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Coprescription of QT interval-prolonging antipsychotics with potentially interacting medications in Thailand

Onanong Waleekhachonloet, Chulaporn Limwattananon and Thananan Rattanachotphanit

Abstract

Background: The US FDA has designated pimozide, thioridazine, and ziprasidone as contraindicated for patients at risk of QT interval prolongation, and assigned haloperidol, olanzapine, paliperidone, quetiapine, and risperidone as associated with a significant risk of QT prolongation. This study aimed to examine trends and hospital variations in concomitant prescribing among these eight selected antipsychotics, and coprescription with interacting drugs known to increase QT prolongation risk.

Methods: Data on outpatient antipsychotic prescriptions during 2012–2015 were obtained from 16 general hospitals and 10 university hospitals nationwide. A time-series analysis was used for estimating trends in coprescription that led to drug interactions.

Results: Coprescribing among the eight antipsychotics ranged from 7.5% for quetiapine to 33.1% for thioridazine. The rate of coprescription with contraindicated interacting drugs was 9.7% for thioridazine and 21.9% for pimozide, and increased by 1.1 and 1.4 percentage points (% pt.) yearly for thioridazine in general and university hospitals, respectively. Coprescribing with interacting drugs with precautions was 2.8% for quetiapine, 7.4% for ziprasidone, and 27.9% for risperidone; these percentages increased yearly by 1.7% pt. for ziprasidone and 2.6% pt. for risperidone in general hospitals, as well as by 1.0% pt. for risperidone in university hospitals. The median proportion of patients exposed to a QT-prolonging interaction was 12.3% across hospitals (interquartile range, 9.9–19.5%). Wide interhospital variation was found in percentages of drug interactions among patients receiving thioridazine, ziprasidone, paliperidone, or olanzapine in general hospitals, and among patients receiving paliperidone or pimozide in university hospitals.

Conclusions: Coprescription of antipsychotics with interacting drugs that could increase the risk of QT prolongation was common in Thailand, and thioridazine, ziprasidone, and risperidone showed increasing trends. We urge the incorporation of a unified list of QT-prolonging antipsychotics and interacting drugs into a computerized drug interaction warning system, and existing national rational drug use campaigns should cover this important issue.

Keywords: antipsychotics, coprescription, drug interactions, QT interval-prolonging

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Introduction

Prolongation of the QT interval can trigger erratic cardiac arrhythmias such as *Torsade de Pointes* (TdP). TdP, characterized by changes in amplitude and twisting of the QRS complex around the isoelectric line on an electrocardiogram (ECG), may result in deterioration due to ventricular tachycardia and fibrillation, leading to sudden cardiac death.[1] The QT interval is the time in milliseconds (ms) between ventricular depolarization and repolarization, as measured by an ECG. Because the QT interval is inversely proportional to the heart rate, the corrected QT interval (QTc), an approximation of the QT

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interval at a heart rate of 60 beats per minute, is used to assess abnormalities in the QT interval.[2] The widely used formula for calculating QTc equates QTc to the QT interval divided by squared root of the cardiac cycle.[3] Based on US Food and Drug Administration (FDA) guidance for industry on the clinical evaluation of QT/QTc interval prolongation, a prolonged QTc interval is defined by a 20-ms increase above the normal level, or >450 ms in men and >470 ms in women.[4] A recent meta-analysis reported that QT prolongation increases both total mortality [relative risk (RR), 1.35; 95% CI, 1.24–1.46] and cardiac mortality (RR, 1.51; 95% CI, 1.29–1.78).[5]

Postmarketing surveillance using large databases has provided evidence that QT prolongation and an increased risk of cardiac arrhythmia are associated with the use of certain antipsychotic drugs. A study monitoring intraindividual changes in ECGs reported 10- to 17-ms changes in the QTc in patients who took quetiapine, thioridazine, risperidone, haloperidol, clozapine, pimozide, ziprasidone, or chlorpromazine for an average of 0.8 years.[6] Moreover, approximately 50% of patients exposed to these drugs had a QTc increase of 20 ms or more.[6] A cross-sectional study of psychiatric services in Italy ($n = 2411$) reported QTc prolongation >450 ms in 14.7% of men and 18.6% of women, and >500 ms in 1.3% of men and 1.0% of women when two or more antipsychotics were prescribed concomitantly.[7] Among patients receiving antipsychotics with a known risk of QT prolongation, ventricular arrhythmia or sudden death rates of 0.14–0.67 per 100 person-years have been reported.[8–10] A meta-analysis of six observational studies reported that quetiapine, olanzapine, haloperidol, risperidone, clozapine, and thioridazine were associated with increased sudden cardiac death with an odds ratio between 1.72 and 4.58.[11]

Concomitant use of antipsychotics to improve treatment outcomes is common. For schizophrenia treatment, concomitant use of antipsychotics was found in 23% of patients in the US,[12] and ranged from 26.2% to 74.0% in Hong Kong, Taiwan, China, Korea, Japan, and Singapore.[13] Concomitant use of QT-prolonging antipsychotics and cytochrome P450 2D6 and 3A4 inhibitors such as fluoxetine, sertraline, azole antifungals, and protease inhibitors could potentiate the risk of QT prolongation.[14,15] Apart from antiarrhythmics, other drugs, such as certain macrolides, antidepressants, and second- and third-generation quinolones, have been well documented to pose a risk of QT prolongation, and caution should be taken when coprescribing such drugs with antipsychotics.[14,15]

A limited number of studies have focused on QT prolongation associated with drugs interacting with antipsychotics.[16–18] An analysis of Medicaid data during 2000–2003 in patients with schizophrenia in the US showed that 23% of the patients were exposed to potentially harmful drug interactions.[16] The majority of the interactions occurred with prescriptions from the same physician or pharmacies. A study including six psychiatric hospitals in Belgium in 2008 found that 7.3% of patients were coprescribed antipsychotics or antidepressants with interacting drugs that posed a risk of prolonged QT, and that different precautionary approaches were implemented at different hospitals.[17] A recent study from Pakistan reported that 51.7% of patients in the psychiatric wards of three hospitals in 2015–2016 were exposed to potential QT-prolonging drug interactions.[18]

Several recommendations for dealing with antipsychotics that pose a risk of QT prolongation, as well as lists of potential drug–drug interactions, are presently available.[1,14,15,19,20] After safety warnings on QT prolongation risk due to thioridazine and haloperidol were announced by regulatory agencies in the UK in 2000 and in Italy in 2007, prescription of these two antipsychotics decreased.[21] In the era of computerized drug prescriptions, awareness of drug interactions and adherence to electronic warnings are expected to increase. However, trend analysis of QT-prolonging antipsychotic-drug interaction has never been reported, and variations in the problem across a large number of hospitals have rarely been analyzed.

With the increasing disease burden of psychiatric patients in Thailand, a number of patients with psychiatric disorders currently receive follow-up care in outpatient departments of general hospitals.[22] In the last decade, computerized warning systems for drug interactions have been implemented widely in Thailand for hospitals to earn accreditation. Individual hospitals use their own discretion in selecting the drug lists to be monitored for potential interaction. In addition, the country's regulatory agency has not addressed the

safety concerns about prescribing QT-prolonging antipsychotics. It is important to understand the proportion of coprescribing QT-prolonging antipsychotics and interacting drugs, especially those classified to have a severe level of drug–drug interaction.

This study aimed to determine the proportion of patients who were coprescribed antipsychotics with potentially interacting drugs, along with their risk of QT prolongation, in outpatient departments of nonpsychiatric hospitals. Exposure to potential drug interactions was examined for time trends and variation across hospitals. Findings from this study can signal an urgent need for strategies to improve awareness and preventive measures for QT-prolonging antipsychotic-drug interaction. Additionally, the evidence for QT changes and outcomes of ventricular arrhythmia and sudden death was reviewed to support the inclusion of study drugs.

Methods

Interactions of antipsychotics and drugs with potential QT prolongation risk

The AZCERT classification (version May 2015)[20] was used to screen the 15 antipsychotics available at the study hospitals and prescribed for more than 50 patients during study period (2012– 2015) for potential risk of QT interval prolongation. Four antipsychotics (chlorpromazine, haloperidol, pimozide, and thioridazine) were classified as known risk of TdP, and seven antipsychotics (aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) were classified as possible risk of TdP. The US FDA product information was used to select the study antipsychotics, and an extensive review of evidence indicating QT prolongation and clinical risks of the selected drugs was used for verification. Eight antipsychotics (haloperidol, pimozide, thioridazine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) were included in the present study. The supporting evidence for their inclusion is presented in Table 1. The US FDA designated pimozide, thioridazine, and ziprasidone as contraindicated for patients at high risk of QT interval prolongation, and the remaining five drugs were associated with a significant risk of QT prolongation. Aripiprazole was not selected because the US FDA has not issued any warning for the drug regarding QT prolongation. Although chlorpromazine has long been used, the US FDA indicated that it was associated with very few case reports of QT prolongation.[23] Chlorpromazine and clozapine were not classified as having a significant risk of QT prolongation by the European Medicines Agency;[19,24] hence, they were excluded.

Concomitant prescribing among the eight selected antipsychotics (namely, antipsychotic polypharmacy) and those coprescribed with interacting drugs known to increase QT prolongation risk were examined. The interacting drugs were identified using both US FDA product information (in two sections, namely, Contraindications and Precautions and warnings) and the textbook *Drug Interaction Facts: the authority on drug interaction 2015*.[15] The selected pairs of drug interactions must be assigned a significance rating of level 1 by the Drug Interaction Facts textbook, defined as a severe (referred to as life-threatening or permanent damage) and be a well-documented interaction.[15]

Potential QT-prolonging drug interactions were divided into three types. The first (referred to as list A) was concomitant use among the eight study antipsychotic drugs. The second (list B) was the concomitant use of thioridazine or pimozide with contraindicated interacting drugs. The third (list C) was the concomitant use of the eight study antipsychotics with interacting drugs with precautions. The contraindication list B and precaution list C were based on drug interaction mechanisms derived from US FDA product information and the Drug Interaction Facts textbook.[15] Other than thioridazine and pimozide, the other six study antipsychotics had only interacting drugs with precautions (list C) (Table 2). To facilitate data presentation for trend analysis, thioridazine and pimozide were in the first set, and all remaining drugs were assigned to the second set.

Data sources

We obtained data on antipsychotic prescriptions from a public health insurance scheme that covers approximately 5 million government employees, pensioners, and their dependents. The beneficiaries of this scheme tend to have a higher socioeconomic status than the average Thai population, and obtain access to health services and prescription drugs free of charge. The data were from 16 general hospitals and 10 university hospitals

Table 1. Summary of evidence on risk of QT prolongation for study antipsychotics*.

Drug	Experiment			RCT			Meta-analysis of RCTs		Observational study					
									VA or SD			QT interval		
	N	Dose (mg/day)	QT change (ms, range)	*N*	Dose (mg/day, range of mean)	QT prolongation, no. of studies (% of patients)§	*N* RCTs	QT difference from placebo, SMD (95% CrI)	*N*	Incidence (per 1000 person-years, range)	Rate ratio (range)	*N*	Change, ms (95% CI)	Prolongation, % of patients‡
Haloperidol	2[25,26]	4–5	3–4	3[38–40]	8.9–11.5	1 (3%)	21[67]	0.11 (0.03, 0.19)	5[8–10, 68,69]	2.7–6.7	1.6–2.5	1[6]	12.3 (8.5, 16.1)	47.9%
	3[27–29]	10–30	5–7											
Pimozide	1[30]	6	13.3	N/A	–	–	N/A	–	N/A	–	–	N/A	–	–
	2[25,26]	7–10	19–24											
Thioridazine	2[31,32]	50	22–37	N/A	–	–	N/A	–	3[8–10]	2.2–4.1	2.2–3.2	N/A	–	–
	1[29]	300	35.6											
Olanzapine	2[29,33]	20	3–8	14[41–54]	10–17.5	1 (3%)	14[67]	0.22 (0.11, 0.31)	3[8–10]	2.8–3.4	1.4–2.0	N/A	–	–
Paliperidone	1[34]	4–8 (IR)	9–10	5[46,49, 55–57]	3–12 (ER)	1 (1%)	8[67]	0.05 (–0.18, 0.26)	N/A	–	–	N/A	–	–
	1[35]	12–18 (ER)	1–4											
Quetiapine	4[29,35–37]	750–800	6–14	3[48,58,59]	307–543	1 (3%)	7[67]	0.17 (0.06, 0.29)	3[8–10]	2.3	1.4–1.8	1[6]	10.1 (7.9, 12.2)	45.5%
Risperidone	1[29]	16	11	8[43,48, 54,60–64]	4–8	2 (3%, 4.5%)	11[67]	0.25 (0.15, 0.36)	4[8–10,68]	3.5–5.0	1.6–3.1	1[6]	11.0 (8.7, 13.4)	49.0%
Ziprasidone	1[28]	40	4.5	7[38,42, 45,48, 53,65,66]	104–139	1 (1%)	4[67]	0.41 (0.31, 0.51)	1[10]	1.4	–	1[6]	14.5 (10.7,18.3)	59.1%
	3[28,29,36]	160–320	15–23											

CI, confidence interval; CrI, credible interval; ER, extended release; IR, immediate release; mg, milligram; ms, millisecond; N, number of studies; N/A, not available; RCT, randomized controlled trial; SD, sudden cardiac death; SMD, standardized mean difference; VA, ventricular arrhythmia.

* The bibliographies of review articles, systematic reviews and meta-analysis of antipsychotics and QT change were manually scanned for relevant studies. An electronic search was conducted using PubMed and Google search engine up to April 30, 2018 for additional studies. The search terms included 'antipsychotics', 'thioridazine', 'pimozide', 'haloperidol', 'olanzapine', 'paliperidone', 'quetiapine', 'risperidone', 'ziprasidone', 'QT change', 'ECG change', 'ventricular arrhythmia', and 'sudden death'.

§ QTc >450 ms in men or >470 ms in women, or an increase in QT interval ⩾10%.

‡ An increase in QT interval ⩾20 ms.

Table 2. Lists of antipsychotic–other drug interactions and mechanisms.

Antipsychotics	Interacting drugs		Mechanism[14,15]
	List*	Drug names	
Thioridazine	B	duloxetine, fluoxetine, fluvoxamine, paroxetine, pindolol, propranolol	Inhibit CYP2D6 leading to delayed thioridazine metabolism.
Pimozide	B	itraconazole, ketoconazole, amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lonavir/ritonavir, nelfinavir, ritonavir, saquinavir, nefazodone	Inhibit CYP3A4 leading to delayed pimozide metabolism.
	B	azithromycin, clarithromycin, erythromycin, citalopram, escitalopram	Increase risk of QT prolongation
	B	sertraline	Increase pimozide plasma level
	B	aprepitant, fluoxetine, fluvoxamine, paroxetine	Inhibit CYP2D6 leading to delayed pimozide metabolism.
	C	efavirenz, posaconazole, voriconazole	Inhibit CYP3A4 leading to delayed pimozide metabolism.
Haloperidol, Pimozide, Thioridazine, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone,	C	amiodarone, disopyramide, dofetilide, procainamide, quinidine, sotalol, cisapride, gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin, arsenic trioxide, chlorpromazine, droperidol, mefloquine, pentamidine, tacrolimus	Increase risk of QT prolongation.
Risperidone	C	fluoxetine, paroxetine, sertraline	Inhibit CYP2D6 leading to delayed risperidone metabolism

*List B, contraindicated, interacting drugs; List C, interacting drugs with precautions
CYP, cytochrome P450.

nationwide, at which outpatient drug expenditures accounted for approximately 70% of the scheme's budget. These study hospitals are among the largest tertiary care facilities, with approximately 500–2000 beds and more than 100,000 outpatient visits each year. In Thailand, patients with psychiatric conditions can have their first visits and follow-up care in health care facilities other than psychiatric hospitals. Drug prescriptions are usually filled in the hospitals' outpatient departments, and one prescription may contain more than one drug item. The data analyzed included drug names, prescribing dates, encrypted patient identification, and hospital codes that had been validated through the fee-for-service claim process. Different identification codes of individually prescribed drugs across hospitals were standardized using the Anatomical Therapeutic Chemical (ATC) classification system, based on ATC level 5, generic name equivalence.[70] The analytic dataset consisted of adult (aged ⩾18 years) patients receiving antipsychotics (ATC code, N05A) and possibly other drugs during 2012–2015. The authors could not obtain access to data on drug dosage regimens, patient demographics, diagnoses for visits, and identification of the doctors who prescribed the drugs. Previous studies on antipsychotic prescribing patterns in Thailand, which have typically been conducted in university hospitals, reported that most patients received drugs at low-to-moderate doses.[71–73] Therefore, the analysis framework

focused on drug interaction patterns with respect to time trends and hospital variations. This study was approved by the Ethics Committee for Human Research, Khon Kaen University (HE592234).

Data analysis

Coprescription of selected antipsychotics with drugs in lists A (antipsychotic polypharmacy), B (contraindicated interacting drugs), and C (interacting drugs with precautions) was identified when the drugs appeared in the same prescriptions. In an overall analysis, the patient cohort over 4 years of study period was accounted for those receiving antipsychotics and for those exposed to each drug pair of potential interactions. The number of patients receiving selected antipsychotics, and the proportion of those exposed to potential interactions with drugs in lists A, B, and C, were calculated yearly with respect to facility types (general hospitals and university hospitals). For patients exposed to more than one pair of drug interactions, each exposure was counted separately. Drug interactions were examined for trends using a time-series analysis. The percentages of patients receiving each of the eight antipsychotics and exposed to the drug interactions in each type (list A, B, or C) was regressed on yearly time points. To account for a serial correlation between observations in adjacent years, a generalized least square that accounted for the correlation was applied using Prais-Winsten transformation.[74] Significant threshold (alpha level) for the statistical tests was set at 0.05. Variation across hospitals in 2015 in the overall drug interactions that led to potential risk of QT prolongation for each selected antipsychotic was examined. The percentage of hospitals with a presence of the coprescribing of antipsychotics with potentially interacting drugs was presented. In addition, median and interquartile range (IQR) across hospitals of the percentage of patients being exposed to the potential drug interactions were determined.

Results

In total, 156,615 antipsychotic prescriptions were written for 26,288 patients during the study period (2012–2015). There were 17 antipsychotics prescribed in total. The three most commonly prescribed antipsychotics were quetiapine (42.4%), risperidone (25.1%), and haloperidol (19.6%). The other five antipsychotics were each prescribed to less than 10% of patients: olanzapine (6.0%), thioridazine (3.2%), ziprasidone (1.2%), paliperidone (1.0%), and pimozide (0.3%).

The analytic dataset contained 22,397 patients with 128,333 prescriptions for the eight study antipsychotics with a risk of potential QT prolongation. Study patients having one, two, three, four, five, six, and more than six prescription visits accounted for 31.8%, 15.1%, 8.4%, 6.0%, 4.7%, 3.8%, and 30.1% of the prescriptions, respectively. The number of patients receiving each study drug over 4 years is presented in Table 3 (first column). The proportion of patients receiving antipsychotic polypharmacy with a risk of QT prolongation (list A) was highest for thioridazine (33.1%), followed by ziprasidone (25.5%), pimozide (24.7%), paliperidone (22.7%), olanzapine (16.9%), risperidone (10.4%), haloperidol (8.7%), and quetiapine (7.5%) (Table 3).

Of the 849 recipients of thioridazine, 4 received thioridazine and pimozide concomitantly. Apart from pimozide, the antipsychotics in list A that were most commonly prescribed with thioridazine were risperidone, haloperidol, and quetiapine. Apart from the antipsychotic polypharmacy, 9.7% of thioridazine recipients were prescribed concomitantly with contraindicated, interacting drugs (list B), and 2.1% of them were prescribed concomitantly with interacting drugs with precautions (list C). Among list B, fluoxetine and propranolol were the top two drugs prescribed concomitantly with thioridazine. Of the 73 recipients of pimozide, apart from the antipsychotic polypharmacy, 21.9% were prescribed concomitantly with drugs in list B and 5.5% were prescribed concomitantly with those in list C.

In addition to thioridazine and pimozide, the six antipsychotics (as in Table 3) were coprescribed with interacting drugs with precautions (list C) in the range between 2.8% of quetiapine recipients ($n = 11{,}144$) and 27.9% of risperidone recipients ($n = 6600$). By the number of patients receiving quetiapine, the top three coprescribed antipsychotics on list A were risperidone, haloperidol, and olanzapine; the top three coprescribed drugs on list C were levofloxacin, amiodarone, and chlorpromazine. For risperidone recipients, the top three coprescribed antipsychotics on list A apart from quetiapine were haloperidol and

Table 3. Number of patients prescribed QT-prolonging antipsychotics with interacting drugs during study period.

Antipsychotics (no. of patients)	Potential drug interaction		
	List*	No. of patients (%)	Concomitant drugs (no. of patients)[$]
Thioridazine (849)	A	281 (33.1)	RPD (99), HAL (94), QTP (47), OZP (20), QTP+RPD (8), ZPS (3), HAL+ZPS (2), HAL+QTP (1), PPD (1), PMZ (1), PMZ+RPD (1), PMZ+QTP (1), OZP+RPD (1), HAL+RPD (1), PMZ+QTP+RPD (1)
	B	82 (9.7)	FOX (42), PPL (34), FVX (4), PRX (1), FVX+PPL (1)
	C	18 (2.1)	CPZ (12), LVF (5), AMD (1)
Pimozide (73)	A	18 (24.7)	RPD (5), QTP (4), OZP (2), HAL (2), TRZ (1), OZP+QTP (1), TRZ+QTP+RPD (1), TRZ+QTP (1), TRZ+RPD (1)
	B	16 (21.9)	FOX (5), STL (5), ESC (3), FVX (3)
	C	4 (5.5)	CPZ (4)
Quetiapine (11,144)	A	837 (7.5)	RPD (382), HAL (213), OZP (119), TRZ (47), ZPS (30), PPD (16), TRZ+RPD (8), HAL+RPD (6), PMZ (4), RPD+PPD (2), OZP+RPD (3), HAL+TRZ (1), TRZ+PMZ (1), PMZ+OZP (1), ZPS+PPD (1), ZPS+RPD (1), HAL+OZP (1), TRZ+PMZ+RPD (1)
	C	311 (2.8)	LVF (117), AMD (100), CPZ (67), MXF (22), CSP (3), TAC (2)
Risperidone (6600)	A	688 (10.4)	QTP (382), TRZ (99), HAL (76), OZP (68), PPD (20), ZPS (14), TRZ+QTP (8), HAL+QTP (6), PMZ (5), QTP+PPD (2), OZP+QTP (3), TRZ+OZP (1), PMZ+TRZ (1), TRZ+HAL (1), ZPS+QTP (1), PMZ+QTP+TRZ (1)
	C	1,840 (27.9)	STL (935), FOX (613), CPZ (167), PRX (32), LVF (22), CPZ+FOX (21), CPZ+STL (16), AMD (13), TAC (4), FOX+STL (4), AMD+STL (2), AMD+FOX (2), MXF (2), LVF+STL (2), AMD+MXF (1), MXF+STL (1), CSP (1), CPZ+PRX (1), PRX+STL (1)
Haloperidol (5148)	A	446 (8.7)	QTP (213), TRZ (94), RPD (76), OZP (28), ZPS (18), QTP+RPD (6), PPD (4), TRZ+ZPS (2), PMZ (2), TRZ+QTP (1), TRZ+RPD (1), OZP+QTP (1)
	C	215 (4.2)	CPZ (171), LVF (22), AMD (17), TAC (3), MXF (2)
Olanzapine (1572)	A	265 (16.9)	QTP (119), RPD (68), HAL (28), TRZ (20), PPD (12), ZPS (9), QTP+RPD (3), PMZ (2), TRZ+RPD (1), PMZ+QTP (1), HAL+QTP (1), ZPS+PPD (1)
	C	53 (3.4)	CPZ (35), LVF (14), AMD (3), TAC (1)
Ziprasidone (325)	A	83 (25.5)	QTP (30), HAL (18), RPD (14), OZP (9), PPD (4), TRZ (3), HAL+TRZ (2), QTP+PPD (1), OZP+PPD (1), QTP+RPD (1)
	C	24 (7.4)	CPZ (23), LVF (1)
Paliperidone (269)	A	61 (22.7)	RPD (20), QTP (16), OZP (12), HAL (4), ZPS (4), QTP+RPD (2), TRZ (1), ZPS+QTP (1), ZPS+OZP (1)
	C	24 (8.9)	CPZ (21), LVF (2), AMD (1)

*List A, Antipsychotic polypharmacy; List B, contraindicated, interacting drugs; List C, interacting drugs with precautions.
[$]A patient may have more than one type of drug interaction.
AMD, amiodarone; CPZ, chlorpromazine; CSP, cisapride; ESC, escitalopram, FOX, fluoxetine; FVX, fluvoxamine; HAL, haloperidol; LVF, levofloxacin; MXF, moxifloxacin; OZP, olanzapine; PMZ, pimozide; PPD, paliperidone; PPL, propranolol; PRX, paroxetine; QTP, quetiapine; RPD, risperidone; STL, sertraline; TAC, tacrolimus; TRZ, thioridazine; ZPS, ziprasidone.

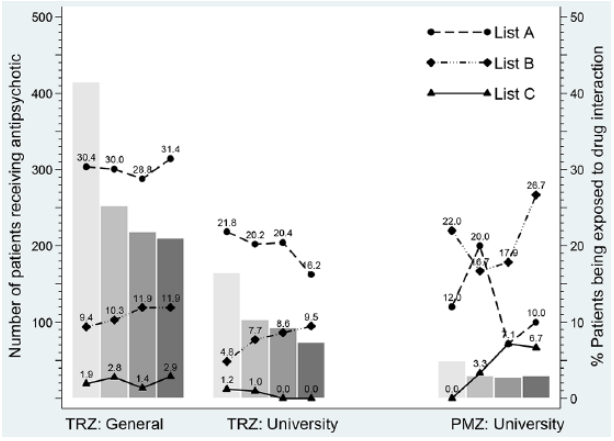

Figure 1. Patients who received thioridazine or pimozide and were exposed to drug interactions, 2012–2015. General, general hospitals; List A, antipsychotics polypharmacy; List B, contraindicated, interacting drugs; List C, interacting drugs with precautions; PMZ, pimozide; TRZ, thioridazine; University, university hospitals.

olanzapine; the top three coprescribed drugs on list C were sertraline, fluoxetine, and chlorpromazine. For haloperidol recipients ($n = 5148$), the top three coprescribed antipsychotics on list A apart from quetiapine and risperidone were olanzapine; the top three coprescribed drugs on list C were chlorpromazine, levofloxacin, and amiodarone. For olanzapine recipients ($n = 1572$), the top three coprescribed drugs on list A were quetiapine, risperidone, and haloperidol, as previously stated; the top three coprescribed drugs on list C were chlorpromazine, levofloxacin, and amiodaraone. For ziprasidone recipients ($n = 325$), the top three coprescribed drugs on list A were quetiapine, haloperidol, and risperidone. For paliperidone recipients ($n = 269$), the top three coprescribed drugs on list A were risperidone, quetiapine, and olanzapine. For ziprasidone and paliperidone, coprescribing with drugs in list C was found in 7.4% and 8.9%, respectively, where the most common interacting drug was chlorpromazine.

Figure 1 depicts trends in the number of patients receiving thioridazine or pimozide and the percentage of those exposed to QT-prolonging drug interactions during 2012–2015. The number of patients receiving thioridazine decreased gradually in both general hospitals and university hospitals. Pimozide was prescribed only in the university hospitals. For thioridazine recipients, an exposure to list A drug interactions in the general hospitals was relatively stable at 28.8–31.4% during the study period. An exposure to list B drug interactions of thioridazine increased in both hospital types from 9.4% to 11.9% or annually by 1.1 percentage points (% pt.) on average ($p < 0.001$) in general hospitals, and from 4.8% to 9.5% or annually by 1.4% pt. on average ($p = 0.033$) in university hospitals. For pimozide recipients in university hospitals, an exposure to list A drug interactions decreased from 12.0% to 10.0% from 2012 to 2015, while exposure to list B (from 22.0% to 26.7%) and list C (from 0.0% to 6.7%) drug interactions increased over the same period with zigzag trends.

Figure 2 depicts 2012–2015 trends in patients exposed to QT-prolonging interactions with drugs in list A or C among patients receiving six antipsychotics; the top three (quetiapine, risperidone, and haloperidol) are shown in Figure 2(a) and the bottom three antipsychotics (olanzapine ziprasidone, and paliperidone) are shown in Figure 2(b). For quetiapine recipients, an exposure to drug interactions did not show a noticeable time trend: for list A, the time trend was approximately 7–9% in general hospitals and 4–6% in university hospitals, and for list C it was 1.2–2.1% in both hospital types (Figure 2a). Among risperidone recipients, those exposed to list A drug interactions increased modestly from 5.4% to 6.3% in general hospitals and from 7.3% to 10.5% in university hospitals from 2012 to 2015. However, an exposure to list C drug interactions of risperidone recipients increased from 18.8% to 27.3% or by the annual average rate of 2.6% pt. ($p = 0.017$) in general hospitals and from

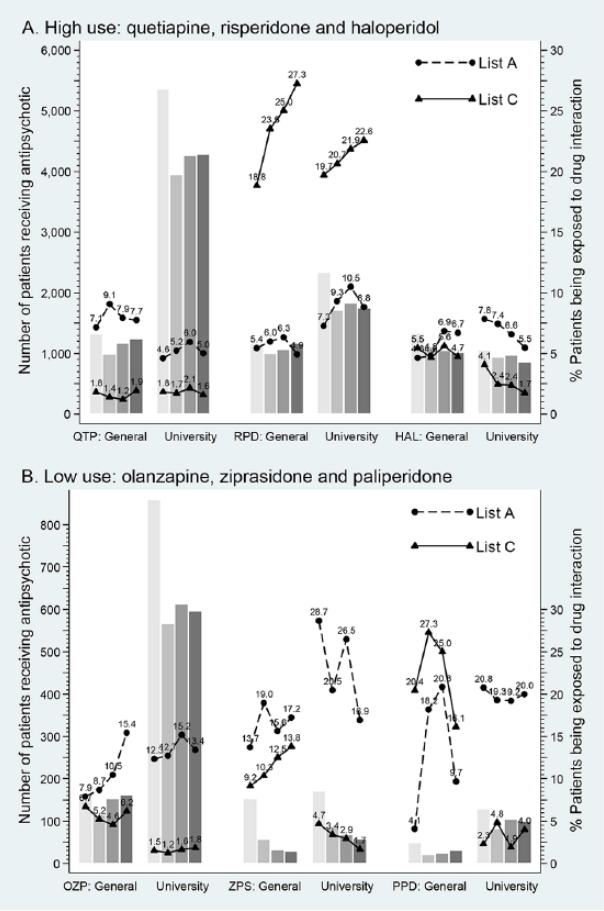

Figure 2. Patients who received antipsychotics and were exposed to drug interactions, 2012–2015.
General, general hospitals; HAL, haloperidol; List A, antipsychotics polypharmacy; List C, interacting drugs with precautions; OZP, olanzapine; PPD, paliperidone; QTP, quetiapine; RPD, risperidone; University, university hospitals; ZPS, ziprasidone.

19.7% to 22.6% or by the annual average rate of 1.0% pt. ($p < 0.001$) in university hospitals. For haloperidol recipients, an exposure to drug interactions was relatively stable in general hospitals for lists A and C, at approximately 4–7%. For university hospitals, haloperidol recipients exposed to list A drug interactions decreased from 7.8% to 5.5%, or by the annual average rate of 0.8% pt. ($p = 0.013$); those exposed to list C decreased from 4.1% to 1.7% or by the annual average rate of 0.6% pt. ($p = 0.046$).

For olanzapine recipients, an increasing trend in patients exposed to list A drug interactions was observed in general hospitals from 7.9% to 15.4% from 2012 to 2015, with an annual average change of 2.4% pt. ($p = 0.043$), whereas those exposed to drug interactions in lists A and C were relatively stable in university hospitals (Figure 2b). Even though the number of patients receiving ziprasidone and paliperidone was small, an exposure to drug interactions was high, except for list C in university hospitals. For ziprasidone, a zigzag trend was observed in patients exposed to drug interactions for list A, and an increasing trend of drug interactions for list C existed from 9.2% to 13.8% or by the annual average rate of 1.7% ($p < 0.001$) in general hospitals. These results contrasted with a zigzag trend observed for list A and a decreasing trend identified for list C from 4.7% to 1.7% or by the annual average rate of 0.9% pt. ($p < 0.001$) in university hospitals. Exposure to drug interactions with paliperidone in general hospitals had an inconsistent trend (4.1–20.8% for list A and 16.1–27.3% for list C), whereas those in university hospitals were relatively stable (19.2–20.8% for list A and 1.9–4.8% for list C).

Table 4. Hospitals with a presence of QT prolongation drug interaction and variation in patients exposed to the interactions in 2015.

Hospital types	Antipsychotics	No. of hospitals having drug	No. of patients receiving antipsychotics	% Hospitals with drug interactions	% Patients with drug interactions per hospital		
					Median	P25	P75
General hospitals	Haloperidol	16	1014	100.0	9.0	6.4	13.5
	Thioridazine	12	210	83.3	42.5	23.5	50.0
	Olanzapine	9	162	77.8	20.0	9.1	25.0
	Paliperidone	5	31	100.0	33.3	16.7	50.0
	Quetiapine	15	1241	86.7	9.8	5.8	14.1
	Risperidone	16	1174	93.8	32.1	27.6	37.5
	Ziprasidone	4	29	75.0	41.7	20.0	42.9
	Overall	16	3506	100.0	15.2	11.3	21.9
University hospitals	Haloperidol	10	859	90.0	6.8	5.5	13.0
	Pimozide	4	30	75.0	36.4	28.6	45.5
	Thioridazine	8	74	75.0	21.5	14.3	25.0
	Olanzapine	10	596	80.0	14.0	12.9	23.6
	Paliperidone	9	100	77.8	50.0	7.9	50.0
	Quetiapine	10	4293	100.0	7.6	5.2	14.1
	Risperidone	10	1754	100.0	29.0	21.9	30.7
	Ziprasidone	8	59	62.5	27.3	18.2	28.6
	Overall	10	7205	100.0	10.0	8.2	13.0
Overall		26	10,711	100.0	12.3	9.9	19.5

P25, 25th percentile; P75, 75th percentile.

The variations in the percentages of overall QT-prolonging drug interactions among general hospitals and university hospitals in 2015 are presented in Table 4. Almost all hospitals carried haloperidol, risperidone, quetiapine, and thioridazine, while few general hospitals had paliperidone and ziprasidone, and four university hospitals had pimozide. For all study drugs, the QT-prolonging interaction was found in 12.3% of patients of the median hospital (IQR, 9.9–19.5%). The overall interaction in the general hospitals (median 15.2%, IQR 11.3–21.9%) was higher than that in the university hospitals (median 10.0%, IQR 8.2–13.0%).

The QT-prolonging interactions were found in a majority of general hospitals, ranging from 75% for ziprasidone to 100% for haloperidol and paliperidone. Across general hospitals, wide variations in the percentages of drug interactions were observed among patients receiving thioridazine, ziprasidone, paliperidone, and olanzapine, as shown by a wide IQR, whereas small variations existed among patients receiving risperidone,

quetiapine and haloperidol. The proportion of university hospitals having patients exposed to QT-prolonging drug interactions ranged from 63% for ziprasidone to 100% for risperidone and quetiapine. Wide variations existed across university hospitals in the percentage of patients receiving paliperidone or pimozide with potential drug interactions.

Discussion

Coprescribing among the eight antipsychotics (list A) ranged from 7.5% for quetiapine to 33.1% for thioridazine. The rate of coprescription with contraindicated, interacting drugs (list B) was 9.7% for thioridazine and 21.9% for pimozide, and increased over the study period for thioridazine. Coprescription of interacting drugs with precautions (list C) was found in 27.9% of patients for risperidone and <10% of patients for other antipsychotics, with a significant increasing trend of risperidone. Significantly decreasing trends in coprescription of haloperidol (with lists A and C drugs) and ziprasidone (with list C drugs) were observed at the university hospitals. The median percentage of patients prescribed QT-prolonging interactions with any of the study antipsychotics per hospital was 12.3% overall, and 15.2% and 10.0% among the general and university hospitals, respectively. Wide interhospital variation in the percentage of drug interactions was found for thioridazine, ziprasidone, paliperidone, and olanzapine at the general hospitals, and for paliperidone and pimozide at the university hospitals.

Similar to findings in other countries,[12,13] the rate of concomitant prescribing of two or more QT-prolonging antipsychotics (list A) in Thailand was relatively high. Although QT-prolonging antipsychotics were known to clinicians, data on QT changes and clinical outcomes specific to each antipsychotic were scattered, and the associated risks were not presented in numerical formats. The relevant information, compiled in Table 1, was an attempt to fill knowledge gaps regarding the significance of QT-prolonging risk due to coprescribing of antipsychotics. Substitution of QT-prolonging antipsychotics with aripiprazole, which has no FDA warnings, is unlikely, as aripiprazole is a high-cost medicine without affordable generic versions. The relatively high percentage (22.7–33.1%) of coprescriptions for thioridazine, ziprasidone, and paliperidone was likely a reflection of the use of these drugs in a small group of patients not responding to conventional antipsychotics.

Coprescription of thioridazine with contraindicated, interacting drugs (list B) and risperidone with interacting drugs with precautions (list C) had not only a high prevalence but also an increasing trend. This finding reflected modest concerns of potential drug interactions by individual prescribers. Although computerized screening tools are widely available, individual hospitals may justify drug interaction lists based on their own circumstances. At present, there are no unified drug interaction lists in Thailand, and public advocacy on precautionary use of antipsychotics is rare. The Ministry of Public Health-sponsored campaign on rational drug use covered issues on drug interactions, but coprescribing of QT-prolonging antipsychotics was not a prioritized issue.[75] The national programs on pharmaceutical care for noncommunicable, chronic diseases that have been implemented in public hospitals for psychiatric conditions are still in their infancy.[76]

The decreasing trend in the coprescription of interacting drugs with precautions (list C) with haloperidol or ziprasidone at university hospitals may be driven by increasing varieties of substitutes in an open academic environment. Higher interhospital variation in the prevalence of drug interactions among general hospitals is an indication that antipsychotics could be prescribed by physicians other than psychiatrists – a practice that was common at the general hospitals but less common at the university hospitals.

Psychiatric conditions are complex, and treatments require a trade-off between efficacy and safety. Many patients continue to experience psychiatric symptoms after standard regimens of treatment. Polypharmacy may be used to achieve a faster therapeutic response. Patients who continue to use the same antipsychotics over a very long period tend to be unwilling to switch medicines, even though they may face treatment complications. In this study, there were no financial barriers to patient access to study antipsychotics, which were fully covered by the patients' insurance scheme. Therefore, the high prevalence of coprescription could probably be associated with use in low-risk patients as well as patient preference.

Some study limitations should be addressed. In this study, all selected antipsychotics were

prescribed in the outpatient setting. Even though health insurance claims are a valid data source for measuring drug exposure and associated risks, the prescription data used in this study limited further analyses of certain aspects. First, the antipsychotic exposure period could not be determined due to a lack of data on drug dosage regimens. The coprescribing rate reported in this study could be underestimated if the same patients were prescribed interacting drugs within the same exposure windows but not during the same prescription visits. Second, there were no linkable data on patient demographics, clinical conditions, laboratory results, or treatment outcomes. Future studies could complement the present study by using primary data collection from patients and prescribers to gain an understanding of the reasons behind the high coprescribing rates, and of the extent to which clinical and treatment conditions or lack of awareness among clinicians have contributed to the problem. In addition, whether the effect of drug interactions on QT prolongation varies with age, cardiovascular disease, smoking, alcohol, drug abuse, or other factors should be examined.

The findings in the present study touched upon clinically significant issues, since coprescription of antipsychotics with major drug interactions was analyzed and evidence supporting QT prolongation and associated clinical risks was summarized for the study antipsychotics. The study results could be generalized to outpatient care settings for the beneficiaries of this government employee scheme across the whole country since the study settings included a number of hospitals, mixed between the Ministry of Public Health's general hospitals and university teaching hospitals nationwide. The study patients were covered by an insurance scheme that provided generous health benefits packages to the beneficiaries, who bear no prescription drug costs. Therefore, the prevalence of drug interactions was unlikely to be confounded by financial barriers on the patient side.

The findings of high prevalence and increasing trends in the coprescribing rates for selected antipsychotics, and of wide variation across hospitals where computerized screening systems are available, implies that the issues of lack of awareness and knowledge in the medical community are applicable to Thailand. Medical education on the QT prolongation risk of antipsychotics could be integrated into the existing national rational drug use campaign, which has been successful in decreasing drug interactions with statins.[77] Protocols using appropriate risk scoring systems for identifying high-risk patients should be developed and implemented throughout the existing pharmaceutical care programs.[78–80] In addition to increasing clinicians' awareness and knowledge, it is necessary to develop unified drug interaction lists to decrease variation across prescribers and health care settings.

Conclusion

A large proportion of Thai patients received antipsychotics with a risk of drug interactions that could increase their risk of QT prolongation. Increasing trends of prescribing QT-prolonging drugs with drug interactions were found for three antipsychotics: thioridazine, risperidone, and ziprasidone. A variation in the percentage of drug interactions across hospitals was observed. A standard list of antipsychotics prone to QT-prolonging drug interactions along with a computerized warning system should be developed and implemented nationwide. In addition, supporting evidence on QT prolongation risk of antipsychotics and potential drug interactions should be integrated into the existing national rational drug use campaign.

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Author contributions

OW contributed to the study concept and design, analysis and interpretation of the data, and drafting of the paper. CL contributed to the study concept and design, analysis and interpretation of the data, drafting of the paper, and revising it critically for intellectual content. TR contributed to the analysis and interpretation of the data and the drafting of the paper. All authors were involved in final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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