ORIGINAL RESEARCH

Antipsychotic Drugs and the Risk of Ventricular Arrhythmia and/or Sudden Cardiac Death: A Nation-wide Case-Crossover Study

Chi-Shin Wu, MD, PhD; Yu-Ting Tsai, MS; Hui-Ju Tsai, MPH, PhD

***Background*—**Antipsychotics have been linked to prolongation of the QT interval. However, little is known about the risk of ventricular arrhythmia (VA) and/or sudden cardiac death (SCD) associated with individual antipsychotic drug use. This study was designed to investigate the association between specific antipsychotic drugs and the risk of VA and/or SCD.

***Methods and Results*—**We conducted a case-crossover study using a nation-wide population-based sample obtained from Taiwan's National Health Insurance Research Database. A total of 17 718 patients with incident VA and/or SCD were enrolled. Conditional logistic regression models were applied to examine the effects of antipsychotic drug use on the risk of VA/SCD during various case and control time windows of 7, 14, and 28 days. The effect of the potency of a human ether-à-go-go-related gene (hERG) potassium channel blockade was also assessed. Antipsychotic drug use was associated with a 1.53-fold increased risk of VA and/or SCD. Antipsychotic drugs with increased risk included clothiapine, haloperidol, prochlorperazine, thioridazine, olanzapine, quetiapine, risperidone, and sulpiride. The association was significantly higher among those with short-term use. Antipsychotics with a high potency of the hERG potassium channel blockade had the highest risk of VA and/or SCD.

***Conclusion*—**Use of antipsychotic drugs is associated with an increased risk of VA and/or SCD. Careful evaluations of the risks and benefits of antipsychotic treatment are highly recommended. **(*J Am Heart Assoc*. 2015;4:e001568 doi: 10.1161/JAHA.114.001568)**

Key Words: antipsychotics • sudden cardiac death • ventricular arrhythmia

Drug-induced ventricular arrhythmia (VA) and sudden cardiac death (SCD) are rare, but severe, adverse events (AEs).[1,2] Medications that could delay ventricular repolarization would provoke torsade de pointes, progress to VA, and consequently lead to SCD. The electrographic QT interval, which represents the time for ventricular depolarization and repolarization to occur, has been shown to be a surrogate marker for assessing the risk of torsade de pointes.[3] Almost all medications that prolong the QT interval also block the human ether-à-go-go-related gene (*HERG*) potassium ion channel.[4]

Antipsychotics are widely used in treating patients with schizophrenia, mood disorders, and certain somatic symptoms. Several antipsychotics, primarily first-generation antipsychotics (FGAs), were classified as torsadogenic drugs and carried a black box warning of sudden death.[5] Second-generation antipsychotics (SGAs), which characteristically cause less neurological adverse effects, have gradually replaced FGAs. In the past decade, concerns also have emerged about the cardiometabolic adverse effects of SGA use.[6]

Whether or not the risk of VA/SCD among SGA users is lower than that among FGA users remains inconclusive. Several studies have demonstrated that SGAs are associated with less torsadogenic risk than FGAs.[7–10] However, such findings could not be consistently confirmed.[11–13] These inconsistent findings were partially attributable to confounding by patient characteristics, such as baseline QT interval, cardiovascular (CV) status, and genetic factors,[14] which usually were unmeasured in observational studies. In addition,

From the Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City, Taiwan (C.-S.W.); College of Public Health, National Taiwan University, Taipei, Taiwan (C.-S.W.); Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan (C.-S.W.); Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan (Y.-T.T., H.-J.T.); Department of Public Health, China Medical University, Taichung, Taiwan (H.-J.T.); Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL (H.-J.T.).

Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/1/5/e001568/suppl/DC1

Correspondence to: Hui-Ju Tsai, MPH, PhD, Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, 35 Keyan Road Zhunan, Miaoli County 350, Taiwan. E-mails: tsaihj@nhri.org.tw, h-tsai@northwestern.edu

Received December 23, 2014; accepted January 24, 2015.

even in the same pharmacological class, there are marked differences in the associated risk of VA/SCD across individual antipsychotics. Meta-analyses of randomized, control trials have shown that the prolongation of QT interval varies across different SGAs.[15] Studies using an AE reporting system database also have indicated that some SGAs have a higher torsadogenicity than others.[16,17] Therefore, identifying antipsychotic drugs that increase the risk of VA/SCD is an important issue in clinical practice. However, owing to the low incidence of drug-induced VA/SCD, there have been relatively few studies to date that have explored the association of torsadogenic risk with individual antipsychotic use.

In this study, we used a case-crossover study design,[18] which is a method to eliminate between-person time-invariant confounders, to investigate the risk of VA/SCD with antipsychotic exposure in a nation-wide population-based claims database. Furthermore, we explored the relationships between antipsychotics with the potency of hERG potassium channels blockade and the risk of VA/SCD and investigated the moderating effects of patient characteristics on such associations.

Methods

Data Source

The National Health Insurance Research Database (NHIRD) is derived from the reimbursement medical claims of the National Health Insurance program in Taiwan, which launched on March 1, 1995. Since then, the NHIRD has collected demographic characteristics, disease diagnoses, and prescription records of out- and inpatient care claims data from Taiwan's National Health Insurance program enrollees representing ≈98% of the 23 million inhabitants in Taiwan.[19] In this study, we used the data set containing subjects who had at least 1 or more prescription records for antipsychotic medications during the period from January 2000 to December 2009. This study protocol was approved by the institutional review board of the National Health Research Institutes, Taiwan.

Study Subjects

Study outcome was defined as one of the following International Classification of Diseases, Ninth Revision, Clinical Modification, diagnostic codes: paroxysmal ventricular tachycardia (427.1); ventricular fibrillation and flutter (427.4); cardiac arrest (427.5); and instantaneous death (798.1); as well as sudden death occurring in less than 24 hours from onset of symptoms (798.2). We identified patients with above-mentioned diagnoses during the period between 2001 and 2009 through the medical records from emergency department (ED) visits or hospitalization claims data.[20,21] Onset of VA/SCD (index date) was defined as the date of the first-time diagnosis of VA/SCD. The exclusion criteria were described as follows: (1) patients aged less than 16 years at the index date; (2) prevalent cases who had any diagnosis of VA/SCD in 2000; (3) patients' sex was unknown; and (4) patients who had been hospitalized within 56 days before the index date. As a result, a total of 17 718 study subjects were included for subsequent analyses. Figure 1 presents a detailed flow chart regarding subject selection.

Exposure to Antipsychotics

The exposure variable was antipsychotic use, which was retrieved from the prescription records (including refills) collected in the NHIRD, which is derived from reimbursement medical claims of the National Health Insurance program in Taiwan. We defined antipsychotics (N05A) according to the Anatomic Therapeutic Chemical (ATC) classification system developed by the World Health Organization Collaborating Center.[22] We investigated the effect of antipsychotic exposure on the risk of VA/SCD in study subjects, based on their antipsychotic exposure status. Specifically, we defined study subjects with the presence of exposure to an antipsychotic if study subjects were identified with the prescription of a particular antipsychotic at least 1 day during the case or control time period. We classified each individual antipsy-

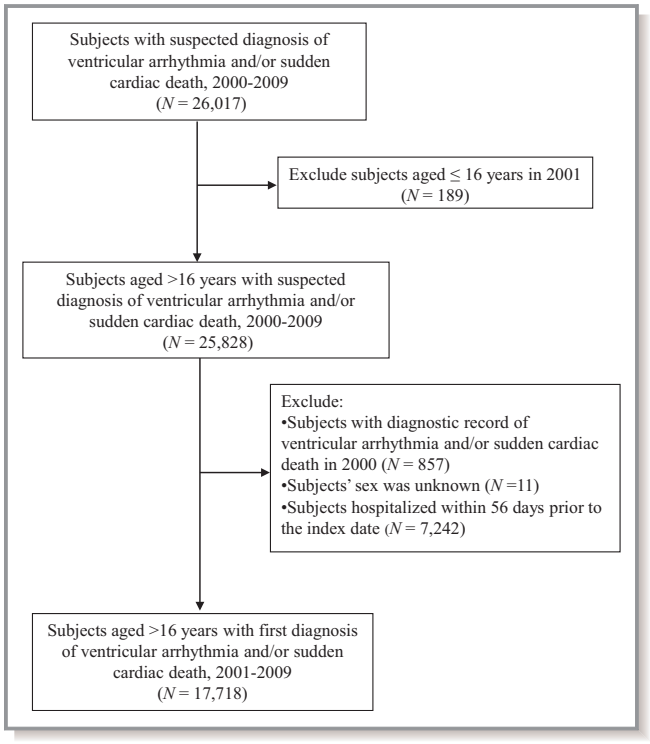

Figure 1. Flow diagram of criteria for inclusion and exclusion in the present study.

chotic drug examined in this study into either FGAs: chlorpromazine, clopenthixol, clothiapine, flupentixol, fluphenazine, haloperidol, loxapine, prochlorperazine, thioridazine, and trifluoperazine; or SGAs: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sulpiride, ziprasidone, and zotepine. Of note, lithium was classified as a mood stabilizer, rather than an antipsychotic drug, although it is coded as "N05AN01" in the ATC system.

Time-Varying Confounding Factors

Time-varying confounders in the subsequent analyses included: health care utilization (calculated as the number of outpatient visits during the case or control periods) and concomitant medication use, including cardiometabolic drugs: antidiabetic agents (A10), anticoagulants (B01), antiarrhythmics (ATC code: C01B), digoxin and other inotropic agents (C01A), nitrates (C01D), other antihypertensives (C02), diuretics (C03), angiotensin converting-enzyme inhibitors and angiotensin, β-blockers (C07), calcium-channel blockers (C08), receptor blockers (C09), statins and other lipid-lowering agents (C10); psychiatric drugs: antidepressants (N06A), antiepileptics (N03A), anxiolytics (N05B), benzodiazepines (ATC codes: N05BA, N05CD, and N05CF); and some drugs with torsadogenic risks, including antiemetics: domperidone; and antibiotics: clarithromycin, erythromycin, halofantrine, pentamidine, and sparfloxacin.

Data Analysis

We examined the associated risk of VA/SCD with antipsychotic exposure using a case-crossover design. In detail, given that each study patient serves as his or her own control in this case-crossover study design, time-invariant confounding factors, including unmeasured time-invariant confounders, are automatically adjusted for in the subsequent analytical models. We applied conditional logistic regression models to examine the effect of antipsychotic exposure on VA/SCD. Crude and adjusted odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were computed using a pair-matched approach to compare and evaluate the effect of antipsychotic use within the period just before the occurrence of VA/SCD (defined as the case period) with a comparable period (defined as the control period). Specifically, the case period was defined as 1 to 14 days before the index date and the control period was defined as 15 to 28 days before the index date. To explore the dose-response effect of antipsychotic use on VA/SCD risk, we categorized average daily dose into 3 ranges: 0, >0 to <0.5, and ≥0.5 defined daily dose.[22] Average daily dose was calculated by dividing cumulative doses by cumulative exposure days during the case or control periods. Furthermore, given that ventricular repolarization involves hERG potassium channels, we analyzed the relationship between the potency of the hERG potassium channel blockade and the risk of VA/SCD. The half maximal inhibitory concentration (IC_{50}) of the hERG potassium channel blockade was obtained from the study by Silvestre et al.[23] We classified antipsychotics into low and high groups, based on the median values of the potency of the hERG potassium channel blockade. Antipsychotics with an unknown defined daily dose or potency of hERG potassium channel blockade were not included in the analyses.

To determine the modifying effect of patient characteristics on VA/SCD risk, we carried out subgroup analyses stratified by various demographic and clinical characteristics of the study patients, including: age, sex, Charlson comorbidity index score,[24] CV diseases (CVDs; yes/no), psychiatric disorders (schizophrenia, dementia, mood disorders, and others), and cumulative days of antipsychotic use in 1 year before VA/SCD, respectively. Interactions between antipsychotic exposure and each of the patient characteristics were assessed.

We tested the robustness of the results by performing several sensitivity analyses. First, given that not all SCD was caused by VA, we repeated these analyses among patients with a definitive record of VA diagnosis. Second, we repeated these analyses using 3 different time windows: 7 days (1 to 7 days before the index date as the case period and 8 to 14 days before the index date as the control period); 14 days (1 to 14 days before the index date as the case period and 14 to 28 days before the index date as the control period); and 28 days (1 to 28 days as the case period and 29 to 56 days as the control period).

We declared statistical significance using 95% CIs or a P value less than 0.05. All of the analyses were performed using SAS for Windows (version 9.2; SAS Institute Inc., Cary, NC).

Results

A total of 17 718 patients with hospitalizations or emergency room visits for VA/SCD between 2001 and 2009 were enrolled (Figure 1). Mean age at the onset of VA/SCD was 63.51 years (SD=17.64), and 45.51% of the study subjects were female. Among the study subjects, 31.35% had a history of cerebrovascular disease, 46.26% had hypertension, and 14.39% had heart failure. Details of patient demographic characteristics, medical and psychiatric comorbidity, Charlson comorbidity index score (CCIS), and cumulative days of antipsychotic use in 1 year before VA/SCD are summarized in Table 1.

Table 2 presents the effect of antipsychotic use on the risk of VA/SCD within a 14-day window. Overall, use of antipsychotics was associated with a 1.53-fold increased risk of

Table 1. Demographic and Clinical Characteristics of Subjects With Ventricular Arrhythmia and/or Sudden Cardiac Death, 2001–2009

Characteristics	N	%
Demographics	17 718	
Age group, y		
17 to 64	7289	41.14
65 to 74	4593	25.92
≥75	5836	32.94
Gender		
Female	8063	45.51
Male	9655	54.49
Clinical		
Medical comorbid disorders (yes, %)		
Cerebrovascular disease	5554	31.35
Chronic pulmonary disease	4821	27.21
Coronary heart disease	3851	21.73
Diabetes mellitus	4620	26.08
Hypertension	8197	46.26
Heart failure	2549	14.39
Conduction disorder	103	0.58
Heart valve disorders	476	2.69
Malignant neoplasm	1430	8.07
Peripheral vascular disease	613	3.46
Psychiatric comorbidity (yes, %)		
Dementia	4922	27.78
Mood disorder	3161	17.84
Schizophrenia and other psychosis	1710	9.65
Anxiety	3059	17.26
Organic brain syndrome	1187	6.70
Charlson comorbidity index score		
0	3581	20.21
1 to 2	5571	31.44
≥3	8566	48.35
Cumulative days of antipsychotic use in 1 year before VA and/or SCD		
≤7	7863	44.38
8 to 28	3385	19.10
≥29	6470	36.52

SCD indicates sudden cardiac death; VA, ventricular arrhythmia.

VA/SCD after controlling for concomitant medication use and health system utilization. When classifying antipsychotics into FGAs and SGAs, we found that the VA/SCD risk among FGA users was slightly higher than that among SGA users (adjusted OR [AOR]=1.66; 95% CI, 1.43 to 1.91 for FGAs; AOR=1.36; 95% CI, 1.20 to 1.54 for SGAs). In terms of individual antipsychotics, a significantly increased risk of VA/SCD was found for clothiapine (AOR=2.16; 95% CI, 1.03 to 4.53), haloperidol (AOR=1.46; 95% CI, 1.17 to 1.83), prochlorperazine (AOR=1.69; 95% CI, 1.32 to 2.17), thioridazine (AOR=1.78; 95% CI, 1.01 to 3.15), quetiapine (AOR=1.29; 95% CI, 1.07 to 1.56), risperidone (AOR=1.39; 95% CI, 1.13 to 1.72), and sulpiride (AOR=1.26; 95% CI, 1.02 to 1.56), respectively. There was a marginal significantly increased risk for olanzapine (AOR=1.64; 95% CI, 0.98 to 2.72). Moreover, we also examined associations between the risk of definitive VA and antipsychotic use. The case number of patients with a definitive diagnosis of VA was 7769. Our results were grossly consistent with our primary analysis; however, the increased risk for clothiapine, thioridazine, quetiapine, and risperidone use was no longer statistically significant (Table S1).

Table 3 presents associations between antipsychotic use and risk of VA/SCD, stratified by various demographic and clinical characteristics. We found that subjects with a shorter duration of antipsychotic use had a higher risk of VA/SCD (AOR=2.11; 95% CI, 1.70 to 2.61 for cumulative days <7 days; AOR=1.38; 95% CI, 1.19 to 1.60 for cumulative days between 8 and 28 days; AOR=1.22; 95% CI, 0.91 to 1.63 for cumulative days ≥29 days). Age, gender, CCIS, and underlying psychiatric illness had no significant modifying effect on the risk of VA/SCD. The *P* value for the interaction with antipsychotic use was 0.96 for age, 0.53 for gender, 0.34 for CCIS, 0.20 for underlying CVDs, and 0.46 for underlying psychiatric illness, individually. Similarly, Table S2 shows consistent results from the stratified analysis among patients with a definitive diagnosis of VA.

Table 4 presents the associations of a defined daily dose and hERG potassium channel blockade with VA/SCD risk. We found that antipsychotics with a high hERG potassium channel blockade were associated with higher VA/SCD risk than those with a low blockade (AOR=1.24; 95% CI, 1.04 to 1.48 for high vs. low). In addition, we observed an inverse dose-response effect (AOR=0.78; 95% CI, 0.56 to 0.70 for high vs. low).

Furthermore, a sensitivity analysis was carried out using different time windows (specifically, 1 to 7 days for case period and 8 to 14 days for control period; 1 to 14 days for case period and 15 to 28 days for control period; and 1 to 28 days for case period and 29 to 56 days for control period, separately). No overt change was found related to the association between antipsychotic use and increased risk of VA/SCD across different time windows (Table S3). However, the difference between FGA and SGA use and risk of VA/SCD was not overt using 28-day windows. The VA/SCD risk for olanzapine use showed a significant increase using 7- or 28-day windows, but there was no significant risk associated with clothiapine use using 7- or 28-day windows.

Table 2. Risk of Ventricular Arrhythmia and/or Sudden Cardiac Death in Relation to Current Antipsychotic Use Among 17 718 Patients

Antipsychotic Class and Agent	Case Period, N	Control Period, N	Crude OR	95% CI	Adjusted OR†	95% CI
Use of antipsychotics*	5625	5117	*1.84*‡	1.67 to 2.03	*1.53*	1.38 to 1.70
First-generation antipsychotics	2070	1770	*2.02*	1.76 to 2.33	*1.66*	1.43 to 1.91
Chlorpromazine	248	218	*1.98*	1.28 to 3.05	1.45	0.93 to 2.27
Clopenthixol	30	25	2.66	0.71 to 10.04	2.40	0.46 to 12.48
Clothiapine	135	117	*2.68*	1.33 to 5.39	*2.16*	1.03 to 4.53
Flupentixol	400	382	1.28	0.92 to 1.78	1.07	0.77 to 1.51
Haloperidol	833	730	*1.83*	1.47 to 2.27	*1.46*	1.17 to 1.83
Loxapine	14	14	1.00	0.14 to 7.10	0.49	0.04 to 5.87
Prochlorperazine	272	172	*2.04*	1.60 to 2.61	*1.69*	1.32 to 2.17
Thioridazine	194	173	*2.17*	1.24 to 3.79	*1.78*	1.01 to 3.15
Trifluoperazine	87	73	*1.88*	1.02 to 3.44	1.37	0.73 to 2.57
Second-generation antipsychotics	4017	3736	*1.63*	1.45 to 1.84	*1.36*	1.20 to 1.54
Amisulpride	90	88	1.14	0.56 to 2.34	0.94	0.45 to 1.96
Aripiprazole	35	34	1.14	0.41 to 3.15	0.90	0.31 to 2.59
Clozapine	141	130	*2.64*	1.09 to 6.38	2.03	0.83 to 4.94
Olanzapine	245	221	*2.01*	1.23 to 3.29	1.64	0.98 to 2.72
Quetiapine	1421	1326	*1.51*	1.26 to 1.82	*1.29*	1.07 to 1.56
Risperidone	1163	1066	*1.67*	1.36 to 2.05	*1.39*	1.13 to 1.72
Sulpiride	1015	930	*1.59*	1.29 to 1.95	*1.26*	1.02 to 1.56
Ziprasidone	27	26	1.20	0.37 to 3.93	0.80	0.24 to 2.67
Zotepine	154	142	1.86	0.97 to 3.56	1.50	0.77 to 2.91

OR indicates odds ratio; SCD, sudden cardiac death; VA, ventricular arrhythmia.

*Given that the case number of patients using fluphenazine, levomepromazine, methotrimeprazine, perphenazine, pimozide, pipotiazine, or paliperidone was quite small, the estimates of VA/SCD risk related to these antipsychotics are not shown.

†Calculated by multivariate conditional logistic regression with adjustment for antidiabetic agents, diuretics, antithrombotic, agents, antihypertensive agents, lipid-modifying agents, antidepressants, and number of inpatient and outpatient visits.

‡*P* value <0.05 is in italics.

Discussion

We found that antipsychotic use was associated with a 1.53-fold increased risk of VA/SCD, after adjusting for time-varying confounding factors. Risk of VA/SCD among FGA users might be higher than that among SGA users. Antipsychotic drugs with an increased risk of VA/SCD included haloperidol, procholorperazine, sulpiride, thioridazpine, quetiapine, and risperidione. Clothiapine and olanzapine were also associated with an increased risk of VA/SCD, although the results from the sensitivity analyses varied across different time windows. We found that the magnitude of associations was greater among patients who had shorter durations of treatment. Age, gender, underlying heart disease, and comorbid psychiatric illness did not modify relative risk of VA/SCD.

Whereas we found that risk of VA/SCD among FGA users was higher than that among SGAs users, interestingly, the difference between FGA and SGA use was more obvious when we restricted our analysis to patients with a definitive diagnosis of VA. These findings are in line with previous epidemiological studies.[7–10] However, the underlying mechanisms for the observed findings that show SGAs to be safer than FGAs have remained largely unclear. One possible explanation might be related to the fact that public concern regarding risk of VA/SCD has risen in recent decades. Thus, SGAs with overt QT prolongation were not introduced into, or were withdrawn from, the market, such as sertindole. It should also be noted that VA/SCD risk of antipsychotic use varied markedly in the same pharmacological class. Thus, we explored VA/SCD risk of individual antipsychotic drugs. We found that most of the FGAs, such as clothiapine, haloperidol, prochlorperazine, and thioridazine, were associated with an increased risk of VA/SCD. The point estimate of VA/SCD risk for clopentixol and trifluoperazine, separately, also showed an increase, although it was not statistically significant. These findings are partially consistent with a previous study.[25] For

Table 3. Risk of Ventricular Arrhythmia and/or Sudden Cardiac Death in Relation to Current Antipsychotic Use Among Study Patients Within the 14-Day Window, Stratified by Demographic and Clinical Characteristics

	Case Period, N	Control Period, N	Crude OR	95% CI	Adjusted OR*	95% CI
All patients (N=17 718)	5625	5117	*1.84*†	1.67 to 2.03	*1.53*	1.38 to 1.70
Subgroup analyses						
Age group, y						
17 to 64 (N=7289)	2544	2334	*1.86*	1.60 to 2.18	*1.48*	1.25 to 1.75
65 to 74 (N=4593)	1321	1197	*1.76*	1.45 to 2.13	*1.55*	1.27 to 1.90
≧75 (N=5836)	1760	1586	*1.88*	1.58 to 2.23	*1.54*	1.28 to 1.85
Sex						
Female (N=8063)	2734	2496	*1.78*	1.55 to 2.05	*1.60*	1.38 to 1.85
Male (N=9655)	2891	2621	*1.90*	1.65 to 2.18	*1.47*	1.26 to 1.70
Charlson comorbidity index score						
0 (N=3581)	1080	999	*1.80*	1.41 to 2.29	1.24	0.95 to 1.63
1 to 2 (N=5571)	1830	1633	*2.08*	1.75 to 2.49	*1.68*	1.39 to 2.03
≧3 (N=8566)	2715	2485	*1.73*	1.50 to 1.99	*1.54*	1.33 to 1.77
Cardiovascular diseases‡						
Yes (N=11 433)	3472	3162	*1.76*	*1.56 to 1.99*	*1.53*	*1.35 to 1.74*
No (N=6285)	2153	1955	*2.02*	*1.70 to 2.40*	*1.50*	*1.24 to 1.81*
Psychiatric disorders						
Schizophrenia (N=1710)	1240	1187	*1.67*	1.26 to 2.21	1.26	0.90 to 1.76
Mood disorders (N=3161)	1485	1363	*1.84*	1.50 to 2.25	*1.44*	1.16 to 1.79
Others (N=12 847)	2900	2567	*1.89*	1.66 to 2.14	*1.61*	1.41 to 1.83
Cumulative days of antipsychotic use in 1 year before VA and/or SCD						
<7 (N=7863)	429	173	*2.94*	2.41 to 3.58	*2.11*	1.70 to 2.61
8 to 28 (N=3385)	1704	1496	*1.55*	1.36 to 1.76	*1.38*	1.19 to 1.60
≧29 (N=6470)	3490	3447	*1.51*	1.15 to 1.98	1.22	0.91 to 1.63

OR indicates odds ratio; SCD, sudden cardiac death; VA, ventricular arrhythmia.

*Calculated by multivariate conditional logistic regression with adjustment for antidiabetic agents, diuretics, antithrombotic, agents, antihypertensive agents, lipid-modifying agents, antidepressants, and number of inpatient and outpatient visits.

†*P* value <0.05 is in italics.

‡Cardiovascular diseases included cerebrovascular disease, coronary heart diseases, heart failure, conduction disorder, hypertension, peripheral vascular disease, and heart valve disorders.

example, Leonard et al. compared VA/SCD risk among individual antipsychotics using a Medicaid claims database and found that haloperidol and chlorpromazine had less-favorable cardiac safety, as compared to olanzapine. However, quetiapine was associated with a 30% decreased risk, compared to olanzapine. In addition, they also reported that risk of VA/SCD with risperidone use was similar to that with olanzapine use.[25] Of note, we found that risk of VA/SCD with ziprasidone use was not statistically significantly, although ziprasidone was linked to QT prolongation. In our study, the number of ziprasidone user was small; therefore, the statistical power might be not enough. In addition, an open-label, randomized, postmarketing trial, Ziprasidone Observational Study of Cardiac Outcomes (n=18 154), compared 1-year mortality rates between ziprasidone and olanzapine. The results showed that ziprasidone was not associated with higher risk of nonsuicidal mortality than olanzapine.[26] In the same study, the results also showed no significant difference between 2 groups in CV mortality or sudden cardiac death. Thus, risk of VA/SCD with ziprasidone use warrants more investigations.

Relative risks of VA/SCD with overall antipsychotic use in the present study were smaller than those found in previous studies, when compared to nonusers.[7,10–13,27–29] Specifically, Honkola et al. suggested that use of psychotropic medication was positively associated with a 4.4-fold increased risk of

Table 4. Risk of Ventricular Arrhythmia and/or Sudden Cardiac Death in Relation to Dose and hERG Potassium Channel Blockade*

	Case Period, N	Control Period, N	Crude OR	95% CI	Adjusted OR	95% CI
Ventricular arrhythmia and/or sudden cardiac death						
Average daily dose†						
Low (<0.5 defined daily dose)	3619	3179	*1.93*§	1.73 to 2.15	*1.60*§	1.43 to 1.80
High (≧0.5 defined daily dose)	1954	1897	*1.54*§	1.31 to 1.80	*1.25*§	1.06 to 1.48
High vs. low			*0.80*§	0.67 to 0.95	*0.78*§	0.56 to 0.70
hERG potassium channel blockade‡						
Low	2626	2443	*1.60*§	1.40 to 1.83	*1.36*§	1.18 to 1.57
High	2789	2495	*2.06*§	1.80 to 2.35	*1.68*§	1.47 to 1.93
High vs. low			*1.29*§	1.08 to 1.53	*1.24*§	1.04 to 1.48

hERG indicates human ether-à-go-go-related gene; OR, odds ratio.
*Antipsychotics with unknown defined daily dose or pIC_{50} were not included in the analysis.
†One defined daily dose of antipsychotics (mg): amisulpride (400); aripiprazole (15); chlorpromazine (300); clopenthixol (100); clozapine (300); flupentixol (6); haloperidol (8); loxapine (100); olanzapine (10); prochlorperazine (100); quetiapine (400); risperidone (5); sulpiride (800); thioridazine (300); ziprasidone (80); zotepine (200).
‡Blockade of hERG channels by antipsychotics (pIC_{50}): amisulpride (5.00); aripiprazole (5.96); chlorpromazine (5.82); clozapine (5.85); haloperidol (7.03); olanzapine (6.64); prochlorperazine (6.11); quetiapine (5.24); risperidone (6.69); sulpiride (5.00); thioridazine (6.70); trifluoperazine (5.85); ziprasidone (6.79); zotepine (6.68).
§P value <0.05 in italics.

SCD during an acute coronary event among subjects in the Finnish Genetic Study of Arrhythmic Events.[29] Straus et al., using data from Integrated Primary Care Information, reported that antipsychotic use was associated with a 3.3-fold increased risk of SCD, as compared to risk among nonusers.[28] Ray et al. found that the adjusted rate ratio of SCD with antipsychotic use was 2.39 using data from Tennessee Medicaid enrollees.[27] Examining cases who die suddenly without an identified cause, Jolly et al. found that both typical and atypical antipsychotics were associated with sudden death, with an AOR of 3.94 and 4.36, respectively.[11] Comparing to patients with glaucoma or psoriasis, Hennessy et al. found that patients with treated schizophrenia had a 1.7- to 3.2-fold increase in rates of cardiac arrest and VA using 3 different Medicaid claims databases.[13] Moreover, previous studies have found a 2- to 4-fold increased risk of VA with antipsychotic use.[7,10,12] It should be noted that schizophrenia itself, the major indication for antipsychotic use, was associated with SCD.[30] Thus, it is likely that the increased risk of SCD might be partially attributable to the underlying psychiatric illness.

Using a case-crossover design, we estimated the effect of antipsychotics on VA/SCD while perfectly controlling for underlying chronic psychiatric and CVDs. Although the estimated risks of VA/SCD in this study are smaller than those reported in previous studies, the observed results are still statistically significant.

We also found that magnitude of VA/SCD risk associated with antipsychotic use was inversely associated with duration of antipsychotic use in the preceding year. These findings indicate that increased VA/SCD risk is largely attributable to patients who only recently started taking antipsychotic drugs. Patients who were exposed to antipsychotics for more than 28 days had no excess risk of VA/SCD. These findings are compatible with those of previous studies showing that risk is highest among short-term users.[28,31]

We did not find an overtly modifying effect of patient characteristics. A slightly greater risk of VA/SCD was found in female users than their counterparts. Previous studies have suggested that females are more vulnerable to VA/SCD risk with antipsychotic use than males. The finding that QT intervals were longer in females than in males by approximately 10 msec might have contributed to this finding.[32]

Underling CVDs are important risk factors related to the development of VA/SCD. Although the relative risk of VA/SCD between patients with or without heart disease was similar in our study, it would be of interest to further investigate the absolute risk of VA/SCD among patients with and without underlying heart disease.

Of interest, we found that the risk of VA/SCD among antipsychotic users was not statistically significant among patients with schizophrenia. One possible explanation is that patients with schizophrenia tend to be long-term users of antipsychotics; therefore, the short-term effect on the risk of VA/SCD could not be estimated.

Blockade of hERG potassium channels was strongly associated with drug-induced QT interval prolongation. Given that the QT interval is difficult to measure correctly, QT prolongation has been thought to be an imprecise indicator for the risk of torsades de pointes. One of the new contributions presented in this study is our exploration of the relationship between the potency of the hERG potassium channel blockade and VA/SCD

risk. Importantly, we found that antipsychotics with a high potential for blocking hERG channels were associated with an increased risk of VA/SCD. This finding is compatible with those in the study by van Noord et al.[31] Our study confirmed the role of hERG potassium channel blockade on the association between antipsychotic use and VA/SCD. Furthermore, the effect of antipsychotic use on VA/SCD was thought to be dose related.[1,12] However, we did not find a dose-response relationship in this study. It should be noted that the dose of antipsychotics is usually slowly titrated from a low to a high dose. Given that we found that VA/SCD risk was the highest during the initial phase of antipsychotic use, the dose-response effect of antipsychotics was not obvious in our study.

Overall, the strengths of our study include: (1) use of a case-crossover study design, which eliminates within-individual time-invariant variables; (2) adjustment for concomitant medications use; (3) use of a nation-wide representative sample with a large case number; (4) assessment of the risk of individual antipsychotics; (5) exploration of the relationship between the potency of potassium channel inhibition and VA/SCD risk; and (6) contribution of findings on the association between antipsychotic use and VA/SCD in an Asian population, which has been underinvestigated on this important matter.

However, this study also had several limitations. First, although all patients with VA/SCD who were treated antipsychotics between 2001 and 2009 were included in this study, the case number was small for assessing the risk of VA/SCD for certain antipsychotics. Thus, the results of the sensitivity analyses were slightly inconsistent. Second, though the case-crossover design could automatically control for all time-invariant confounders, it is likely that our results were still confounded by time-variant factors, such as electrolyte imbalance, acute psychiatric distress, drug-drug interaction, and changes in heart function. However, we adjusted for the concomitant use of various CV and proarrhythmic drugs, serving as proxy measures to minimize the confounding factors, in the analytical models. Third, the case-crossover design might be vulnerable to changes in prescription patterns over time. However, the time-trend bias would be limited owing to the fact that the examined time windows were quite short in this study. Fourth, the validation of VA/SCD in the NHIRD is a critical concern. To improve diagnostic validity, we identified VA/SCD using diagnoses from medical claims records of ED visits and hospitalizations. Of note, a previous validation study using similar algorithms reported that the positive predictive value of VA/SCD was 85.3%.[20] Fifth, it is known that the underlying etiology of SCD is heterogeneous, including acute myocardial infarction, VA, hypertensive heart diseases, and so on.[33] Among these, VA is one of the common causes leading to SCD. Thus, we further restricted our analysis to those only with a definitive VA diagnosis, for which our results showed gross consistency. Although VA is a heterogeneous diagnostic entity, we could not identify the subtype of VA using medical claims data. The effect of antipsychotic use on the heterogeneous type of VA warrants further investigations. Sixth, there was no information about the actual use of the prescribed antipsychotics. However, nonadherence would most likely result in nondifferentiated misclassification of the exposure, which would lead to underestimation of the actual risk. Finally, given that the data used for this study were only available between 2000 and 2009, we only excluded prevalent cases that had any diagnosis of VA/SCD in 2000. It was likely that some subjects with a history of VA/SCD before 2000 were included in this study; however, the case number would be small. Therefore, the influence of prevalent VA/SCD cases should be limited, even some study subjects with a history of VA/SCD before 2000.

Conclusions

In this study, we found that antipsychotic use was associated with increased risk of VA/SCD. SGAs might be safer than FGAs in terms of risk for VA/SCD. Patients who were new antipsychotic users tended to have the highest risks. Although underlying CVD did not increase relative risk of VA/SCD with antipsychotics use, it might still increase absolute risk of VA/SCD. From the perspective of clinical implications, antipsychotic drugs should be prescribed cautiously during the initial treatment phase. A careful assessment of the risks and benefits of antipsychotic treatment is recommended, as is EKG monitoring, among those with underlying CVDs.[34]

Acknowledgments

For authors' contributions to this work, Dr Chi-Shin Wu conceptualized and designed the study, as well as approved the final manuscript as submitted. Yu-Ting Tsai performed analyses, prepared the presented tables and figures, and reviewed the manuscript. Dr Hui-Ju Tsai supervised the study, drafted the initial manuscript, and approved the final manuscript as submitted. The authors thank Tami R. Bartell at Ann & Robert H. Lurie Children's Hospital of Chicago Stanley Manne Children's Research Institute for English editing. This study is based, in part, on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by the National Health Research Institutes (Registered Nos.: 99081, 99136, 99287, 101014, NHRID-101-548, and NHIRD-103-042). The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

Sources of Funding

Dr Tsai is supported, in part, by a grant from the National Health Research Institutes (PI: Tsai, PH-102-PP-14, PH-103-SP-14, and PH-103-SP-05). Dr Wu is supported by a grant

from the Far Eastern Memorial Hospital (FEMH-2012-C-010 and FEMH-2013-C-005).

Disclosures

None.

References

1. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry*. 2001;158:1774–1782.
2. Nielsen J, Graff C, Kanters JK, Toft E, Taylor D, Meyer JM. Assessing QT interval prolongation and its associated risks with antipsychotics. *CNS Drugs*. 2011;25:473–490.
3. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart*. 2003;89:1363–1372.
4. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350:1013–1022.
5. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs*. 2002;62:1649–1671.
6. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2012;8:114–126.
7. Liperoti R, Gambassi G, Lapane KL, Chiang C, Pedone C, Mor V, Bernabei R. Conventional and atypical antipsychotics and the risk of hospitalization for ventricular arrhythmias or cardiac arrest. *Arch Intern Med*. 2005;165:696–701.
8. Mehta S, Chen H, Johnson M, Aparasu RR. Risk of serious cardiac events in older adults using antipsychotic agents. *Am J Geriatr Pharmacother*. 2011;9:120–132.
9. Wang PS, Schneeweiss S, Setoguchi S, Patrick A, Avorn J, Mogun H, Choudhry NK, Brookhart MA. Ventricular arrhythmias and cerebrovascular events in the elderly using conventional and atypical antipsychotic medications. *J Clin Psychopharmacol*. 2007;27:707–710.
10. Murray-Thomas T, Jones ME, Patel D, Brunner E, Shatapathy CC, Motsko S, Van Staa TP. Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: a study with the general practice research database. *Cardiovasc Psychiatry Neurol*. 2013;2013:247486.
11. Jolly K, Gammage MD, Cheng KK, Bradburn P, Banting MV, Langman MJ. Sudden death in patients receiving drugs tending to prolong the QT interval. *Br J Clin Pharmacol*. 2009;68:743–751.
12. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. 2009;360:225–235.
13. Hennessy S, Bilker WB, Knauss JS, Margolis DJ, Kimmel SE, Reynolds RF, Glasser DB, Morrison MF, Strom BL. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *BMJ*. 2002;325:1070.
14. Aberg K, Adkins DE, Liu Y, McClay JL, Bukszar J, Jia P, Zhao Z, Perkins D, Stroup TS, Lieberman JA, Sullivan PF, van den Oord EJ. Genome-wide association study of antipsychotic-induced QTc interval prolongation. *Pharmacogenomics J*. 2012;12:165–172.
15. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lassig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382:951–962.
16. Poluzzi E, Raschi E, Koci A, Moretti U, Spina E, Behr ER, Sturkenboom M, De Ponti F. Antipsychotics and torsadogenic risk: signals emerging from the US FDA Adverse Event Reporting System database. *Drug Saf*. 2013;36:467–479.
17. Raschi E, Poluzzi E, Godman B, Koci A, Moretti U, Kalaba M, Bennie M, Barbui C, Wettermark B, Sturkenboom M, De Ponti F. Torsadogenic risk of antipsychotics: combining adverse event reports with drug utilization data across Europe. *PLoS One*. 2013;8:e81208.
18. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.
19. Wu CS, Chang CM, Chen CY, Wu EC, Wu KY, Liang HY, Chao YL, Chung WS, Tsai HJ. Association between antidepressants and venous thromboembolism in Taiwan. *J Clin Psychopharmacol*. 2013;33:31–37.
20. Hennessy S, Leonard CE, Freeman CP, Deo R, Newcomb C, Kimmel SE, Strom BL, Bilker WB. Validation of diagnostic codes for outpatient-originating sudden cardiac death and ventricular arrhythmia in Medicaid and Medicare claims data. *Pharmacoepidemiol Drug Saf*. 2010;19:555–562.
21. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying ventricular arrhythmias using administrative and claims data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):148–153.
22. WHO Collaborating Centre for Drug Statistic Methodology. *Guidelines for ATC Classification and DDD Assignment*. Oslo: WHO; 2009.
23. Silvestre JS, O'Neill MF, Prous JR. Evidence for a crucial modulating role of the sodium channel in the QTc prolongation related to antipsychotics. *J Psychopharmacol*. 2014;28:329–340.
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
25. Leonard CE, Freeman CP, Newcomb CW, Bilker WB, Kimmel SE, Strom BL, Hennessy S. Antipsychotics and the risks of sudden cardiac death and all-cause death: cohort studies in Medicaid and dually-eligible Medicaid-Medicare beneficiaries of five states. *J Clin Exp Cardiolog*. 2013;suppl 10:1–9.
26. Strom BL, Eng SM, Faich G, Reynolds RF, D'Agostino RB, Ruskin J, Kane JM. Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). *Am J Psychiatry*. 2011;168:193–201.
27. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry*. 2001;58:1161–1167.
28. Straus SM, Bleumink GS, Dieleman JP, van der Lei J, tJong GW, Kingma JH, Sturkenboom MC, Stricker BH. Antipsychotics and the risk of sudden cardiac death. *Arch Intern Med*. 2004;164:1293–1297.
29. Honkola J, Hookana E, Malinen S, Kaikkonen KS, Junttila MJ, Isohanni M, Kortelainen ML, Huikuri HV. Psychotropic medications and the risk of sudden cardiac death during an acute coronary event. *Eur Heart J*. 2012;33:745–751.
30. Koponen H, Alaraisanen A, Saari K, Pelkonen O, Huikuri H, Raatikainen MJ, Savolainen M, Isohanni M. Schizophrenia and sudden cardiac death: a review. *Nord J Psychiatry*. 2008;62:342–345.
31. van Noord C, Sturkenboom MC, Straus SM, Witteman JC, Stricker BH. Non-cardiovascular drugs that inhibit hERG-encoded potassium channels and risk of sudden cardiac death. *Heart*. 2011;97:215–220.
32. Drici MD, Clement N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. *Drug Saf*. 2001;24:575–585.
33. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;104:2158–2163.
34. Shah AA, Aftab A, Coverdale J. QTc prolongation with antipsychotics: is routine ECG monitoring recommended? *J Psychiatr Pract*. 2014;20:196–206.