapine	Conditional risk of TdP	Conditional risk of TdP	Antidepressant	Antipsychotic	25 (8.7)
Lithium- Pantoprazole	Possible risk of TdP	Conditional risk of TdP	Antipsychotic	PPI	21 (7.3)
Haloperidol- Risperidone	Known risk of TdP	Conditional risk of TdP	Antipsychotic	Antipsychotic	12 (4.2)
Haloperidol- Quetiapine	Known risk of TdP	Conditional risk of TdP	Antipsychotic	Antipsychotic	10 (3.5)
Escitalopram- Haloperidol	Known risk of TdP	Known risk of TdP	Antidepressant	Antipsychotic	9 (3.1)
Fluoxetine- Haloperidol	Conditional risk of TdP	Known risk of TdP	Antidepressant	Antipsychotic	8 (2.8)
Olanzapine- Pantoprazole	Conditional risk of TdP	Conditional risk of TdP	Antipsychotic	PPI	8 (2.8)
Domperidone- Risperidone	Known risk of TdP	Conditional risk of TdP	Antiemetic	Antipsychotic	7 (2.4)
Quetiapine- Risperidone	Conditional risk of TdP	Conditional risk of TdP	Antipsychotic	Antipsychotic	7 (2.4)
Mirtazapine- Pantoprazole	Possible risk of TdP	Conditional risk of TdP	Antipsychotic	PPI	7 (2.4)
Fluoxetine- Quetiapine	Conditional risk of TdP	Conditional risk of TdP	Antidepressant	Antipsychotic	7 (2.4)
Fluoxetine- Risperidone	Conditional risk of TdP	Conditional risk of TdP	Antidepressant	Antipsychotic	7 (2.4)
Escitalopram- Ciprofloxacin	Known risk of TdP	Known risk of TdP	Antidepressant	Antimicrobial	6 (2.1)
Escitalopram- Domperidone	Known risk of TdP	Known risk of TdP	Antidepressant	Antinausea	6 (2.1)
Metronidazole- Olanzapine	Conditional risk of TdP	Conditional risk of TdP	Antimicrobial	Antipsychotic	6 (2.1)
Escitalopram- Halofantrine	Known risk of TdP	Known risk of TdP	Antidepressant	Antimalarial	6 (2.1)
Escitalopram- Quetiapine	Known risk of TdP	Conditional risk of TdP	Antidepressant	Antipsychotic	4 (1.4)
Donepezil- Memantine	Known risk of TdP	Possible risk of TdP	Antidementia	Antidementia	4 (1.4)

AzCERT=Arizona Center for Education and Research on Therapeutics; [a]TdP risk was based on AzCERT QT (CredibleMeds) Drugs Lists 1-3; [b]Percentage calculated in total number of QT-prolonging drug-drug interactions i.e., 288

females, subjects who are using diuretics concomitantly and patients with other co-morbidities notably diabetes or diarrhoea.[49]

Ondansetron hydrochloride brings about antiemetic action by antagonizing 5-hydroxy tryptamine type 3 (5-HT3) receptors. These antiemetics prolong QT-interval and have been reported to lead to arrhythmias and SCD.[50] Ondansetron-induced hypokalemia arises out of its effect on nephron, the effect on renal tubule is thought to be unique for ondansetron and it has been determined not to be a class-effect. Hypokalemia is a modifiable risk factor for drug-induced TdP.

Certain adverse events are specifically pertinent to the elderly population. Pre-existing cardiovascular diseases make elderly patients more vulnerable to cardiac side effects of antibiotic. Use of seven antimicrobial classes (macrolides, fluoroquinolones, antimalarials, pentamidine, antifungal azoles, antivirals (NNRTIs & PIs), & antituberculars (bedaquiline, delamanid)) have been observed to result in QT-prolongation. The use of fluoroquinolones requires awareness about the risk of cardiac events, mainly represented by QTc prolongation and risk of arrhythmia. Despite the well-established, strong and extensive proof of antibiotic-induced QT-prolongation with consequent lethal ventricular arrhythmias, this outcome is usually overlooked by clinicians.[51,52]

Changes in older adults are important considerations when selecting an antimalarial medication for prophylaxis or treatment. Some common adverse events with antimalarial agents that warrant more consideration in older adults are a risk for QT-prolongation and hypoglycemia. Many antimalarial drugs can cause QT prolongation, and in older adults, there is increased risk of this due to pre-existing cardiovascular disease, use of concurrent QT-prolonging drugs and age-related increases in QT interval.[53] Antimalarial agents like quinine and halofantrine can result in QT-interval prolongation. Akin to halofantrine, at standard doses quinine has proclivity to cause QT-interval prolongation. Halofantrine produces dose-dependent extension of QT-interval whereas mefloquine is not known to produce any effect on QT-interval. However, lumefantrine is a very weak blocker of hERG cardiac K+ channels when compared with halofantrine. Lumefantrine has been evaluated widely and is believed not to cause significant adverse cardiac effects in vivo, with minimal effects on the electrocardiogram.[54]

With domperidone doses >30 mg/day, there appears to be elevated probability of ventricular arrhythmias and associated SCD, as per 2012 Health Canada advisory for patients and health care professionals. This warning was reissued in 2015. Two case-control studies of adult patients unravelled a nexus between domperidone and ventricular arrhythmias and SCD.[55] When stratified by age, this risk was especially encountered in patients >60 years of age.[55]

Donepezil, a commonly prescribed cholinesterase inhibitor for managing Alzheimer's disease, has been known to lead to bradyarrhythmias and TdP. Case reports exposed that donepezil could lead rarely to serious bradycardia necessitating implantation of pacemaker and lethal ventricular arrhythmia (TdP).[56]

Table 5: Severity, Documentation and Risk Stratification of QT Interval Prolonging Drug–Drug Interactions in elderly patients in our study with the aid of 3 online Drug–Drug Interactions Checker

Drug Pairs	Medscape Drug Interactions Checker	Epocrates Online Interaction Check	Drugs.com Interactions Checker
Escitalopram + Risperidone	No interactions found	Monitor/Modify Therapy: monitor sodium: combo may increase risk of SIADH, hyponatremia, CNS depression, psychomotor impairment, serotonin syndrome (additive effects)	Major (Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit) MONITOR CLOSELY: Escitalopram can cause dose-dependent prolongation of the QT interval. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. In a double-blind, placebo-controlled ECG study consisting of 113 healthy subjects, the change from baseline in QTc (Fridericia-corrected) was 4.3 msec for escitalopram 10 mg/day and 10.7 msec for the supratherapeutic dosage of 30 mg/day. Based on the established exposure-response relationship, the predicted QTc change from placebo under the Cmax for 20 mg/day is 6.6 msec. Cases of QT interval prolongation and torsade de pointes have been reported during postmarketing use. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances (e.g., hypokalemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug (s) involved and dosage (s) of the drug (s). In addition, central nervous system- and/or respiratory-depressant effects may be additively or synergistically increased in patients taking escitalopram with certain other drugs that cause these effects, especially in elderly or debilitated patients. MANAGEMENT: Caution is recommended if escitalopram is used in combination with other drugs that can prolong the QT interval. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. When escitalopram is used in combination with other drugs that cause CNS and/or respiratory depression, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Ambulatory patients should be counseled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their doctor if they experience excessive or prolonged CNS effects that interfere with their normal activities.
Escitalopram + Olanzapine	No interactions found	Caution advised: combo may increase risk of CNS depression, psychomotor impairment, serotonin syndrome (additive effects)	Moderate (Moderately clinically significant. Usually avoid combinations; use it only under special circumstances) MONITOR: It is uncertain whether olanzapine causes clinically significant prolongation of the QT interval. In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportion of patients experiencing potentially important changes in ECG parameters, including QT, QTcF (Fridericia-corrected), and PR intervals. In clinical trials, clinically meaningful QTc prolongations (QTcF>=500 msec at any time post-baseline in patients with baseline QTcF<500 msec) occurred in 0.1% to 1% of patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. Published studies have generally reported no significant effect of olanzapine on QTc interval, although both QTc prolongation and QTc shortening have also been reported. There have been a few isolated case reports of QT prolongation in patients receiving olanzapine. However, causality is difficult to establish due to confounding factors such as concomitant use of drugs that cause QT prolongation and underlying conditions that may predispose to QT prolongation (e.g., hypokalemia, congenital long QT syndrome, preexisting conduction abnormalities). MANAGEMENT: Some authorities recommend caution when olanzapine is used with drugs that are known to cause QT prolongation. ECG monitoring may be advisable in some cases, such as in patients with a history of cardiac arrhythmias or congenital or family history of long QT syndrome. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope.

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Drug Pairs	Medscape Drug Interactions Checker	Epocrates Online Interaction Check	Drugs.com Interactions Checker
Fluoxetine + Olanzapine	No interactions found	Caution advised: combo may increase risk of CNS depression, psychomotor impairment (additive effects)	Moderate (Moderately clinically significant. Usually avoid combinations; use it only under special circumstances) MONITOR: It is uncertain whether olanzapine causes clinically significant prolongation of the QT interval. In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportion of patients experiencing potentially important changes in ECG parameters, including QT, QTcF (Fridericia-corrected), and PR intervals. In clinical trials, clinically meaningful QTc prolongations (QTcF>=500 msec at any time post-baseline in patients with baseline QTcF<500 msec) occurred in 0.1% to 1% of patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. Published studies have generally reported no significant effect of olanzapine on QTc interval, although both QTc prolongation and QTc shortening have also been reported. There have been a few isolated case reports of QT prolongation in patients receiving olanzapine. However, causality is difficult to establish due to confounding factors such as concomitant use of drugs that cause QT prolongation and underlying conditions that may predispose to QT prolongation (e.g., hypokalemia, congenital long QT syndrome, preexisting conduction abnormalities). MANAGEMENT: Some authorities recommend caution when olanzapine is used with drugs that are known to cause QT prolongation. ECG monitoring may be advisable in some cases, such as in patients with a history of cardiac arrhythmias or congenital or family history of long QT syndrome. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope.
Lithium + Pantoprazole	No interactions found	No significant interaction (s) known or found for selected drugs. Caution always advised with multiple medications.	Unknown (No interaction information available) No interactions were found for the selected drugs. This does not necessarily mean no interactions exist.
Haloperidol + Risperidone	4 interactions found: (A) Monitor closely (3) 1. Haloperidol and risperidone both increase QTc interval. Modify therapy/Monitor closely. 2. Haloperidol and risperidone both increase antidopaminergic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome. Use Caution/ Monitor. 3. Haloperidol and risperidone both increase sedation. Use Caution/ Monitor. (B) Minor (1) 4. Haloperidol will increase the level or effect of risperidone by affecting hepatic enzyme CYP2D6 metabolism. Minor/Significance Unknown.	Monitor/Modify Therapy: Monitor BP: combo may incr. risk of CNS depression, psychomotor impairment, hypotension, extrapyramidal sx (additive effects)	Major (Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit) MONITOR CLOSELY: Haloperidol can cause dose-related prolongation of the QT interval. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. Haloperidol treatment alone has been associated with a number of reported cases of torsade de pointes and sudden death. The majority of cases involved intravenous administration or use of higher than recommended dosages. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances (e.g., hypokalemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug (s) involved and dosage (s) of the drug (s). In addition, certain agents with anticholinergic properties (e.g., sedating antihistamines; antispasmodics; neuroleptics; phenothiazines; skeletal muscle relaxants; tricyclic antidepressants) may have additive parasympatholytic and central nervous system-depressant effects when used in combination with haloperidol. Excessive parasympatholytic effects may include paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures.

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Table 5: Contd...

Drug Pairs	Medscape Drug Interactions Checker	Epocrates Online Interaction Check	Drugs.com Interactions Checker
			MANAGEMENT: Caution is recommended if haloperidol is used in combination with other drugs that can prolong the QT interval, particularly when administered intravenously or at higher than recommended dosages. Haloperidol is not approved by the FDA for intravenous administration. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. In addition, if combination therapy with agents with anticholinergic properties is required, caution is advised, particularly in the elderly and those with underlying organic brain disease. Patients should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and/or hallucinations. Ambulatory patients should be counseled to avoid activities requiring mental alertness until they know how these agents affect them. A reduction in anticholinergic dosages may be necessary if excessive adverse effects develop.
Haloperidol + Quetiapine	3 interactions found: (A) Monitor closely (3) 1. Haloperidol and quetiapine both increase antidopaminergic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome. Use Caution/Monitor. 2. Haloperidol and quetiapine both increase sedation. Use Caution/Monitor. 3. Quetiapine, haloperidol. Either increases toxicity of the other by QTc interval. Use Caution/Monitor. Avoid use with drugs that prolong QT and in patients with risk factors for prolonged QT interval. Postmarketing cases show QT prolongation with overdose in patients with concomitant illness or with drugs known to cause electrolyte imbalance or prolong QT.	Avoid/Use Alternative: avoid combo: combo may incr. risk of QT prolongation, cardiac arrhythmias, hypotension, CNS depression, psychomotor impairment, extrapyramidal sx, anticholinergic adverse effects (additive effects)	Major: Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit. MONITOR CLOSELY: Haloperidol can cause dose-related prolongation of the QT interval. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. Haloperidol treatment alone has been associated with a number of reported cases of torsade de pointes and sudden death. The majority of cases involved intravenous administration or use of higher than recommended dosages. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances (e.g., hypokalemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug (s) involved and dosage (s) of the drug (s). In addition, certain agents with anticholinergic properties (e.g., sedating antihistamines; antispasmodics; neuroleptics; phenothiazines; skeletal muscle relaxants; tricyclic antidepressants) may have additive parasympatholytic and central nervous system-depressant effects when used in combination with haloperidol. Excessive parasympatholytic effects may include paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures. MANAGEMENT: Caution is recommended if haloperidol is used in combination with other drugs that can prolong the QT interval, particularly when administered intravenously or at higher than recommended dosages. Haloperidol is not approved by the FDA for intravenous administration. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. In addition, if combination therapy with agents with anticholinergic properties is required, caution is advised, particularly in the elderly and those with underlying organic brain disease. Patients should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and/or hallucinations. Ambulatory patients should be counseled to avoid activities requiring mental alertness until they know how these agents affect them. A reduction in anticholinergic dosages may be necessary if excessive adverse effects develop.

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Drug Pairs	Medscape Drug Interactions Checker	Epocrates Online Interaction Check	Drugs.com Interactions Checker
Escitalopram + Haloperidol	1 interaction found: (A) Monitor closely (1) 1. Haloperidol and escitalopram both increase QTc interval. Use Caution/Monitor.	Monitor/Modify Therapy: monitor ECG, sodium: combo may incr. risk of QT prolongation, cardiac arrhythmias, SIADH, hyponatremia, CNS depression, psychomotor impairment, serotonin syndrome (additive effects)	Major: Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit. MONITOR CLOSELY: Escitalopram can cause dose-dependent prolongation of the QT interval. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. In a double-blind, placebo-controlled ECG study consisting of 113 healthy subjects, the change from baseline in QTc (Fridericia-corrected) was 4.3 msec for escitalopram 10 mg/day and 10.7 msec for the supratherapeutic dosage of 30 mg/day. Based on the established exposure-response relationship, the predicted QTc change from placebo under the Cmax for 20 mg/day is 6.6 msec. Cases of QT interval prolongation and torsade de pointes have been reported during postmarketing use. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances (e.g., hypokalemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug (s) involved and dosage (s) of the drug (s). In addition, central nervous system- and/or respiratory-depressant effects may be additively or synergistically increased in patients taking escitalopram with certain other drugs that cause these effects, especially in elderly or debilitated patients. MANAGEMENT: Caution is recommended if escitalopram is used in combination with other drugs that can prolong the QT interval. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. When escitalopram is used in combination with other drugs that cause CNS and/or respiratory depression, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Ambulatory patients should be counseled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their doctor if they experience excessive or prolonged CNS effects that interfere with their normal activities.
Fluoxetine + Haloperidol	3 interactions found: (A) Serious-Use Alternative (2) 1. Fluoxetine will increase the level or effect of haloperidol by affecting hepatic enzyme CYP2D6 metabolism. Avoid or Use Alternate Drug. 2. Haloperidol will increase the level or effect of fluoxetine by affecting hepatic enzyme CYP2D6 metabolism. Avoid or Use Alternate Drug. (B) Monitor closely (1) 3. Fluoxetine and haloperidol both increase QTc interval. Modify Therapy/ Monitor Closely.	Avoid/Use Alternative: Use alternative or monitor ECG, sodium; consider decr. haloperidol dose: combo may incr. haloperidol levels, risk of QT prolongation, cardiac arrhythmias, SIADH, hyponatremia, CNS depression, psychomotor impairment, other adverse effects (hepatic metab. inhibited, additive effects)	Moderate: Moderately clinically significant. Usually avoid combinations; use it only under special circumstances. MONITOR: Coadministration with fluoxetine may increase the plasma concentrations of certain neuroleptic agents and potentiate the risk of extrapyramidal adverse effects. The proposed mechanism is inhibition of CYP450 2D6 metabolism by fluoxetine and its active metabolite, norfluoxetine. In 10 psychiatric patients stabilized on risperidone therapy (4 to 6 mg/ day), the addition of fluoxetine (20 mg/day) led to a mean 4-fold increase in plasma risperidone concentrations and a 75% increase in levels of active moiety (i.e. sum of the concentrations of risperidone and its active 9-hydroxy metabolite). One patient developed severe akathisia and two developed Parkinsonian symptoms within the first two weeks. In contrast, mean plasma concentrations of haloperidol were elevated by just 20% following the addition of fluoxetine (20 mg/day for 7 to 10 days) in eight psychotic patients stabilized on haloperidol, and extrapyramidal side effects did not increase appreciably. However, haloperidol has been implicated clinically in various case reports, as has the phenothiazine fluphenazine. Some believe that a pharmacodynamic interaction may be partially responsible, as fluoxetine alone has been associated with extrapyramidal symptoms, possibly due to serotonergic inhibition of nigrostriatal dopaminergic pathways.

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Drug Pairs	Medscape Drug Interactions Checker	Epocrates Online Interaction Check	Drugs.com Interactions Checker
			MANAGEMENT: Caution is recommended if fluoxetine is prescribed with phenothiazines or other neuroleptic agents that are thought to be metabolized by CYP450 2D6. Plasma neuroleptic levels and pharmacologic effects should be closely monitored and the dosage (s) adjusted accordingly, particularly following initiation or discontinuation of fluoxetine in patients who are stabilized on their neuroleptic regimen. Patients should be advised to contact their physician if they develop extrapyramidal symptoms such as tremor, shuffling gait, drooling, a mask-like face, tongue stiffness, muscle spasms or rigidity, and involuntary movements. Due to the long half-life of fluoxetine and norfluoxetine, the risk of an interaction may exist for an extended period (up to several weeks) after discontinuation of fluoxetine.
Olanzapine + Pantoprazole	No interactions found	No significant interaction (s) known or found for selected drugs. Caution always advised with multiple medications.	No interactions were found between the selected drugs. This does not necessarily mean no interactions exist. Always consult your healthcare provider.
Domperidone + Risperidone	No results	No results	No suggestions found
Quetiapine + Risperidone	3 interactions found: (A) Monitor closely (3) 1. Quetiapine and risperidone both increase antidopaminergic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome. Use Caution/Monitor. 2. Quetiapine and risperidone both increase sedation. Use Caution/Monitor. 3. Quetiapine, risperidone. Either increases toxicity of the other by QTc interval. Use Caution/Monitor. Avoid use with drugs that prolong QT and in patients with risk factors for prolonged QT interval. Postmarketing cases show QT prolongation with overdose in patients with concomitant illness or with drugs known to cause electrolyte imbalance or prolong QT.	Monitor/Modify Therapy: monitor BP: combo may incr. risk of CNS depression, psychomotor impairment, extrapyramidal sx, hypotension (additive effects)	Moderate (Moderately clinically significant. Usually avoid combinations; use it only under special circumstances) GENERALLY AVOID: There is some concern that quetiapine may have additive cardiovascular effects in combination with other drugs that are known to prolong the QT interval of the electrocardiogram. In clinical trials, quetiapine was not associated with a persistent increase in QT intervals, and there was no statistically significant difference between quetiapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters including QT, QTc, and PR intervals. However, QT prolongation and torsade de pointes have been reported during postmarketing use in cases of quetiapine overdose and in patients with risk factors such as underlying illness or concomitant use of drugs known to cause electrolyte imbalance or increase QT interval. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances (e.g., hypokalemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug (s) involved and dosage (s) of the drug (s). In addition, certain agents with anticholinergic properties (e.g., sedating antihistamines; antispasmodics; neuroleptics; phenothiazines; skeletal muscle relaxants; tricyclic antidepressants) may have additive parasympatholytic and central nervous system-depressant effects when used in combination with quetiapine. Excessive parasympatholytic effects may include paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures. MANAGEMENT: Coadministration of quetiapine with other drugs that can prolong the QT interval should generally be avoided. Caution and clinical monitoring are recommended if concomitant use is required. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. In addition, if combination therapy with agents with anticholinergic properties is required, caution is advised, particularly in the elderly and those with underlying organic brain disease. Patients should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and/or hallucinations. Ambulatory patients should be counseled to avoid activities requiring mental alertness until they know how these agents affect them. A reduction in anticholinergic dosages may be necessary if excessive adverse effects develop.

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Drug Pairs	Medscape Drug Interactions Checker	Epocrates Online Interaction Check	Drugs.com Interactions Checker
Mirtazapine + Pantoprazole	No interactions found	No interactions found	No interactions found in database
Fluoxetine + Quetiapine	1 interaction found: (A) Monitor closely (1) 1. Quetiapine, fluoxetine. Either increases toxicity of the other by QTc interval. Use Caution/ Monitor. Avoid use with drugs that prolong QT and in patients with risk factors for prolonged QT interval. Postmarketing cases show QT prolongation with overdose in patients with concomitant illness or with drugs known to cause electrolyte imbalance or prolong QT.	Caution advised: combo may incr. risk of CNS depression, psychomotor impairment, serotonin syndrome (additive effects)	Moderate (Moderately clinically significant. Usually avoid combinations; use it only under special circumstances) GENERALLY AVOID: There is some concern that quetiapine may have additive cardiovascular effects in combination with other drugs that are known to prolong the QT interval of the electrocardiogram. In clinical trials, quetiapine was not associated with a persistent increase in QT intervals, and there was no statistically significant difference between quetiapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters including QT, QTc, and PR intervals. However, QT prolongation and torsade de pointes have been reported during postmarketing use in cases of quetiapine overdose and in patients with risk factors such as underlying illness or concomitant use of drugs known to cause electrolyte imbalance or increase QT interval. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances (e.g., hypokalemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug (s) involved and dosage (s) of the drug (s). In addition, certain agents with anticholinergic properties (e.g., sedating antihistamines; antispasmodics; neuroleptics; phenothiazines; skeletal muscle relaxants; tricyclic antidepressants) may have additive parasympatholytic and central nervous system-depressant effects when used in combination with quetiapine. Excessive parasympatholytic effects may include paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures. MANAGEMENT: Coadministration of quetiapine with other drugs that can prolong the QT interval should generally be avoided. Caution and clinical monitoring are recommended if concomitant use is required. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. In addition, if combination therapy with agents with anticholinergic properties is required, caution is advised, particularly in the elderly and those with underlying organic brain disease. Patients should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and/or hallucinations. Ambulatory patients should be counseled to avoid activities requiring mental alertness until they know how these agents affect them. A reduction in anticholinergic dosages may be necessary if excessive adverse effects develop.
Fluoxetine + Risperidone	2 interactions found: (A) Serious-Use alternative (1) 1. Fluoxetine will increase the level or effect of risperidone by affecting hepatic enzyme CYP2D6 metabolism. Avoid or Use Alternate Drug. (B) Monitor closely (1) 2. Fluoxetine and risperidone both increase QTc interval. Use Caution/Monitor.	Monitor/Modify Therapy: ORAL RISPERIDONE: max 8 mg/day; IM RISPERIDONE: consider decr. dose to 12.5 mg; SC RISPERIDONE: consider decr. 120 mg dose to 90 mg: combo may incr. risperidone levels, risk of CNS depression, psychomotor impairment, serotonin syndrome, other adverse effects (hepatic metab. inhibited, additive effects)	Moderate (Moderately clinically significant. Usually avoid combinations; use it only under special circumstances) MONITOR: Coadministration with fluoxetine may increase the plasma concentrations of certain neuroleptic agents and potentiate the risk of extrapyramidal adverse effects. The proposed mechanism is inhibition of CYP450 2D6 metabolism by fluoxetine and its active metabolite, norfluoxetine. In 10 psychiatric patients stabilized on risperidone therapy (4 to 6 mg/day), the addition of fluoxetine (20 mg/day) led to a mean 4-fold increase in plasma risperidone concentrations and a 75% increase in levels of active moiety (i.e. sum of the concentrations of risperidone and its active 9-hydroxy metabolite). One patient developed severe akathisia and two developed Parkinsonian symptoms within the first two weeks. In contrast, mean plasma concentrations of haloperidol were elevated by just 20% following the addition of fluoxetine (20 mg/day for 7 to 10 days) in eight psychotic patients stabilized on haloperidol, and extrapyramidal side effects did not increase appreciably. However, haloperidol has been implicated clinically in various case reports, as has the phenothiazine fluphenazine. Some believe that a pharmacodynamic interaction may be partially responsible, as fluoxetine alone has been associated with extrapyramidal symptoms, possibly due to serotonergic inhibition of nigrostriatal dopaminergic pathways.

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Drug Pairs	Medscape Drug Interactions Checker	Epocrates Online Interaction Check	Drugs.com Interactions Checker
			MANAGEMENT: Caution is recommended if fluoxetine is prescribed with phenothiazines or other neuroleptic agents that are thought to be metabolized by CYP450 2D6. Plasma neuroleptic levels and pharmacologic effects should be closely monitored and the dosage (s) adjusted accordingly, particularly following initiation or discontinuation of fluoxetine in patients who are stabilized on their neuroleptic regimen. Patients should be advised to contact their physician if they develop extrapyramidal symptoms such as tremor, shuffling gait, drooling, a mask-like face, tongue stiffness, muscle spasms or rigidity, and involuntary movements. Due to the long half-life of fluoxetine and norfluoxetine, the risk of an interaction may exist for an extended period (up to several weeks) after discontinuation of fluoxetine.
Escitalopram + Ciprofloxacin	No interactions found	No interactions found	No interactions found in database
Escitalopram + Domperidone	No interactions found	No interactions found	No interactions found in database
Metronidazole + Olanzapine	No interactions found	No interactions found	Minor (Minimally clinically significant. Minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan) Limited data suggest that metronidazole may rarely prolong the QT interval of the electrocardiogram. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. There have been isolated reports of QT prolongation and ventricular arrhythmias occurring in patients treated with metronidazole. However, a causal relationship has not been established, as nearly all published reports have involved underlying conditions and/or concomitant medications that predispose to QT prolongation. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances (e.g., hypokalemia, hypomagnesemia). In addition, the extent of drug-induced QT prolongation is dependent on the particular drug (s) involved and dosage (s) of the drug (s). Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope.
Escitalopram + Halofantrine	No interactions found	No interactions found	Major: Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit. CONTRAINDICATED: Halofantrine can cause dose-related prolongation of the QT interval at recommended therapeutic doses. QTc interval prolongation and death have been reported during combination use of halofantrine and mefloquine. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. MANAGEMENT: Coadministration of halofantrine with other drugs that can prolong the QT interval is considered contraindicated. The manufacturer recommends performing an ECG before initiating halofantrine therapy and monitoring cardiac rhythm during and for 8 to 12 hours after completion of therapy.
Escitalopram + Quetiapine	1 interaction found: (A) Monitor closely (1) 1. Quetiapine, escitalopram. Either increases toxicity of the other by QTc interval. Use Caution/Monitor. Avoid use	Caution advised: combo may incr. risk of CNS depression, psychomotor impairment, serotonin syndrome (additive effects)	Major: Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit. MONITOR CLOSELY: Escitalopram can cause dose-dependent prolongation of the QT interval. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. In a double-blind, placebo-controlled ECG study consisting of 113 healthy subjects, the change from baseline in QTc (Fridericia-corrected) was 4.3 msec

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Table 5: Contd...

Drug Pairs	Medscape Drug Interactions Checker	Epocrates Online Interaction Check	Drugs.com Interactions Checker
	with drugs that prolong QT and in patients with risk factors for prolonged QT interval. Postmarketing cases show QT prolongation with overdose in patients with concomitant illness or with drugs known to cause electrolyte imbalance or prolong QT.		for escitalopram 10 mg/day and 10.7 msec for the supratherapeutic dosage of 30 mg/day. Based on the established exposure-response relationship, the predicted QTc change from placebo under the Cmax for 20 mg/day is 6.6 msec. Cases of QT interval prolongation and torsade de pointes have been reported during postmarketing use. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances (e.g., hypokalemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug (s) involved and dosage (s) of the drug (s). In addition, central nervous system- and/or respiratory-depressant effects may be additively or synergistically increased in patients taking escitalopram with certain other drugs that cause these effects, especially in elderly or debilitated patients. MANAGEMENT: Caution is recommended if escitalopram is used in combination with other drugs that can prolong the QT interval. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. When escitalopram is used in combination with other drugs that cause CNS and/or respiratory depression, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Ambulatory patients should be counseled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their doctor if they experience excessive or prolonged CNS effects that interfere with their normal activities.
Donepezil + Memantine	No interactions found	No interactions found	No interactions found in database

[#] For Drugs.com Interactions Checker: Major=Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit; Moderate=Moderately clinically significant. Usually avoid combinations; use it only under special circumstances; Minor=Minimally clinically significant. Minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan; Unknown=No information available

Table 6: Prevalence of TdP risk factors in the study population

Risk factor	Patients (*n*)
Cardiovascular Disease (s)	45
Digoxin Use	3
Dyselectrolytemia	21
Thyroid Dysfunction	4
Hypogonadism and/or ADT use (in men)	2
Women using OCPs (containing drospirenone)	0
Polypharmacy	
Minor (2-4 Drugs)	101
Major (≥5 Drugs)	98
Use of >1 TdP inducing agent	147

ADT=Androgen Deprivation Therapy (e.g. for prostate cancer); OCPs=Oral Contraceptive Pills; Total number of patients=208

Memantine, an N-methyl-D-aspartate glutamate receptor antagonist, has been used to manage moderate to severe Alzheimer's disease with amelioration of behavioral and psychological symptoms of dementia. A recent case-report highlighted QTc-prolongation from 438 to 504 ms following exposure of memantine for Alzheimer's disease. A case in which unintentional rechallenge with memantine caused QTc-prolongation has also been documented in medical scientific literature.[57]

Prevalence of high-risk QT prolonging drug-drug interactions involving antipsychotics and/or antidepressants

Simultaneous administration of ≥ 2 drugs listed in List 1 of AzCERT/CredibleMeds is fraught with considerable danger and linked with heightened risk of QT interval prolongation, torsadogenicity, and SCD. In this study, many QT-extending drug-drug interactions comprised of neuroleptic-neuroleptic, neuroleptic-antidepressant and antidepressant-antidepressant medication combinations. Polytherapy involving antipsychotic antidepressant drug combinations have been documented to usher in notable QT-interval elongation and TdP. Simultaneous intake of antipsychotic and antidepressant medications results in cumulative impact on QTc-interval. The arrhythmogenic propensity for antipsychotics differs remarkably. Risperidone, olanzapine, quetiapine, and haloperidol were antipsychotics most commonly involved in QT-prolonging drug-drug interactions in elderly in the present study. Escitalopram and fluoxetine were antidepressants most commonly observed in QT-prolonging drug-drug interactions in this study in geriatric patients.

An elevated chance of SCD and all-cause mortality has been linked to use of both typical and atypical antipsychotics.[48]

Table 7: Characteristics of subjects with prolonged QTcB values (≥ 500 ms or ≥60 ms change (increment) from baseline) in the study population subgroups (*n*=11)

Risk Factors	Medications	Reason for QTc prolongation	QTcB (Initial)	QTcB (Final)
F, Thy, CVD	Haloperidol, Risperidone, Pantoprazole	Psychiatric + adjunct drugs	410	490
F, Low K, CVD	Olanzapine, Chlorthalidone, Pantoprazole	Psychiatric + adjunct drugs	512	430
F, Low Ca, CVD	Olanzapine, Hydrochlorothi- azide, Mirtazapine	Psychiatric + adjunct drugs	504	418
F, Low Mg, CVD, Dementia	Risperidone, Hydrochlorothi- azide, Donepezil, Memantine	Psychiatric + adjunct drugs	500	442
Low K, CVD, ADT, PolyP	Risperidone, Hydrochlorothi- azide, Pantoprazole, Domperidone, Bicalutamide	Psychiatric + adjunct drugs	442	510
Low K, CVD, Dementia, PolyP	Escitalopram, Hydrochlorothi- azide, Dexlansoprazole, Domperidone, Donepezil, Memantine	Psychiatric + adjunct drugs	502	514
Low Mg, CVD, Dementia, PolyP	Fluoxetine, Spironolactone, Omeprazole, Domperidone, Donepezil, Memantine	Psychiatric + adjunct drugs	430	492
CVD, Dementia, PolyP	Fluoxetine, Spironolactone, Quetiapine, Domperidone, Donepezil, Memantine	Psychiatric + adjunct drugs	446	512
CVD, ADT, PolyP	Risperidone, Amiodarone Pantoprazole, Domperidone, Enzalutamide	Psychiatric + adjunct drugs + Arrhythmia	505	508
Low K, CVD, Malaria, PolyP	Escitalopram, Chlorthalidone Pantoprazole, Domperidone, Halofantrine	Psychiatric + adjunct drugs	500	508
Low K, CVD, TB, PolyP	Risperidone, Escitalopram Bedaquiline, Levofloxacin, Lithium	Psychiatric + adjunct drugs	430	498

F=Female; Thy=Thyroid disorder; CVD=cardiovascular disorder; ADT=Androgen deprivation therapy; PolyP=Polypharmacy; TB=MDR Tuberculosis

Antipsychotics documented to have known TdP risk are associated with most elevated chance for mortality, followed by agents with possible TdP risk, and lastly those not documented in the AzCERT/CredibleMeds TdP classification. Thioridazine (greatest risk), pimozide, droperidol, mesoridazine, and i.v. haloperidol (cumulative dose > 2 mg) pose significantly high risk of QTc prolongation among FGAs (traditional antipsychotics).[58] Amisulpride, sertindole, and ziprasidone pose significantly high risk of QTc-prolongation among SGAs (atypical newer antipsychotics).[58] On the other hand, amongst SGAs (atypical newer antipsychotics), aripiprazole and lurasidone have been documented to possess clinically insignificant proclivity for QTc-prolongation.[58] Asenapine and iloperidone are capable of producing clinically comparable QTc-prolongation as olanzapine, quetiapine, and risperidone.[58]

Olanzapine and risperidone have minimal effects on the QT interval, but can be associated with other adverse effects, such as orthostatic hypotension. Clinicians should be cautious in regard to geriatric patients who may be receiving multiple QT-interval-prolonging medications and should consider an ECG for QT-interval evaluation before administration. The oral route of administration is preferred because of fewer adverse effects.[59]

Use of SSRI citalopram was documented to produce greatest and most frequent QTc-prolonging effect in elderly patients. Citalopram was associated with a two to four times increased incidence of TdP in elderly patients, compared with TdP 3-classified sertraline and amitriptyline users. The results support that the TdP risk classification of antidepressants should be taken into consideration when prescribing to older people.[19] Use of SSRI citalopram and SNRI mirtazapine was reported to slightly heighten risk of VA/SCD compared to SSRI paroxetine and TCA amitriptyline.[58] Many SSRIs (notably citalopram) and SNRIs have been suspected in case reports of TdP. TCAs are known to cause more than twice the extent of QTc-prolongation than SSRIs. Alternative standard antidepressants did not lead to QTc-prolongation.

Various classes of psychotropic and non-psychotropic agents with the risk of QT-prolonging drug – drug interactions in elderly patients

In present study, antidepressants (27.7%), proton pump inhibitors (17.5%), antipsychotics (16.3%), antinausea (8.8%), antimicrobials (7.5%), H2 receptor antagonists (2.9%), antihistamines (2.3%), anticonvulsants (1.9%), antidementia agents (1.9%), diuretics (1.9%), and antineoplastic and immunomodulating agents (1.5%) were the drugs noted to expose geriatric patients to highest risk of QT-prolonging drug-drug interactions [Table 3]. It is perplexingly unsettling that bulk of the prescribed drugs (48.8%) bear a considerable risk of TdP (AzCERT classification: Known risk of TdP).[12]

40.3% of antipsychotics and 15.4% of antidepressants were implicated with the risk of QT prolonging drug – drug interactions.[60] However, 90.3% of antidepressants and 88.5% of antipsychotics have been reported to be linked with risk of QT-prolonging drug-drug interactions in another study.[44] Curtis *et al.*, reported that 4.4 million prescriptions of torsadogenic medications were handed out to 1.1 million patients.[45] Khan *et al.*[46] from Pakistan documented that 55.5% of antipsychotics and 32.4% of antidepressants could be associated with liability of QT-prolonging drug – drug interactions.

A Colombian research project with 525,498 recruited geriatric patients by Moreno-Gutierrez *et al.* reported that 10.6% were

prescribed ≥ 1 drug conferring TdP risk.[42] A recent study from North Jordan on elderly outpatients by Al-Azayzih *et al*. documented that 3114 patients out of a total of 5319 patients (58.5%) were using medications bearing TdP risk. 62.3% (n = 1939) patients were prescribed 1 TdP inducing agents and many patients were receiving 5 − 6 distinct TdP-inducing agents.[47] In this current study, we report a high usage of TdP inducing drugs. 11.5% (n = 24), 34.1% (n = 71), 38.5% (n = 80), and 15.9% (n = 33) elderly patients in our study were taking ≤ 2, 3 ± 4, 5-6, and > 6 drugs (i.e., exposed to polypharmacy) with TdP risk, respectively [Table 1].

Risk factors predisposing to QT-interval prolonging drug – drug interactions and TdP in elderly patients

In our study sample, apart from psychiatric illnesses, 45 elderly patients were suffering from cardiovascular diseases, 3 patients were using digoxin for CHF, 21 patients were using diuretics, whereas medications for thyroid disorders were prescribed to 4 patients. Two elderly men were administered androgen deprivation therapy (ADT). Minor polypharmacy (use of 2 − 4 drugs) was the second most common risk factor observed in 101 out of 208 elderly patients. Major polypharmacy (use of ≥ 5 drugs) was the third most common risk factor observed in 98 out of 208 elderly patients. One hundred and forty seven elderly patients received more than one QT-interval prolonging agent. Thirty potential QT-interval prolonging drug-drug interactions were noticed where the interacting medications were both from AzCERT/CredibleMeds List 1 (i.e., Drugs with Known Risk of TdP) which is a fraction of the population observed, but nonetheless hazardous.

QT-interval extending drug-drug combination use heighten TdP risk owing to both additive antagonism at cardiac inward-rectifier potassium ion (hERG) channels and alterations in tissue pharmacokinetic biotransformation interactions. Diuretic use is the commonest reason for hypokalemia, recorded in about 44.8% of TdP and 32.1% of LQTS cases in the 10-year French Pharmacovigilance Database Analysis.

ECG findings and incidence of TdP in elderly patients

There was a low incidence of QTc prolongation in our study and only one incidence of TdP in an elderly female subject who was managed but failed to survive. This finding is congruent with the low incidence of QTc and TdP in the general clinical population.[61,62]

Because of the risk of QTc prolongation & possibility of lethal TdP, electrocardiograms (ECGs) are used during treatment for monitoring QTc; however, this practice varies greatly among clinicians and across hospitals. The use of ECG as a biomarker for TdP has also been disputed given the natural variations in QTc intervals.[58,63] Some experts believe that psychiatric medications can be prescribed safely without routine ECGs in low-risk subjects,[58,63] especially as the practice of psychiatry moves away from first-generation antipsychotics to potentially safer second-generation agents.[64] Conversely, a large study by Ray *et al*.[48] found the incidence of sudden cardiac death in users of both typical and atypical antipsychotics to be two-fold that of nonusers. Such studies prompted the clinical practice of obtaining pretreatment ECGs on all patients.

We assessed the precautions and follow-up provided for all outpatients who were included in this study. Unfortunately, systematic performance of an ECG before (baseline) and after initiation of a QT-prolonging drug or QT-prolonging drug combinations as a safety measure was not done at our institution by the attending physicians most of the time. Other risk factors of the patients (besides lab results) were also not systematically documented most of the time. Where documentation about risk factors of the patients was not adequate, we sought the cooperation of our clinical collaborators to elicit this information. This highlights the pressing need for clear protocols and strategies for implementation to motivate care providers with clarity in the context of drug use guidelines for rational and safe prescribing in psychiatry. The available international guidelines[63,65-67] are not implemented in clinical practice and there is a lack of an Indian Guideline.

Conclusions

Our current study results imply that a huge proportion of geriatric patients in our Psychiatry OPD have been administered both drugs and drug combinations linkable with a heightened proclivity towards QT-interval prolongation in line with findings among the general population of psychiatry outpatients.[27] ECG and other relevant laboratory investigations were not ordered on regular basis in psychiatry. This bolsters the need for implementation of ECG monitoring protocols and appropriate laboratory investigations. Moreover, our results are suggestive of the fact that the TdP risk associated with individual medications must be scrutinized in order to derive an acceptable and tolerable risk-benefit judgement, especially in clinical scenarios with additional risk factors, to avoid mishaps. Therefore, we need to exigently embrace precautionary safety interventions, to be vigilant and forestall QT-prolongation and TdP in clinical settings. ACCF and AHA endorse that an ECG be done before or 8–12 h following initiation of a QT-prolonging drug, after dose escalation of the QT-prolonging drug or in overdose of a QT-prolonging drug. Furthermore, reliable evidence-based online drug information resources such as AzCERT/CredibleMeds Drug Lists,[12] medscape drug interactions Checker,[29] epocrates online interaction check[30], and Drugs.com drug interactions checker[31] can facilitate clinicians in selecting drugs for psychiatric patients. A wise choice of medications is imperative to preclude serious adverse outcomes.

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Conflicts of interest

There are no conflicts of interest.

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