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

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Abstract

Background: Psychotropic medications extend corrected QT (QTc) period in the electrocardiogram (ECG). Psychiatric patients exposed to ⩾1 psychotropic medication(s) represent a group with marked probability of drug-activated QTc-prolongation. Prolonged QTc interval in elderly patients (age > 60 years) is connected to greater risk of all-cause and coronary heart disease deaths. This study aimed at investigating pattern of utilization of QTc-interval protracting medications, QT-extending drug interactions, and prevalence of QTc-interval extending hazard 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 1 October 2017 to 30 August 2019 employing the pertinent prescriptions.

Results: A total of 832 elderly patients (age 60 years or more) visiting the Psychiatry OPD during the aforementioned study duration were investigated. About 420 (50.5%) patients were males while 412 (49.5%) were females. Of the 832 patients, 588 (70.7%) were using interacting agents with capacity to produce TdP. Almost 1152 interacting torsadogenic medication pairs were unraveled. As per AzCERT/CredibleMeds Classification, 1016 (48.8%), 724 (34.8%), and 248 (12%) agents with potential to interact were identified with 'known', 'possible', and 'conditional risk of TdP', respectively. The common interacting medications belonged to antidepressant (288), proton pump inhibitor (364), antipsychotic (340), antinausea (184), antimicrobial (156), and H_2 receptor antagonist (60) therapeutic categories. The all-inclusive frequency of potentially inappropriate psychotropic (PIP) agents administered was 62% (1343/2166) with Beers Criteria 2019, and 46% (997/2166) with STOPP Criteria 2015.

Conclusion: Many geriatric patients were administered drugs and drug combinations with heightened proclivity toward QT-interval prolongation. Furthermore, reliable evidence-based online drug knowledge resources, such as AzCERT/CredibleMeds Drug Lists, Medscape Drug Interactions Checker, Epocrates Online Interaction Check, and Drugs.com Drug Interactions Checker, can facilitate clinical professionals in selecting drugs for psychiatric patients. A wise choice of medications is imperative to preclude serious adverse sequelae. Therefore, we need to exigently embrace precautionary safety means, be vigilant, and forestall QT-extension and TdP in clinical environments.

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Introduction

It has been estimated that the annual global mortality resulting from sudden cardiac death (SCD) as a sequelae of ventricular tachyarrhythmias is roughly 6 million.[1,2] An estimated 20% of mortality in developed countries is attributable to SCD.[3–5] Approximately 10.3% of total deaths occur due to SCD in India.[6] Extension of the QT interval is a confirmed hazard factor for Torsade de Pointes (TdP) finally ending in ventricular tachycardia and fibrillation (VT/VF) and SCD.[5,7–9] As stated in the expert group, ground rules of the American Heart Association (AHA) as well as the American College of Cardiology Foundation (ACCF), a QTc-interval exceeding 470 ms in case of adult males and 480 ms in case of adult females is deemed to be aberrant.[7] There is an elevated proclivity toward TdP development when QTc interval $\geqslant$ 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).[10]

A sizable collection of >280 drugs (comprising of typical and atypical neuroleptics, typical and atypical antidepressants, antihistamines, prokinetics, proton pump inhibitors, anti-infectives, etc.) capable of leading to QT-prolongation based on reliable clinical documentation is accessible at AzCERT/CredibleMeds.[11]

An interplay between one or more risk factors affecting individual propensity toward QT-prolongation have been identified in the medical literature. Elderly patients commonly possess many of these risk factors. Owing to age-associated pharmacokinetic and pharmacodynamic alterations, there is an escalated proclivity to adverse events in geriatric patients. To cite an example, about 10% of patients aged $\geqslant$75 years are known to be affected by congestive heart failure.[12] Moreover, elderly patients are more likely to be prescribed diuretics. Diuretic-induced hypokalemia and hypomagnesaemia might accentuate drug-induced TdP risk.[13,14] In addition, elderly patients are more at risk of high levels of offending drug owing to reduced renal clearance, reduced hepatic biotransformation capacity, as well as polypharmacy-related drug–drug interactions.[15]

In general, any modality to obviate or decrease the recurrence of TdP must espouse an appraisal of such hazard factors which are patient-centric, drug-centric, and clinical scenario-centric, comprising of medication–medication interactions and comorbid illnesses. Not many epidemiological studies have investigated the interactive vital facets of repetitive use of QTc-interval protracting agents, QT-extending medication–medication interactions, and an analytical account of risk factors and concomitant illnesses for QTc-interval extension in geriatric patients visiting the Psychiatry OPD, particularly in developing nations. As far as we are aware, a similar analytical pharmacoepidemiological task has not been performed in elderly patients in India.

The detrimental consequences of psychotropics far outweigh their medical utility, particularly in cases where they could be availed by more prudent and wise means, have been looked upon as potentially inappropriate medications (PIMs).[16] Sagacious use of psychotropics is crucial to obviate drug-induced adverse events in geriatric patients. With the aim of capturing the ambit of PIM precisely, multiple criteria have been forwarded.[17] Just 2 years back, significant articulations related to psychotropic prescriptions have been incorporated into Beers Criteria 2019 and Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) Criteria 2015.[16,18]

Our teaching hospital is a national-level tertiary care hospital. Our patients are referred from all

over India and are representative of the national population to a large extent. This study was, therefore, implemented in order to investigate the nature of utilization of QTc-interval extending agents, QT-protracting medication–medication interactions, and account of variables for QTc-interval elongation hazard in elderly patients visiting the Psychiatry OPD in a referral and teaching hospital in India.

Materials and methods

Study design and methods have been previously described in detail.[19] Briefly, 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 1 October 2017 to 30 August 2019. In this study, researchers (BD and SK) attended 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 executed for a span of more than 1.5 complete years. Randomization was applied for the days of the week on which such surveys were executed. Research and ethical approval for this study were approved by Research Cell (Sanction Letter No. IM/RC98/2016/23 dated 28.09.2017) and Institutional Ethics Committee (Approval Letter No. AIIMS/IEC/17/234 dated 06.09.2017), respectively, of the All India Institute of Medical Sciences (AIIMS), Rishikesh, Uttarakhand, India. In addition, all the patients provided their written, informed consent to participate in this study.

TdP-engendering agents were determined and typecasted into four groups in accordance with the most current version of AzCERT/CredibleMeds QT Drug Lists (12 May 2020).[11]

ATC (Anatomic Therapeutic Chemical) Classification System codes of WHO Collaborating Center for Drug Statistics Methodology were utilized as deemed fit.[20]

We assessed the proportion of elderly patients (on psychotropic and other adjunctive medications with a propensity for QT protraction) 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 ($QTc = QTc/(RR)^{0.5}$). QTc between 450 and 500 ms in males and QTc between 470 and 500 ms in females were considered borderline prolonged. QTc $\geqslant$ 500 ms or with $>$60 ms of difference from baseline were deemed extended. These cutoffs were chosen based on documentation in the scientific literature as evidenced by elevated risk of SCD or arrhythmias.

The 20 most frequently used QTc-protracting drug–drug interactions were investigated employing freely available online evidence-based Medscape Drug Interaction Checker,[21] Epocrates Online,[22] and Drugs.com Drug–Drug Interactions Checker.[23]

Hazard factors present in the patients and capable of causing prolongation of the QTc interval and TdP (viz., cardiovascular disease,[24,25] prescription use of digoxin,[8] dyselectrolytemia,[26] thyroid dysfunction,[27,28] hypogonadism, and androgen deprivation therapy (ADT) (in men),[29] treatment with oral contraceptive pills (OCPs) consisting of drospirenone (in women),[30–32] polypharmacy,[33] and use of $>$1 agent with an elevated probability of TdP[7,34] were noted and exposed to scrutiny based on knowledge culled from treatment records and OPD case-sheets.

For the purpose of scrutinizing the quantum of potentially inappropriate psychotropic (PIP) prescriptions in geriatric patients, we employed the American Geriatric Society's Beers Criteria 2019 and British Geriatric Society's STOPP Criteria 2015.[16,17]

Statistical analysis: We employed descriptive as well as inferential statistics on the data from this study. Presentation of categorical data has been done as frequencies and percentages, whereas continuous data are declared as median (interquartile range (IQR)). Application of logistic regression analysis was resorted to examine the odds ratios (ORs) as predictors of QT-prolonging drug–drug interactions. Statistical significance

was fixed at $p < 0.05$. Microsoft Excel and IBM SPSS statistics version 23 was employed for all statistical analyses.

Results

A total of 832 elderly patients (age 60 years or more) attending the Psychiatry OPD during the study duration were taken into account. About 420 (50.5%) patients were males and 412 (49.5%) were females in this study (Table 1). Many of the elderly patients pertained 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). Majority of the patients were getting 5–6 drugs. The median count of medications used was 5 (IQR = 4–6). A large chunk of our elderly patients visiting 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 832 geriatric patients, 588 patients (70.7%) were prescribed interacting medications with the capability to usher in TdP (Table 2). The interacting medication–medication pairs with torsadogenic liability were computed to be 1152 in this analysis.

As per the AzCERT/CredibleMeds Classification, 1016 (48.8%) of the interacting medications were related with a 'known risk of TdP', 724 (34.8%) of interacting medications were related with a 'possible risk of TdP' and 248 (12%) of the interacting medications were related with a 'conditional risk of TdP' (Table 3). Interacting medications were commonly prescribed from antidepressant (576), proton pump inhibitor (364), antipsychotic (340), antinausea (184), antimicrobial (156), and H_2 receptor antagonist (60) therapeutic categories (Table 3). Table 4 provides an analysis of the top-20 torsadogenic drug–drug interactions, and in addition, their AzCERT Classification (CredibleMeds Risk Stratification), and therapeutic categories/classes. A total of 108 interacting medication–medication pairs where both are endowed with AzCERT listing as torsadogenic agents with a 'known risk of TdP' were recorded. A great many investigated medication–medication interactions linkable with TdP risk could interact pharmacodynamically rather than pharmacokinetically. The most recurrent medication–medication interacting duets with a pharmacodynamic basis were escitalopram-risperidone (132), escitalopram-olanzapine (128), fluoxetine-olanzapine (100), lithium-pantoprazole (84), and haloperidol-risperidone (48). A few torsadogenic interacting pairs with a pharmacokinetic basis were also spotted, viz., omeprazole-sertraline (12), omeprazole-amitriptyline (12), ciprofloxacin-amitriptyline (4), ketoconazole-imipramine (4), and cimetidine-amitriptyline (4) (Table 4).

The most recurrent medications with a capability of inducing QT-extending medication–medication interactions were escitalopram (384), olanzapine (284), risperidone (236), fluoxetine (188), haloperidol (156), pantoprazole (144), quetiapine (112), and domperidone (52) (Table 4).

The evidence-based identification and risk-stratification of QT interval extending medication–medication interactions in this study as gleaned from Medscape Drug Interactions Checker, Epocrates Online Interactions Checker, and Drugs.com Drug Interactions Checker are obtainable in Table 5.

In our study population, 180 elderly patients were afflicted with cardiovascular diseases, 12 elderly patients were prescribed digoxin for congestive cardiac failure, 84 were prescribed diuretics, whereas drugs for thyroid afflictions were used by 16 elderly patients. In our study, eight elderly males were receiving antiandrogens (bicalutamide and enzalutamide) for prostatic cancer. 'Minor polypharmacy'(use of 2–4 drugs) was the third most recurrent hazard factor noticed in 404 patients. 'Major polypharmacy'(use of $\geqslant$5 drugs) was the second most recurrent risk factor detected in 392 patients. 588 patients received >1 QT-interval protracting agents (Table 6).

Of the 832 geriatric patients in this study, 625 patients (75.1%) were advised ECG(s) by the attending psychiatrists in our institution. Of these 625 subjects, 121 (19.4%) male subjects had QTc > 450 ms and 63 (10.1%) female subjects had QTc > 470 ms. There were two incidences of TdP in elderly female subjects who were managed; one of them failed to survive. Of these, 11 (1.8%) subjects had QTc $\geqslant$ 500 ms or >60 ms of increment from baseline (Table 7).

Upon logistic regression (TABLE8Table 8), univariate analysis pointed out that the occurrence of QT-prolonging drug–drug interactions was significantly associated with >6 drugs (OR=3.4; 95% confidence interval (CI)=1.6–6.8; p=0.008), antidepressants (OR=8.9; 95% CI=5.7–16.4; p=0.001), proton pump inhibitors (OR=10.2; 95% CI=6.2–15.9; p=0.002), antipsychotics (OR=4.5; 95% CI=1.7–8.3; p=0.006), antinausea (OR=5.3; 95% CI=2.7–9.5; p=0.004), antimicrobials (OR=8.1; 95% CI=4.2–14.7; p=0.003), H2-receptor antagonists (OR=3.2; 95% CI=1.1–7.4; p=0.005), and antidementia (OR=6.3; 95% CI=4.4–11.2; p=0.006). Multivariate analysis pointed out that the occurrence of QT-prolonging drug–drug interactions was significantly associated with >6 drugs (OR=4.1; 95% CI=1.2–9.4; p=0.02), antidepressants (OR=7.4; 95% CI=3.2–12.1; p=0.03), proton pump inhibitors (OR=8.6; 95% CI=4.7–12.4; p=0.01), antipsychotics (OR=5.8; 95% CI=2.3–8.9; p=0.02), antinausea (OR=6.4; 95% CI=2.5–11.3; p=0.001), antimicrobials (OR=7.7; 95% CI=3.5–13.6; p=0.02), H2-receptor antagonists (OR=5.7; 95% CI=3.4–12.3; p=0.002), and antidementia (OR=12.2; 95% CI=6.1–19.6; p=0.001).

Table 9 describes the frequency of PIP drugs for geriatric patients complying with Beers Criteria 2019 and STOPP Criteria 2015[16–18]. The all-inclusive frequency of PIP agents administered was 62% (1343/2166) in compliance with Beers Criteria 2019. The five most common psychotropic PIMs prescribed were olanzapine, risperidone, haloperidol, quetiapine, and mirtazapine in our study. The all-inclusive frequency of PIP agents administered was 46% (997/2166) as per the STOPP Criteria 2015. The four most common psychotropic PIMs prescribed were mirtazapine, chlordiazepoxide, dothiepin, and escitalopram in our study. Beers Criteria 2019 dredged a greater quantum of PIMs when compared with STOPP Criteria 2015.

Discussion

Our results unravel frequent prescriptions of drug–drug combinations bearing documented hazard of TdP in geriatric psychiatry patients aged ⩾60. Most of these medication–medication interactions could result in QT-extension owing to pharmacodynamic reasons rather than pharmacokinetic underpinnings. A sizable chunk of elderly patients were exposed to minor and major

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

Variable	Patients (*n*)	%[a]
Sex	832	100
Male	420	50.5
Female	412	49.5
Age groups		
60–69	372	44.7
70–79	296	35.6
80–89	104	12.5
⩾90	60	7.2
No. of drugs prescribed per patient[b]		
⩽2	96	11.5
3–4	284	34.1
5–6	320	38.5
>6	132	15.9
Diagnosis		
Major depression	340	40.9
Schizophrenia	92	11.1
Bipolar affective disorder (BAD)	80	9.6
Conversion disorder	72	8.7
Anxiety	64	7.7
Mania	56	6.7
Dissociative disorder	44	5.3
Cannabis abuse	24	2.9
Acute psychosis	20	2.4
Psychosis	20	2.4
Obsessive compulsive disorder (OCD)	20	2.4
Coexisting illness(es)		
Acid peptic disorders	44	5.3
Tuberculosis	36	4.3
Cancer/metastatic carcinoma	36	4.3
Epilepsy	32	3.8

(Continued)

Table 1. (Continued)

Variable	Patients (*n*)	%[a]
Diabetes mellitus	28	3.4
Ischemic heart disease (IHD)	24	2.9
Dementia	24	2.9
Rheumatic disease	24	2.9
Congestive cardiac failure	20	2.4
Cardiac arrhythmias	20	2.4
Hypertension	20	2.4
Benign prostatic hypertrophy (BPH)	20	2.4
Dyslipidemias	16	1.9
Parkinson's disease	16	1.9
Bronchial asthma	12	1.4
Cerebrovascular disease	12	1.4
HIV/AIDS	12	1.4
Malaria	8	1
Mycoses (superficial)	8	1
Thyroid dysfunction	8	1
Hepatitis B	4	0.5
Hepatitis C	4	0.5
COPD	4	0.5
Paraplegia/hemiplegia	4	0.5
Renal disease	4	0.5

[a]Percentage computed based on a total number of 832 patients;
[b]All prescribed medications imply QT protracting agents and other medications.

Table 2. Prevalence of QT interval protracting medication–medication interactions in elderly patients.

Prevalence (parameters)	Patients (*n*)	%[a]
Overall prevalence	588	70.7
QT-MMI per patient		
1–2	100	12.0
2–4	332	39.9
>4	156	18.8
Sex-wise prevalence		
Male	336	40.4
Female	252	30.3
Age-wise prevalence		
60–69	248	29.8
70–79	224	26.9
80–89	64	7.7
>90	52	6.3

QT-MMI: QT extending medication–medication interactions.
[a]Percentage ciphered from total count of 832 elderly patients.

polypharmacy involving high-risk TdP-inducing agents. Majority of medications used by elderly psychiatric patients are known to result in QT-interval extension.

Risperidone, olanzapine, quetiapine, and haloperidol were neuroleptics most commonly involved in potential QT-protracting medication–medication interactions in the elderly in this study. Escitalopram and fluoxetine were antidepressants most frequently observed in potential QT-extending medication–medication interactions in this study in geriatric patients. There was a low incidence of QTc protraction in our study and two cases of lethal TdP in two elderly female subjects who were managed; one of the two failed to survive. There was a high incidence of PIP agent prescription in our study as can be comprehended from our results.

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

Beuscart *et al.*[35] studied prescriptions for psychotropic agents to older patients aged ⩾75 in a 222-bedded French general hospital setting and ⩾3 psychotropic agent co-prescriptions for ⩾3 days were found in 374 stays of total of 11,929 stays (3.1%). Almost 89.2% of these 374 co-prescriptions contained unacceptable drug combinations (viz., concurrent prescription of ⩾2 agents belonging to same psychotropic class (duplication) and/or unjustifiable prescriptions without valid therapeutic indication).

In another Belgian cross-sectional study executed in a psychiatry establishment, 7.3% of patients were taking interacting agents with an associated hazard of TdP.[36]

In a retrospective cohort study, Curtis *et al.*[37] determined that 2.2% of patients were administered interacting agents with TdP risk. Khan *et al.*[38] from Pakistan determined that 51.7% patients in their study were prescribed interacting agents with TdP hazard.

Moreno-Gutierrez *et al.*[34] 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. About 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 prescribed drugs with TdP hazard. About 62.3% ($n=1939$), 29.8% ($n=929$), 6.6% ($n=207$), and 1.1% ($n=33$) patients were administered 1, 2, 3, and 4 drugs (i.e. exposed to polypharmacy) with TdP risk, respectively.[39]

In this work, we noticed an exposure of 70.7% of Psychiatry OPD elderly outpatients ⩾60 years old to drug–drug interactions with torsadogenic hazard (Table 2).

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

Characteristics of geriatric patients using drugs with liability for QT extension and TdP

About 44.7% and 35.6% of elderly patients visiting the Psychiatry OPD were 60–69 years of age and 70–79 years of age, respectively. About 12.5% of patients were 80–89 years of age while

Table 3. AzCERT hazard stratification and therapeutic classes of medications implicated in QT-interval extending medication–medication interactions in elderly patients.

Stratification scheme	*n* (interacting drugs)	%[a]
AzCERT (CredibleMeds) hazard stratification		
'Known risk of TdP'(List 1)	1016	48.8
'Possible risk of TdP'(List 2)	724	34.8
'Conditional risk of TdP'(List 3)	248	12.0
Not included in AzCERT QT drugs lists (List 4)[b]	92	4.4
Therapeutic categories		
Antidepressant (N06A)	576	27.7
Proton pump inhibitor (A02BC)	364	17.5
Antipsychotic (N05A)	340	16.3
Antinausea (A04AA)	184	8.8
Antimicrobial (J01MA/J01FA)	156	7.5
H2-Receptor Antagonist (A02BA01/02/03)	60	2.9
Antihistamine (R06AD)	48	2.3
Anticonvulsant (N03AX11)	40	1.9
Antidementia (N06D)	40	1.9
Diuretics (C03)	40	1.9
Antineoplastic and immunomodulating agents (L01/L02/L03)	32	1.5
Antimalarial (P01B)	24	1.2
Antifungal (D01AC)	20	1.0
Calcium channel blocker (C08CA01)	20	1.0
Antituberculars (J04A)	20	1.0
Antidiabetics (A10A/A10B)	20	1.0
Beta blocking agents (C07A)	16	0.8
Antiarrhythmics (C01B/C01E)	16	0.8
Drugs for airway obstructive diseases (R03)	12	0.6
Antivirals (J05A)	12	0.6

(Continued)

Table 3. (Continued)

Stratification scheme	*n* (interacting drugs)	%[a]
Platelet aggregation inhibitors (B01AC)	8	0.4
Lipid modifying agents (C10A/C10B)	8	0.4
Antithyroid (H03B)	4	0.2
Antiparkinsonian Drugs (N04)	4	0.2
Drugs for BPH (G04C)	4	0.2
Agents acting on renin angiotensin system (C09)	4	0.2

AzCERT, Arizona Center for Education and Research on Therapeutics (CredibleMeds); BPH, Benign Prostatic Hypertrophy; TdP, Torsades de Pointes.
Total count of QT-interval protracting medication–medication interactions, that is, 1152.
[a]Percentage computed from number of all interacting medications, that is, 2080.
[b]'Not included in AzCERT QT drugs lists (List 4)' = total number of drugs to avoid in congenital long QT (List 4) = 72 (including 12 two-drug combinations); this list contains drugs exclusively from List 4; co-incidental drugs from CredibleMeds Lists 1–3 have been precluded.

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 increment in death rates in patients above age 65, who are taking first- and second-generation antipsychotics (FGA and SGA) in comparison to people on a placebo.[40]

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 hazard for QT extension in older adults whereas other SSRIs and SNRIs do not appear to confer any serious liability 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, females, subjects who are using diuretics concomitantly and patients with other comorbidities notably diabetes or diarrhea.[41]

Ondansetron hydrochloride brings about antiemetic action by antagonizing 5-hydroxy tryptamine type 3(5-HT3) receptors. These antiemetics protract the QT-interval and have been reported to lead to arrhythmias and SCD.[42] 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 hazard factor for TdP caused by drug use.

The use of seven antimicrobial classes (macrolides, fluoroquinolones, antimalarials, pentamidine, antifungal azoles, antivirals (NNRTIs and PIs), and antituberculars (bedaquiline and delamanid)) have been observed to result in QT-protraction. 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.[43]

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 feeble 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 electrocardiograph.[44]

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. When stratified by age, this risk was especially encountered in patients >60 years of age.[45]

Case reports exposed that donepezil could lead rarely to serious bradycardia necessitating implantation of pacemaker and lethal ventricular arrhythmia (TdP).[46]

A recent case-report highlighted QTc-prolongation from 438 to 504 ms following exposure of memantine for Alzheimer's disease. An instance where

Table 4. Top-20 QT-extending medication–medication interaction duets noted in the elderly patients.

QT –MMIs	TdP risk[a]		Therapeutic class		Frequency
	Drug 1	Drug 2	Drug 1	Drug 2	QT-prolonging drug–drug interactions: *n* (%)[b]
Escitalopram – risperidone	Known	Conditional	Antidepressant	Antipsychotic	132 (11.5)
Escitalopram – olanzapine	Known	Conditional	Antidepressant	Antipsychotic	128 (11.1)
Fluoxetine – olanzapine	Conditional	Conditional	Antidepressant	Antipsychotic	100 (8.7)
Lithium – pantoprazole	Possible	Conditional	Antipsychotic	PPI	84 (7.3)
Haloperidol – risperidone	Known	Conditional	Antipsychotic	Antipsychotic	48 (4.2)
Haloperidol – quetiapine	Known	Conditional	Antipsychotic	Antipsychotic	40 (3.5)
Escitalopram – haloperidol	Known	Known	Antidepressant	Antipsychotic	36 (3.1)
Fluoxetine – haloperidol	Conditional	Known	Antidepressant	Antipsychotic	32 (2.8)
Olanzapine – pantoprazole	Conditional	Conditional	Antipsychotic	PPI	32 (2.8)
Domperidone – risperidone	Known	Conditional	Antiemetic	Antipsychotic	28 (2.4)
Quetiapine – risperidone	Conditional	Conditional	Antipsychotic	Antipsychotic	28 (2.4)
Mirtazapine – pantoprazole	Possible	Conditional	Antipsychotic	PPI	28 (2.4)
Fluoxetine – quetiapine	Conditional	Conditional	Antidepressant	Antipsychotic	28 (2.4)
Fluoxetine – risperidone	Conditional	Conditional	Antidepressant	Antipsychotic	28 (2.4)
Escitalopram – ciprofloxacin	Known	Known	Antidepressant	Antipsychotic	24 (2.1)
Escitalopram – domperidone	Known	Known	Antidepressant	Antinausea	24 (2.1)
Metronidazole – olanzapine	Conditional	Conditional	Antimicrobial	Antipsychotic	24 (2.1)
Escitalopram – halofantrine	Known	Known	Antidepressant	Antimalarial	24 (2.1)
Escitalopram – quetiapine	Known	Conditional	Antidepressant	Antipsychotic	16 (1.4)
Donepezil – memantine	Known	Possible	Antidementia	Antidementia	16 (1.4)

AzCERT, Arizona Center for Education and Research on Therapeutics; PPI, Proton-Pump Inhibitor; QT-MMIs, QT-extending medication–medication interactions.
[a]TdP hazard stratification was based on AzCERT QT (CredibleMeds) Drugs Lists 1–3.
[b]Percentage determined from total number of QT-extending medication–medication interactions, that is, 1152.

inadvertent rechallenge with memantine precipitated QTc-protraction has also been documented in medical scientific literature.[47]

Prevalence of high-risk QT extending medication–medication 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 liability of QT interval extension, torsadogenicity, and SCD. In this study, various QT-extending medication–medication 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.

Table 5. Severity, documentation, and risk stratification of QT interval prolonging drug–drug interactions in elderly patients in our study with the aid of three online drug–drug interactions checker.

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
1	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.'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
2	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.'
3	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.'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
4	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.'
5	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 rx(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.'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
6	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.'		'**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.'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
7	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.'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
8	Fluoxetine + haloperidol	Three 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. 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.'
9	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.'
10	Domperidone + risperidone	'No results'	'No results'	'No suggestions found'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
11	Quetiapine + risperidone	Three 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 rx, 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.'
12	Mirtazapine + pantoprazole	'No interactions found'	'No interactions found'	'No interactions found in database'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
13	Fluoxetine + quetiapine	One 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.'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
14	Fluoxetine + risperidone	Two 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. 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.'
15	Escitalopram + ciprofloxacin	'No interactions found'	'No interactions found'	'No interactions found in database'
16	Escitalopram + domperidone	'No interactions found'	'No interactions found'	'No interactions found in database'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
17	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.'
18	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 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.'

(Continued)

Table 5. (Continued)

Serial no.	Drug pairs	Medscape drug interactions checker	Epocrates online interaction check	Drugs.com interactions checker
19	Escitalopram + quetiapine	One interaction found: **'(A) Monitor closely (1)** 1. Quetiapine, escitalopram. 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)'	'**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.'
20	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' ".

An elevated chance of SCD and all-cause death has been linked to use of both typical and atypical antipsychotics.[40] Antipsychotics documented to have 'known TdP risk' are associated with most elevated chance for lethality, followed by agents with 'possible TdP risk' and finally those not documented in the AzCERT/CredibleMeds TdP classification. Thioridazine (maximal risk), pimozide, droperidol, mesoridazine, and i.v. haloperidol (cumulative dose > 2 mg) pose significantly high risk of QTc protraction among FGAs (traditional antipsychotics). Amisulpride, sertindole, and ziprasidone pose significantly high risk of QTc-prolongation among SGAs (atypical newer antipsychotics). On the contrary, among SGAs, aripiprazole and lurasidone have been documented to possess clinically insignificant proclivity for QTc-prolongation. Asenapine and iloperidone are capable of producing clinically comparable QTc-prolongation as olanzapine, quetiapine, and risperidone.[48]

Use of SSRI citalopram has been documented to usher in maximal QTc-prolonging effect. Use of SSRI citalopram and SNRI mirtazapine was noticed to marginally heighten hazard of VA/SCD correlated to SSRI, paroxetine and TCA, and amitriptyline.[48] Many SSRIs (especially 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.

Different classes of psychotropic and non-psychotropic medications with the hazard of QT protracting medication–medication interactions in elderly patients

In this 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 liability of QT-extending medication–medication interactions (Table 3). The bulk of the prescribed drugs (48.8%) bear a considerable hazard of TdP (AzCERT hazard stratification: 'Known risk of TdP').[11]

In one study, 40.3% of antipsychotics and 15.4% of antidepressants were involved with hazard of QT extending medication–medication interactions.[49] However, 90.3% of antidepressants and 88.5% of neuroleptics have been reported to be linked with hazard of QT-extending medication–medication interactions in another study.[36] Curtis *et al.*,[37] reported that 4.4 million prescriptions of torsadogenic medications were handed out to 1.1 million patients. Khan *et al.*[38] from Pakistan documented that 55.5% of antipsychotics and 32.4% of antidepressants could be associated with liability of QT-extending medication–medication interactions.

A Colombian research project with 525,498 recruited geriatric patients by Moreno-Gutierrez *et al.*[34] reported that 10.6% were prescribed ⩾1 drug conferring TdP risk. A recent study from North Jordan on elderly outpatients by Al-Azayzih *et al.*[39] documented that 3114 patients out of a total of 5319 patients (58.5%) were using medications bearing TdP risk. About 62.3% (n = 1939) patients were prescribed 1 TdP-inducing agent and many patients were receiving 5–6 distinct TdP-inducing agents. In this study, we report a steep usage of TdP-inducing drugs. About 11.5% (n = 96), 34.1% (n = 284), 38.5% (n = 320), and 15.9% (n = 132) 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).

Table 6. Frequency of TdP hazard factors in the study population.

Hazard factor	Patients (n)
Cardiovascular disease(s)	180
Digoxin use	12
Dyselectrolytemia	84
Thyroid dysfunction	16
Hypogonadism and/or ADT use (in men)	8
Women using OCPs (consisting of drospirenone)	0
Polypharmacy	
Minor (2–4 drugs)	404
Major (⩾5 drugs)	392
Use of >1 TdP-engendering agent	588

ADT, androgen deprivation therapy (e.g. for prostate cancer); OCPs, oral contraceptive pills.
Total number of patients = 832.

Table 7. Detailed characteristics of subjects with prolonged QTc values (⩾500 ms or ⩾60 ms change (increment) from baseline) in the study population subgroups ($n = 11$).

Risk factors	Medications	Reason for QTc prolongation	QTc (initial)	QTc (final)
QTc values (⩾500 ms at baseline)				
F, Low K, CVD	Olanzapine, chlorthalidone, pantoprazole	Psychiatric + adjunct drugs	512	430
F, Low Ca, CVD	Olanzapine, hydrochlorothiazide, mirtazapine	Psychiatric + adjunct drugs	504	418
F, Low Mg, CVD, dementia	Risperidone, hydrochlorothiazide, donepezil, memantine	Psychiatric + adjunct drugs	500	442
Low K, CVD, dementia, PolyP	Escitalopram, hydrochlorothiazide, dexlansoprazole, domperidone, donepezil, memantine	Psychiatric + adjunct drugs	502	514
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
QTc values (⩾60 ms change (increment) from baseline)				
F, Thy, CVD	Haloperidol, risperidone, pantoprazole	Psychiatric + adjunct drugs	410	490
Low K, CVD, ADT, PolyP	Risperidone, Hydrochlorothiazide, pantoprazole, domperidone, bicalutamide	Psychiatric + adjunct drugs	442	510
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
Low K, CVD, TB, PolyP	Risperidone, escitalopram, bedaquiline, levofloxacin, lithium	Psychiatric + adjunct drugs	430	498

ADT, androgen deprivation therapy; CVD, cardiovascular disorder; F, female; PolyP, polypharmacy; TB, MDR tuberculosis; Thy, thyroid disorder.

Hazard factors and proclivity toward QT-interval extending medication–medication interactions and TdP in elderly patients

In our study population, other than psychiatric afflictions, 180 elderly patients were diagnosed with cardiovascular diseases, 12 patients were taking digoxin for CHF, 84 patients were taking diuretics, whereas drugs for thyroid disorders were used by 16 patients. 8 elderly men were administered ADT. 'Minor polypharmacy'(use of 2–4 drugs) was the second most recurrent hazard factor noted in 404 out of 832 elderly patients. 'Major polypharmacy'(use of ⩾5 drugs) was the third most recurrent liability factor determined in 392 out of 832 elderly patients. About 588 elderly patients were prescribed more than one

Table 8. Data from logistic regression analysis for risk factors.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Sex				
Female	1 (0.6–1.8)	0.07	–	–
Age categories				
60–69	Reference		Reference	
70–79	1.2 (0.6–3.2)	0.08	0.8 (0.2–1.4)	0.06
80–89	1.4 (0.3–4.6)	0.06	1.1 (0.4–1.7)	0.05
⩾90	1.6 (0.4–5.1)	0.07	1.4 (0.3–4.7)	0.01
All prescribed drugs				
⩽2	Reference		Reference	
3–4	1.6 (0.5–3.8)	0.07	1.2 (0.3–1.9)	0.06
5–6	1.8 (0.6–4.9)	0.05	1.7 (0.3–2.8)	0.04
>6	3.4 (1.6–6.8)	0.008	4.1 (1.2–9.4)	0.02
Diagnoses				
Tuberculosis	1.8 (0.4–4.2)	0.06	–	–
Cancer/metastatic carcinoma	2.3 (0.9–5.4)	0.05	–	–
Diabetes mellitus	0.7 (0.1–1.0)	0.02	0.5 (0.2–1.2)	0.4
Ischemic heart disease (IHD)	2.6 (0.9–4.3)	0.04	–	–
Dementia	3.2 (1.1–5.4)	0.01	1.4 (1.0–3.9)	0.01
Congestive cardiac failure	3.4 (1.2–6.5)	0.001	3.6 (1.3–7.4)	0.04
Hypertension	0.5 (0.1–0.8)	0.05	0.7 (0.2–1.8)	0.06
HIV/AIDS	3.9 (1.7–8.6)	0.04	3.6 (1.8–5.4)	0.05
Malaria	3.6 (1.7–4.5)	0.05	3.2 (1.2–11.4)	0.2
Hepatitis B	2.1 (1.4–7.6)	0.03	2.6 (1.2–6.9)	0.02
Hepatitis C	3.7 (1.8–5.6)	0.04	3.4 (1.5–7.1)	0.05
Renal disease	3.9 (1.4–6.7)	0.003	4.6 (1.8–7.5)	0.04
QT prolonging drug classes				
Antidepressant	8.9 (5.7–16.4)	0.001	7.4 (3.2–12.1)	0.03
Proton pump inhibitor	10.2 (6.2–15.9)	0.002	8.6 (4.7–12.4)	0.01
Antipsychotic	4.5 (1.7–8.3)	0.006	5.8 (2.3–8.9)	0.02
Antinausea	5.3 (2.7–9.5)	0.004	6.4 (2.5–11.3)	0.001
Antimicrobial	8.1 (4.2–14.7)	0.003	7.7 (3.5–13.6)	0.02
H2-receptor antagonist	3.2 (1.1–7.4)	0.005	5.7 (3.4–12.3)	0.002
Antidementia	6.3 (4.4–11.2)	0.006	12.2 (6.1–19.6)	0.001

CI, confidence interval; OR, odds ratios.

Table 9. PIP List based on Beers Criteria 2019 and STOPP Criteria 2015.

PIM drug class(es)	Frequency of patients as per Beers Criteria 2019 (%)	Frequency of patients as per STOPP Criteria 2015 (%)
Unrelated to diagnosis		
Antidepressants		
Amitriptyline	2	2
Clomipramine	1	1
Dothiepin	–	10
Imipramine	6	6
Mirtazapine	30	30
Nortriptyline	3	3
Paroxetine	2	2
Escitalopram (caused hyponatremia)	7	7
Mirtazapine (caused hyponatremia)	1	–
Fluoxetine (caused hyponatremia)	2	2
Paroxetine (caused hyponatremia)	3	3
Antipsychotics (conventional)		
Haloperidol	145	–
Antipsychotics (atypical)		
Quetiapine	88	–
Olanzapine	290	–
Aripiprazole	1	–
Risperidone	280	–
Clozapine	5	–
Benzodiazepines (short-acting)		
Alprazolam	4	–
Lorazepam	10	–
Oxazepam	2	–
Benzodiazepines (long-acting)		
Chlordiazepoxide	12	12
Clonazepam	6	6
Z-Drugs		
Zolpidem	2	–
Antiparkinsonian drugs		
Benzhexol	16	–
Clinically relevant drug–drug interactions		
Lithium + frusemide	6	–
Polypharmacy with ⩾3 CNS-active agents	543	–

PIM, potentially inappropriate medication; PIP, potentially inappropriate psychotropics.

QT-interval extending agent. Around 108 potential QT-interval protracting medication–medication interactions were noted where the interacting drugs both belonged to AzCERT/CredibleMeds List 1 (i.e. drugs with 'Known Risk of TdP') which is a small slice of the sample observed, but nonetheless hazardous.

ECG findings and incidence of TdP in elderly patients

There was a low incidence of QTc protraction in our study, and two incidences of lethal TdP in two elderly female subjects who were managed; one of the two failed to survive. This finding is representative of the low frequency of QTc and TdP among patients' in general.[50,51]

Because of the hazard of QTc extension and possibility of lethal TdP, electrocardiograms (ECGs) must be scrutinized during drug administration for keeping track of QTc interval extension (if any); however, this custom differs widely amid clinicians and across hospitals. The utility of ECG as a biomarker for TdP is also contentious, given the innate alterations in QTc intervals.[48,52,53]

PIP agent prescription in geriatric patients

There was a high incidence of PIP agent prescription in our study as can be comprehended from our results. Our findings are similar with a work conducted by Soerensen *et al.*,[54] who reported that about 66% of their geriatric patients attending the psychiatry department of a university hospital were taking at least one PIP. In another retrospective, cross-sectional design study by Kolshus *et al.*,[55] of the 65 patients (aged ⩾90 years), 23 (35.4%) received long-term benzodiazepines as PIP agents. In depressed geriatric patients, SSRIs are the antidepressants of choice. However, a sizable chunk of depressed elderly patients are still being managed with TCAs which are considered as PIP as per STOPP Criteria 2015.[56] This is because the use of TCAs and SNRIs in the elderly leads to troublesome anticholinergic side effects. SNRI usage has also been linked to an escalated association with cerebrovascular events in comparison to SSRIs.[57] Beers Criteria 2019 incorporates a comprehensive enlisting of conventional and atypical neuroleptics which should not be administered in geriatric age group (especially those with dementia, delirium, cognitive malfunction, history of falls, and/or fractures) irrespective of the psychiatric diagnosis/state as they may induce intense anticholinergic and extrapyramidal effects. The five leading psychotropic PIMs prescribed were olanzapine, risperidone, haloperidol, quetiapine, and mirtazapine in our study.[58,59] However, dementia and delirium are the only states with contraindication of neuroleptics in elderly patients. The four leading psychotropic PIMs prescribed were mirtazapine, chlordiazepoxide, dothiepin, and escitalopram in our study.

Conclusion

This 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 toward QT-interval prolongation. ECG and other pertinent laboratory tests were not asked for on usual basis in psychiatry. The available international guidelines[7,52,53,60,61] are not executed in clinical practice, and there is lack of an Indian Guideline. This boosts the demand for execution of ECG auditing protocols and pertinent laboratory investigations. ACCF and AHA endorse that an ECG be done prior to or 8–12 h after initiation of a QT extending drug, after stepping-up doses of the QT extending drug or in overdose of a QT protracting drug. Furthermore, reliable evidence-based online drug knowledge resources such as AzCERT/CredibleMeds Drug Lists,[11] Medscape Drug Interactions Checker,[21] Epocrates Online Interaction Check,[22] and Drugs.com Drug Interactions Checker[23] can facilitate clinical professionals in selecting drugs for psychiatric patients. A wise choice of medications is imperative to preclude serious adverse outcomes. Based on the results, we have proposed an algorithmic model for facilitating physicians and clinical pharmacists to wisely prescribe drugs which have QT prolonging potential and to curb excessive use of such agents. In this study, there was very frequent use of PIP medications. This issue needs to be dealt with exigently to obviate hazardous sequelae.

Author contributions

BD: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization.

SKR: Data curation, Writing - review & editing.

AA: Data curation, Writing-review & editing.

BK: Writing - review & editing.

VSR: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing - review & editing.

Conflict of interest statement

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References

1. Josephson M and Wellens HJ. Implantable defibrillators and sudden cardiac death. *Circulation* 2004; 109: 2685–2691.
2. Mehra R. Global public health problem of sudden cardiac death. *J Electrocardiol* 2007; 40: S118–S122.
3. Myerburg RJ, Kessler KM and Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med* 1993; 119: 1187–1197.
4. Myerburg RJ, Interian A Jr, Mitrani RM, *et al.* Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol* 1997; 80: 10F–19F.
5. van Noord C, Eijgelsheim M and Stricker BH. Drug- and non-drug associated QT interval prolongation. *Br J Clin Pharmacol* 2010; 70: 16–23.
6. Rao BH. Global burden of sudden cardiac death and insights from India. *Indian Heart J* 2014; 66: S18–S23.
7. Drew BJ, Ackerman MJ, Funk M, *et al.* Prevention of Torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol* 2010; 55: 934–947.
8. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; 350: 1013–1022.
9. U.S. Department of Health and Human Services. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, https://www.fda.gov/media/71372/download (accessed October 2005).
10. Moss AJ, Schwartz PJ, Crampton RS, *et al.* The long QT syndrome: a prospective international study. *Circulation* 1985; 71: 17–21.
11. Woosley RL, Heise CW , Gallo T, et al. QTdrugs List, www.CredibleMeds.org (accessed 23 July 2020).
12. Kannel WB and Pinsky JL. Trends in cardiac failure incidence and causes of three decades in the Framingham study. *J Am Coll Cardiol* 1991; 17: 87A.
13. Taylor SH. Diuretic therapy in congestive heart failure. *Cardiol Rev* 2000; 8: 104–114.
14. Kay GN, Plumb VJ, Arciniegas JG, *et al.* Torsades de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. *J Am Coll Cardiol* 1983; 2: 806–817.
15. Wade OL. Drug therapy in the elderly. *Age Ageing* 1972; 1: 65–73.
16. American Geriatrics Society Beers Criteria® Update Expert Panel Fick DM, Semla TP, Steinman M, *et al.* 2019 American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019; 67: 674–694.
17. Motter FR, Fritzen JS, Hilmer SN, *et al.* Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. *Eur J Clin Pharmacol* 2018; 74: 679–700.
18. O'Mahony D, O'Sullivan D, Byrne S, *et al.* STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015; 144: 213–218.
19. Das B, Rawat VS, Ramasubbu SK, *et al.* Frequency, characteristics and nature of risk factors associated with use of QT interval prolonging medications and related drug–drug interactions in a cohort of psychiatry patients. *Therapies* 2019; 74: 599–609.

20. WHO collaborating centre for drug statistics methodology. ATC/DDD Index 2017, https://www.whocc.no/atc_ddd_index/ (accessed 23 July 2020).

21. Medscape drug interaction checker, https://reference.medscape.com/drug-interactionchecker (accessed 23 July 2020).

22. Epocrates online interaction check, https://online.epocrates.com/interaction-check (accessed 23 July 2020).

23. Drugs.Com drug interactions checker, https://www.drugs.com/drug_interactions.html (accessed 23 July 2020).

24. Heemskerk CPM, Pereboom M, van Stralen K, *et al*. Risk factors for QTc interval prolongation. *Eur J Clin Pharmacol* 2018; 74: 183–191.

25. Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: role of the pharmacist in risk assessment, prevention and management. *Can Pharm J* 2016; 149: 139–152.

26. Mok NS, Tong CK and Yuen HC. Concomitant-acquired long QT and Brugada syndromes associated with indapamide-induced hypokalemia and hyponatremia. *Pacing Clin Electrophysiol* 2008; 31: 772–775.

27. Kumar A, Bhandari AK and Rahimtoola SH. Torsade de pointes and marked QT prolongation in association with hypothyroidism. *Ann Intern Med* 1987; 106: 712–713.

28. Koh TW. Risk of torsades de pointes from oral erythromycin with concomitant carbimazole (methimazole) administration. *Pacing Clin Electrophysiol* 2001; 24: 1575–1576.

29. Salem J-E, Waintraub X, Courtillot C, *et al*. Hypogonadism as a reversible cause of torsades de pointes in men. *Circulation* 2018; 138: 110–113.

30. Salem J-E, Alexandre J, Bachelot A, *et al*. Influence of steroid hormones on ventricular repolarization. *Pharmacol Ther* 2016; 167: 38–47.

31. Sitruk-Ware R. Pharmacological profile of progestins. *Maturitas* 2008; 61: 151–157.

32. Salem J-E, Dureau P, Bachelot A, *et al*. Association of oral contraceptives with drug-induced QT interval prolongation in healthy nonmenopausal women. *JAMA Cardiol* 2018; 13: 877–882.

33. Bjerrum L, Rosholm JU, Hallas J, *et al*. Methods for estimating the occurrence of polypharmacy by means of a prescription database. *Eur J Clin Pharmacol* 1997; 53: 7–11.

34. Moreno-Gutierrez PA, Gaviria-Mendoza A, Canon MM, *et al*. High prevalence of risk factors in elderly patients using drugs associated with acquired torsades de pointes chronically in Columbia. *Br J Clin Pharmacol* 2016; 82: 504–511.

35. Beuscart J-B, Ficheur G, Miqueu M, *et al*. Co-prescriptions of psychotropic drugs to older patients in a general hospital. *Eur Geriatr Med* 2017; 8: 84–89.

36. Vandael E, Marynissen T, Reyntens J, *et al*. Frequency of use of QT-interval prolonging drugs in psychiatry in Belgium. *Int J Clin Pharm* 2014; 36: 757–765.

37. Curtis LH, Ostbye T, Sendersky V, *et al*. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. *Am J Med* 2003; 114: 135–141.

38. Khan K, Ismail M, Haider I, *et al*. 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: 1256–1264.

39. Al-Azayzih A, Gharaibeh S, Jarab AS, *et al*. Prevalence of torsades de pointes inducing drugs usage among elderly outpatients in North Jordan hospitals. *Saudi Pharm J* 2018; 26: 1146–1154.

40. Ray WA, Chung CP, Murray KT, *et al*. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; 360: 225–235.

41. Chrysant SG. Proton pump inhibitor-induced hypomagnesemia complicated with serious cardiac arrhythmias. *Expert Rev Cardiovasc Ther* 2019; 17: 345–351.

42. Lee DY, Trinh T and Roy SK. Torsades de Pointes after Ondansetron Infusion in 2 Patients. *Tex Heart Inst J* 2017; 44: 366–369.

43. Mason JW. Antimicrobials and QT prolongation. *J Antimicrob Chemother* 2017; 72: 1272–1274.

44. Bakshi R, Hermeling-Fritz I, Gathmann I, *et al*. An integrated assessment of the clinical safety of artemether-lumefantrine: a new oral fixed-dose combination antimalarial drug. *Trans R Soc Trop Med Hyg* 2000; 94: 419–424.

45. Johannes CB, Varas-Lorenzo C, McQuay LJ, *et al*. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case–control study. *Pharmacoepidemiol Drug Saf* 2010; 19: 881–888.

46. Vogel SM, Mican LM and Smith TL. Donepezil-induced QTc prolongation: a case report. *Mental Health Clinician* 2019; 9: 128–132.

47. Kajitani K, Yanagimoto K, Monji A, *et al*. Memantine exacerbates corrected QT interval

prolongation in Alzheimer's disease: a case report from an unintentional rechallenge. *J Am Geriatr Soc* 2016; 64: 232–233.

48. Beach SR, Celano CM, Noseworthy PA, *et al*. QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics* 2013; 54: 1–13.
49. Haueis P, Greil W, Huber M, *et al*. Evaluation of drug interactions in a large sample of psychiatric inpatients: a data interface for mass analysis with clinical decision support software. *Clin Pharmacol Ther* 2011; 90: 588–596.
50. Sarganas G, Garbe E, Klimpel A, *et al*. Epidemiology of symptomatic drug-induced long QT syndrome and torsades de pointes in Germany. *Europace* 2014; 16: 101–108.
51. Vandael E, Vandenberk B, Willems R, *et al*. Risk management of hospitalized psychiatric patients taking multiple QTc-prolonging drugs. *J Clin Psychopharmacol* 2017; 37: 540–545.
52. Shah AA, Aftab A and Coverdale J. QTc prolongation with antipsychotics: is routine ECG monitoring recommended. *J Psychiatr Pract* 2014; 20: 196–206.
53. Leiberman JA, Merrill D, Parameswarain S, *et al*. APA guidance on the use of antipsychotic drugs and cardiac sudden death, https://omh.ny.gov/omhweb/advisories/adult_antipsychotic_use_attachement.html (accessed 23 July 2020).
54. Soerensen AL, Lisby M, Nielsen LP, *et al*. Improving medication safety in psychiatry–a controlled intervention study of nurse involvement in avoidance of potentially inappropriate prescriptions. *Basic Clin Pharmacol Toxicol* 2018; 123: 174–181.
55. Kolshus E, Freyne A, Callanan I, *et al*. Psychotropic prescribing in the oldest old attending a geriatric psychiatry service: a retrospective, cross-sectional study. *Ir J Psychol Med* 2013; 30: 187–196.
56. Al-Omar HA, Al-Sultan MS and Abu-Auda HS. Prescribing of potentially inappropriate medications among the elderly population in an ambulatory care setting in a Saudi military hospital: trend and cost. *Geriatr Gerontol Int* 2013; 13: 616–621.
57. Leong C, Alessi-Severini S, Enns MW, *et al*. Cerebrovascular, cardiovascular, and mortality events in new users of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors: a propensity score-matched population-based study. *J Clin Psychopharmacol* 2017; 37: 332–340.
58. Byerly MJ, Weber MT, Brooks DL, *et al*. Antipsychotic medications and the elderly. *Drugs Aging* 2001; 18: 45–61.
59. Miller DD, Caroff SN, Davis SM, *et al*. Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry* 2008; 193: 279–288.
60. Barnes T, Davison S, Ferrier IN, *et al. Consensus statement on high-dose antipsychotic medication*. London: Royal College of Psychiatrists, 2005.
61. Ames D, Camm J, Cook P, *et al*. Minimizing the risks associated with QTc prolongation in people with schizophrenia. A consensus statement by the Cardiac Safety in Schizophrenia Group. *Encephale* 2002; 28: 552–556.