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Comparative Risk of Seizure With Use of First- and Second-Generation Antipsychotics in Patients With Schizophrenia and Mood Disorders

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ABSTRACT

Objective: To compare the risk of antipsychotic-related seizure (ARS) by identifying seizures first diagnosed within 12 months after starting new antipsychotics, using a 12-year total population health claims database from Taiwan.

Methods: Seizure events were identified through emergency department visits or hospitalization with a diagnosis of convulsion (*ICD-9-CM*: 780.3) or epilepsy (*ICD-9-CM*: 345). Subjects had an *ICD-9-CM* diagnosis of schizophrenia, bipolar disorders, or major depressive disorders. Incidence rates of ARS were calculated by person-years of exposure. The ARS risk, adjusted for patient characteristics and medical conditions, of individual antipsychotics versus risperidone was examined by high-dimensional propensity score stratification analyses, followed by sensitivity analyses.

Results: The overall 1-year incidence rate of ARS was 9.6 (95% CI, 8.8–10.4) per 1,000 person-years (550 ARS events among 288,397 new antipsychotic users). First-generation antipsychotics were marginally associated with a higher ARS risk than second-generation antipsychotics (adjusted hazard ratio [aHR] = 1.34; 95% CI, 0.99–1.81; $P = .061$). Most antipsychotics, first- or second-generation, had comparable ARS risks versus risperidone. Notably, clozapine (aHR = 3.06; 95% CI, 1.40–6.71), thioridazine (aHR = 2.90; 95% CI, 1.65–5.10), chlorprothixene (aHR = 2.60; 95% CI, 1.04–6.49), and haloperidol (aHR = 2.34; 95% CI, 1.48–3.71) had higher ARS risks than risperidone, whereas aripiprazole (aHR = 0.41; 95% CI, 0.17–1.00; $P = .050$) had a marginally lower ARS risk. Sensitivity analyses largely confirmed such findings.

Conclusions: Higher vigilance for ARS is warranted during use of clozapine, chlorprothixene, thioridazine, and haloperidol. The possible lower ARS risk associated with aripiprazole can be clinically significant but needs to be confirmed by larger-scale systematic studies. The comparative ARS risks of antipsychotics supplement empirical knowledge for making judicious choices in prescribing antipsychotics.

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Seizure is one important side effect that influences the physician's choice among the wide varieties of first- and second-generation antipsychotics (FGAs and SGAs).[1,2] Even with the SGAs, despite their proclaimed improved side effect profiles, seizure remains a frequent adverse event.[3–5] Concern for antipsychotic-related seizure (ARS) is particularly pertinent following the vast growth in the prescription of SGAs after their indications were expanded to bipolar and depressive disorders.[6,7] Despite such import, current knowledge of ARS risk is largely based on sporadic case reports and pharmacovigilance databases. The few prospective clinical studies of ARS were limited to specific antipsychotics and had significant methodological limitations.[8–10] No systematic study has compared the relative ARS risks among antipsychotics to guide clinical prescription.

One study analyzing Spanish pharmacovigilance data asserted that SGAs were associated with greater risk of seizure than FGAs.[10] Another study using the World Health Organization (WHO) adverse drug reactions database found that clozapine, chlorprothixene, and quetiapine were the 3 antipsychotics most commonly associated with convulsion.[9] These pharmacovigilance-based studies shared inherent methodological shortcomings: the report of seizure events was sporadic, and the number and characteristics of the base populations receiving individual antipsychotics were unknown, so the true incidence rates of individual antipsychotics and the impacts of potential risk factors could not be determined. An alternative approach examined the relative rate of ARS of selected SGAs by using pooled data across clinical trials. The results indicated that clozapine, olanzapine, and quetiapine were associated with greater seizure risks than other SGAs, such as aripiprazole, risperidone, and ziprasidone.[8] Nevertheless, because of the substantial heterogeneities within the study populations and designs across studies, a conclusion is difficult to draw. Empirical knowledge of the epileptogenic propensity and risk factors of individual antipsychotics will greatly inform the making of rational and safe choices of antipsychotics, to avoid placing both patients and physicians at risk.

The current study, therefore, aimed to estimate the comparative seizure risk of antipsychotics in the presence of complex medical conditions by examining the 1-year incidence rate of new-onset seizure after starting antipsychotic treatment. We analyzed a nationwide population-based dataset, using a retrospective cohort study design and strictly defined temporality criteria to estimate new-onset ARS incidence rates associated with all marketed FGAs and SGAs.

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Clinical Points

- Drug-induced seizure is a severe rare adverse effect; however, few large-scale epidemiologic studies have explored the comparative seizure risks among antipsychotics.
- Most antipsychotics were comparable with risperidone in terms of antipsychotic-related seizure. However, clozapine, chlorprothixene, haloperidol, and thioridazine were associated with significantly higher seizure risks. Aripiprazole may have a lower risk of antipsychotic-related seizure.

METHODS

Data Source

This retrospective cohort study utilized the National Health Insurance Research Database (NHIRD) derived from the reimbursement claims records of the National Health Insurance (NHI) program in Taiwan. The NHI program is a single-payer compulsory program and has enrolled 22.6 million individuals, representing 98% of the Taiwanese population. The NHIRD includes demographic characteristics, diagnoses, procedures, and prescription claims records. The prescription claims records contain medication types, prescription date, dosage, and duration of drug supply. In gathering the data, all information that could be used to identify insured individuals and medical care providers was anonymized to ensure confidentiality. The NHIRD has been used for pharmacoepidemiologic studies and research on medical, neurologic, and psychiatric disorders, including epilepsy.[11,12]

Study Population

The study cohort included all subjects registered in the NHIRD between January 1, 2001, and December 31, 2012, older than 15 years and with a diagnosis of schizophrenia (*ICD-9-CM* code: 295.x), bipolar disorders (*ICD-9-CM* code: 296.x, except 296.2 and 296.3), or major depressive disorders (*ICD-9-CM* code: 296.2 or 296.3) who received a new antipsychotic medication after an antipsychotic-free period of at least 1 year. Patients using multiple antipsychotic drugs on the index date (date of the new antipsychotic prescription) were excluded. As development of epilepsy or convulsion was the main study outcome, patients who had received these diagnoses before the index date were excluded. Subjects with underlying neurologic disorders, including brain tumor, central nervous system (CNS) infections, head injury, stroke, dementia, or organic brain syndrome, were also excluded, since it was difficult to determine whether the seizures were solely attributable to antipsychotic use. In addition, subjects first exposed to injectable antipsychotics were also excluded because of the different pharmacokinetics. Given the very infrequent use of fluphenazine, levomepromazine, loxapine, clopenthixol, pimozide, and thiothixene, individuals using these antipsychotics were not included in the analysis. In total, 288,397 new antipsychotic users were identified in this study. The flowchart of subject enrollment is shown in Supplementary eFigure 1.

Antipsychotic Exposure

Antipsychotics (N05A), as defined by the Anatomical Therapeutic Chemical Classification System,[13] were identified and further classified into FGAs or SGAs. FGAs included chlorpromazine, chlorprothixene, clothiapine, flupentixol, haloperidol, perphenazine, prochlorperazine, thioridazine, and trifluoperazine; SGAs included amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sulpiride, ziprasidone, and zotepine. Risperidone was chosen as the reference drug because it is one of the most commonly prescribed SGAs worldwide and its seizure risk is generally considered low.[2,8]

Study End Point

The study end point was defined as the first time that seizure developed after treatment with the new antipsychotics was started. Seizure event was identified through emergency department visits or hospitalization with a diagnosis of convulsion (*ICD-9-CM*: 780.3) or epilepsy (*ICD-9-CM*: 345). Subjects thus identified were further traced for follow-up electroencephalography (EEG) examination and/or antiepileptic drug prescription within 90 days after the seizure diagnosis to provide further internal validation. Seizure events occurring concomitantly with or after the development of major CNS risk factors, including head injury, CNS infection, brain tumor, stroke, dementia, or organic brain syndrome, were excluded.

Patient Characteristics and Potential Confounders

Patient characteristics during the 1-year period prior to the index date were assessed and included demographics, major and comorbid psychiatric disorders, medical comorbid conditions, concomitant use of psychotropic medications, and health care utilization (Table 1). Major psychiatric disorders included schizophrenia, bipolar disorders, and major depressive disorders. Comorbid psychiatric conditions included alcohol use disorder, substance use disorder, mental retardation, and autism spectrum disorder. Medical comorbidities included headache, cancer, hypertension, diabetes mellitus, dyslipidemia, chronic pulmonary disease, and chronic renal failure. Concomitant medications included anticholinergic agents, antidepressants, antiepileptic drugs, benzodiazepines, and lithium. Antidepressants were further classified into tricyclic antidepressants, selective serotonin reuptake inhibitors, and other antidepressants. Antiepileptic drugs were categorized into mood-stabilizing antiepileptics and other antiepileptics. Health care utilization indices included hospitalization and the number of outpatient visits in the preceding year.

Statistical Analysis

Descriptive statistics of the patient characteristics are provided. Based on the number of patients, the summation of

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Table 1. Baseline Characteristics of New Users of Second-Generation Antipsychotics

Characteristic	Amisulpride (n = 5,653), %	Aripiprazole (n = 7,118), %	Clozapine (n = 2,536), %	Olanzapine (n = 9,126), %	Paliperidone (n = 748), %	Quetiapine (n = 35,446), %	Risperidone (n = 31,089), %	Sulpiride (n = 109,571), %	Ziprasidone (n = 891), %	Zotepine (n = 4,115), %
Age										
15–39 y	60.8	61.9	44.3	53.0	67.4	43.4	56.9	46.6	63.4	59.1
40–64 y	33.7	32.8	50.4	36.9	29.3	40.9	32.5	40.7	30.9	37.2
≥ 65 y	5.5	5.3	5.4	10.1	3.3	15.7	10.6	12.8	5.7	3.6
Gender, male	45.9	41.0	55.2	46.0	49.2	41.5	50.3	43.0	43.9	57.2
Psychiatric disorders										
Schizophrenia	50.8	35.1	78.9	44.8	86.0	15.3	65.1	31.1	59.0	45.5
Bipolar disorder	30.1	33.2	13.8	35.3	8.4	51.4	21.8	34.6	29.9	36.7
Major depressive disorder	29.5	38.8	14.5	31.6	15.9	38.7	25.3	44.8	23.1	29.8
Mental retardation	2.4	2.8	1.2	1.9	3.5	1.3	4.0	1.7	4.3	3.1
Autism spectrum disorder	0.3	1.1	0.4	0.3	0.3	0.2	0.8	0.2	0.1	0.1
Alcohol use disorder	3.1	1.6	2.2	2.5	0.8	4.4	2.6	3.3	2.7	7.0
Substance use disorder	3.7	3.0	3.7	3.1	3.2	6.3	3.0	3.0	4.4	9.7
Medical comorbidity										
Headache	16.6	19.1	8.4	17.1	13.4	21.7	13.7	24.4	15.7	16.2
Cancer	2.1	2.1	2.0	3.7	1.3	4.5	2.1	2.9	1.7	1.9
Hypertension	11.2	11.7	10.4	13.9	9.5	22.0	12.5	18.6	11.8	9.6
Diabetes mellitus	6.6	6.8	7.0	6.0	5.1	10.7	6.7	8.4	7.5	6.1
Dyslipidemia	7.3	8.3	5.2	7.0	5.6	12.4	5.8	10.0	7.2	5.5
Chronic pulmonary disease	5.2	5.7	5.9	7.6	5.6	9.8	6.8	10.3	5.3	7.0
Chronic renal failure	0.7	0.7	0.8	1.1	0.4	2.5	1.2	1.3	1.1	1.0
Concomitant medication use										
Anticholinergics	19.3	6.7	17.2	9.7	22.3	3.4	27.7	17.5	12.9	22.1
Antidepressants										
TCAs	13.0	12.2	10.1	12.7	9.2	21.2	10.1	19.7	13.4	16.4
SSRIs	34.0	41.8	18.7	38.5	16.7	48.2	25.8	37.2	35.4	34.6
Other antidepressant	26.2	34.4	13.2	31.4	11.2	47.6	16.5	27.5	25.4	36.5
Antiepileptics										
MSAs	10.5	11.4	16.4	17.2	6.1	19.4	12.9	7.8	16.7	25.5
Other antiepileptics	2.0	2.5	1.4	2.2	1.3	3.5	1.5	2.1	4.2	1.7
Benzodiazepine	80.3	79.2	67.3	81.4	67.4	90.9	75.5	85.0	80.2	88.3
Lithium	1.8	2.5	5.0	6.0	1.5	4.0	3.1	2.3	3.7	8.7
Health system utilization										
No. of outpatient visits										
< 10	46.0	37.4	69.2	41.8	63.1	24.1	52.1	30.1	45.6	42.8
10–19	24.8	26.8	13.6	22.8	19.0	23.8	22.0	22.5	24.6	23.8
≥ 20	29.2	35.8	17.2	35.4	17.9	52.1	25.9	47.4	29.9	33.5
Hospitalization	16.6	16.0	31.9	25.6	30.1	23.5	22.3	19.2	20.4	30.2

Abbreviations: MSA = mood-stablizing antiepileptic, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

the follow-up period, and the number of seizure events, the crude incidence rate of seizure for each antipsychotic drug was calculated. In primary analysis, we used "as-treated" analysis to estimate the ARS risk among those who continued their initial antipsychotic therapy. Patients were censored when seizure occurred; when major CNS risk factors developed or treatment was discontinued, switched to, or augmented with another antipsychotic; at the end of the study period; or at the end of the 1-year follow-up, whichever came first. A 30-day gap was allowed between the discontinuation and the start of the next prescription. If patients discontinued their initial antipsychotic therapy, they would be followed up for another 30 days after the end of the drug supply of the last prescription. In the case of switch to or augmentation with another antipsychotic, patients would be censored on the date of prescription of another antipsychotic drug.

Cox proportional hazards regression was used to examine whether individual patient characteristics and potential confounders were associated with risk of ARS. To capture important proxies for unmeasured confounders, a high-dimensional propensity score stratification approach was used.[14,15] In brief, all variables were comprehensively collected from prescribed medications, outpatient and inpatient diagnoses, and performed examinations and procedures in the year preceding the initiation of antipsychotic treatment. All included variables were sorted by their potential for biasing the association between antipsychotic use and seizure risk. The top 400 variables thus selected, together with the above-mentioned patient characteristics and potential confounders, were used to create a high-dimensional propensity score for subjects using a specific antipsychotic drug to compare pairwise with those using risperidone, the reference drug.

To test for the robustness of the results, we performed several sensitivity analyses. First, we used conventional covariate approaches with adjustment for the above-mentioned characteristics and confounders. Second, we used the "first-exposure-carried-forward" approach to avoid informative censoring. In this approach, patients would be followed up until the end of the 1-year observation period

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Table 2. Baseline Characteristics of New Users of First-Generation Antipsychotics

Characteristic	Chlorpromazine (n = 8,922), %	Chlorprothixene (n = 782), %	Clothiapine (n = 3,580), %	Flupentixol (n = 3,329), %	Haloperidol (n = 16,656), %	Perphenazine (n = 455), %	Prochlorperazine (n = 37,627), %	Thioridazine (n = 4,743), %	Trifluoperazine (n = 6,010), %
Age									
15–39 y	46.0	44.1	53.1	52.0	43.7	35.6	48.9	46.1	35.1
40–64 y	43.2	48.7	40.6	40.3	39.6	45.7	34.2	42.4	47.0
≥ 65 y	10.7	7.2	6.2	7.7	16.8	18.7	16.8	11.6	17.9
Gender, male	49.7	59.2	55.5	50.8	51.4	31.0	31.0	44.4	35.3
Psychiatric disorders									
Schizophrenia	17.6	30.7	20.1	64.8	53.3	22.0	20.1	22.9	25.7
Bipolar disorder	39.7	49.4	41.5	18.5	26.4	37.4	41.5	43.5	32.0
Major depressive disorder	48.7	26.9	46.9	27.4	29.4	44.8	45.8	42.5	47.1
Mental retardation	0.8	0.9	2.6	2.8	2.1	0.0	0.2	2.3	0.7
Autism spectrum disorder	0.2	0.4	0.1	0.4	0.4	0.0	0.0	0.6	0.1
Alcohol use disorder	4.9	6.6	8.0	3.2	6.0	0.9	3.0	5.0	1.1
Substance use disorder	8.9	6.1	13.8	3.4	4.8	0.9	2.0	7.7	1.4
Medical comorbidity									
Headache	23.7	20.8	19.2	15.0	16.9	36.7	34.8	26.0	33.5
Cancer	4.5	2.9	2.9	1.9	4.4	2.9	4.1	3.4	2.8
Hypertension	18.7	18.5	13.0	12.6	19.1	26.2	23.0	18.1	24.7
Diabetes mellitus	9.2	8.7	7.0	6.2	9.5	8.1	11.0	9.0	10.0
Dyslipidemia	9.8	10.2	8.5	5.3	8.0	10.8	11.0	9.0	12.2
Chronic pulmonary disease	10.3	9.2	8.5	8.4	10.7	16.5	11.5	11.4	9.9
Chronic renal failure	2.4	1.5	1.0	0.8	2.4	1.3	2.5	1.7	0.9
Concomitant medication use									
Anticholinergics	7.4	10.5	18.6	63.0	47.0	21.5	1.0	9.9	21.2
Antidepressants									
TCAs	24.4	16.4	25.6	15.3	14.1	15.6	14.4	31.5	15.7
SSRIs	30.7	52.9	47.8	22.1	17.6	11.9	14.1	42.4	15.0
Other antidepressant	36.3	40.9	49.7	17.1	16.9	14.9	14.2	43.3	14.6
Antiepileptics									
MSAs	11.0	9.8	20.6	7.7	9.9	7.3	4.0	13.4	4.7
Other antiepileptics	3.2	2.0	2.5	1.3	2.7	6.4	3.0	2.2	2.2
Benzodiazepine	84.5	94.0	96.1	84.4	81.7	80.9	65.6	92.9	75.5
Lithium	4.9	5.5	6.8	4.1	4.9	1.3	0.4	5.4	1.0
Health system utilization									
No. of outpatient visits									
< 10	26.5	34.4	31.4	53.6	43.9	21.3	23.9	25.1	26.8
10–19	22.2	23.0	24.8	18.5	20.1	22.0	22.9	20.9	21.2
≥ 20	51.3	42.6	43.7	27.9	36.1	56.7	53.2	54.0	52.0
Hospitalization	25.0	19.8	31.5	25.6	28.3	15.4	19.7	24.3	14.0

Abbreviations: MSA = mood-stabilizing antiepileptic, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

or seizure occurred and would not be censored for treatment change. Finally, we excluded patients with comorbid conditions including mental retardation, autism spectrum disorders, and alcohol- and substance-related disorders because patients with these diseases might have underlying neurologic deficits, which might increase seizure risk.

The statistical significance of association was assessed using 95% confidence intervals (CIs) or a *P* threshold of .05. Adjustment of multiple comparisons was not considered, since this analysis was exploratory in nature. All of the analyses were performed using SAS version 9.2 (SAS Institute; Cary, North Carolina).

RESULTS

We identified 288,397 new antipsychotic users over the study period (schizophrenia: 34.0%; bipolar disorder: 35.6%; and major depressive disorder: 39.6%). The details of the baseline characteristics of the study population classified by antipsychotic use are shown in Tables 1 and 2. The most frequently prescribed antipsychotic medication was sulpiride (38.0%), followed by prochlorperazine (13.1%), quetiapine (12.3%), risperidone (10.8%), and haloperidol (5.8%).

In all, 550 seizure events occurred during the 57,562 person-years follow-up period. The crude point estimate of the seizure incidence rate for FGAs (13.4; 95% CI, 11.4–15.7) was higher than that for SGAs (8.4; 95% CI, 7.6–9.3). The incidence rate of seizure for risperidone, the reference drug, was 7.1 (95% CI, 5.4–9.3). The incidence rate of seizure varied widely among individual antipsychotics, ranging from 3.9 (95% CI, 1.6–8.1) for aripiprazole to 34.9 (95% CI, 12.8–75.9) for chlorprothixene (Table 3).

We found that younger age and male gender conferred a higher risk of ARS (Table 4). Among the psychiatric disorders, schizophrenia, alcohol use disorder, and mental

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Table 3. Incidence Rate of Seizure by Antipsychotic Drug

Drug	No. of Patients	Person-Years	No. of Events	Incidence Rate[a]	95% Confidence Interval
Overall	288,397	57,562	550	9.6	8.8–10.4
Class					
FGAs	82,104	11,910	160	13.4	11.4–15.7
SGAs	206,293	46,523	390	8.4	7.6–9.3
Drug					
Amisulpride	5,653	1,320	16	12.1	6.9–19.7
Aripiprazole	7,118	1,784	7	3.9	1.6–8.1
Chlorpromazine	8,922	1,537	17	11.1	6.4–17.7
Chlorprothixene	782	172	6	34.9	12.8–75.9
Clothiapine	3,580	802	5	6.2	2.0–14.5
Clozapine	2,536	972	13	13.4	7.1–22.9
Flupentixol	3,329	774	6	7.8	2.8–16.9
Haloperidol	16,656	3,135	53	16.9	12.7–22.1
Olanzapine	9,126	2,218	12	5.4	2.8–9.4
Paliperidone	748	192	1	5.2	0.1–29.0
Perphenazine	455	52	1	19.3	0.5–107.6
Prochlorperazine	37,627	3,656	40	10.9	7.8–14.9
Quetiapine	35,446	9,612	84	8.7	7.0–10.8
Risperidone	31,089	7,835	56	7.1	5.4–9.3
Sulpiride	109,571	21,534	185	8.6	7.4–9.9
Thioridazine	4,743	970	25	25.8	16.7–38.0
Trifluoperazine	6,010	813	7	8.6	3.5–17.7
Ziprasidone	891	185	1	5.4	0.1–30.0
Zotepine	4,115	871	15	17.2	9.6–28.4

[a]Per 1,000 person-years.
Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

Table 5. Risk of Seizure With Antipsychotic Use Within 365 Days[a]

	Unadjusted Model HR (95% CI)	High-Dimensional Propensity Score Stratification HR (95% CI)
Class (SGAs as reference)		
FGAs	**1.34 (1.11–1.62)**	1.34 (0.99–1.81)
Drug (risperidone as reference)		
Amisulpride	1.60 (0.91–2.81)	1.62 (0.86–3.05)
Aripiprazole	0.58 (0.26–1.31)	0.41 (0.17–1.00)
Chlorpromazine	1.29 (0.75–2.22)	1.03 (0.52–2.05)
Chlorprothixene	**4.53 (1.95–10.53)**	**2.60 (1.04–6.49)**
Clothiapine	0.82 (0.33–2.04)	0.64 (0.23–1.75)
Clozapine	**2.33 (1.27–4.27)**	**3.06 (1.40–6.71)**
Flupentixol	1.05 (0.45–2.43)	0.98 (0.39–2.43)
Haloperidol	**2.06 (1.41–3.01)**	**2.34 (1.48–3.71)**
Olanzapine	0.74 (0.40–1.38)	0.73 (0.36–1.48)
Paliperidone	1.03 (0.14–7.76)	0.78 (0.10–6.36)
Perphenazine	1.75 (0.24–12.71)	1.28 (0.17–9.71)
Prochlorperazine	0.95 (0.61–1.48)	1.21 (0.64–2.27)
Quetiapine	1.25 (0.89–1.76)	1.26 (0.80–2.00)
Sulpiride	1.08 (0.80–1.46)	1.19 (0.85–1.68)
Thioridazine	**3.16 (1.97–5.08)**	**2.90 (1.65–5.10)**
Trifluoperazine	0.85 (0.38–1.88)	0.91 (0.37–2.28)
Ziprasidone	0.69 (0.10–4.99)	0.55 (0.07–4.12)
Zotepine	**2.23 (1.26–3.94)**	1.66 (0.85–3.24)

[a]Bold indicates a statistically significant difference ($P < .05$).
Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

retardation were associated with a higher risk of ARS. Renal insufficiency was the only medical condition associated with a higher seizure propensity. Anticholinergics, selective serotonin reuptake inhibitors, and mood-stabilizing and other antiepileptics were associated with increased ARS risk, while lithium was associated with decreased ARS risk.

Table 4. Multivariate Cox Proportional Hazards Regression Model for Risk of Antipsychotic-Related Seizure

	Hazard Ratio (95% CI)	*P* Value
Age		
15–39 y	1.00	
40–64 y	0.74 (0.61–0.90)	.002
≥65 y	0.80 (0.57–1.12)	.200
Gender, male	1.34 (1.12–1.60)	.002
Psychiatric disorders		
Schizophrenia	1.71 (1.24–2.36)	.001
Bipolar disorder	1.24 (0.84–1.82)	.287
Major depressive disorder	0.94 (0.69–1.28)	.695
Mental retardation	1.95 (1.31–2.90)	.001
Autism spectrum disorder	1.97 (0.86–4.51)	.107
Alcohol use disorder	2.65 (1.98–3.56)	<.001
Substance use disorder	1.31 (0.93–1.85)	.120
Medical comorbidity		
Headache	1.02 (0.81–1.27)	.886
Cancer	1.35 (0.87–2.08)	.179
Hypertension	1.13 (0.86–1.48)	.392
Diabetes mellitus	1.12 (0.81–1.55)	.502
Dyslipidemia	0.75 (0.52–1.06)	.102
Chronic pulmonary disease	0.73 (0.52–1.01)	.061
Chronic renal failure	1.81 (1.07–3.05)	.026
Concomitant medication use		
Anticholinergics	1.42 (1.14–1.77)	.002
Antidepressants		
TCAs	1.12 (0.90–1.41)	.311
SSRIs	1.47 (1.21–1.80)	<.001
Other antidepressant	0.83 (0.67–1.02)	.077
Antiepileptics		
MSAs	1.71 (1.37–2.14)	<.001
Other antiepileptics	5.31 (4.02–7.02)	<.001
Benzodiazepine	1.03 (0.80–1.33)	.801
Lithium	0.45 (0.24–0.85)	.014
Health system utilization		
No. of outpatient visits		
<10	1.00	
10–19	0.85 (0.67–1.08)	.184
≥20	0.90 (0.71–1.15)	.410
Hospitalization	1.50 (1.24–1.81)	<.001

Abbreviations: MSA = mood-stabilizing antiepileptic, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

In primary analysis with high-dimensional propensity score stratification (Table 5), the FGAs as a group were marginally associated with a higher risk of ARS than the SGAs (adjusted hazard ratio [aHR] = 1.34; 95% CI, 0.99–1.81; $P = .061$). For individual antipsychotics, most were comparable to risperidone in terms of ARS risk. Of note, clozapine (aHR = 3.06; 95% CI, 1.40–6.71), thioridazine (aHR = 2.90; 95% CI, 1.65–5.10), chlorprothixene (aHR = 2.60; 95% CI, 1.04–6.49), and haloperidol (aHR = 2.34; 95% CI, 1.48–3.71) were associated with a higher seizure risk than risperidone. In contrast, the seizure risk with aripiprazole (aHR = 0.41; 95% CI, 0.17–1.00; $P = .050$) was marginally lower than that of risperidone.

In all sensitivity analyses, we found that use of FGAs was associated with a statistically significantly higher risk of seizure than use of SGAs (Supplementary eTables 1, 2B, and 3B). Clozapine, haloperidol, and thioridazine were consistently associated with a higher seizure risk than risperidone. The finding that chlorprothixene carried a higher seizure risk than risperidone was also confirmed by sensitivity analyses, except in analysis using a sample

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excluding patients with comorbid mental conditions. Aripiprazole had a statistically significantly lower seizure risk in analysis using the first-exposure-carried-forward approach (Supplementary eTable 2B) and a marginally lower seizure risk in analysis excluding comorbid mental conditions ($P = .09$) (Supplementary eTable 3B), but not in analyses using conventional covariate adjustment approaches (Supplementary eTable 1).

DISCUSSION

The current study is the first and largest systematic study to estimate and compare the ARS risks associated with FGAs and SGAs available on the Taiwan market in patients with schizophrenia and mood disorders. In terms of methodology, the validity of the ARS diagnosis was improved by including only those presenting with clinically significant seizures at the hospital and emergency department[16]; the ARS diagnosis was further supported by the high proportion of included subjects (90.1%) considered to warrant EEG and/or anticonvulsant treatments. Furthermore, multiple analytic strategies, including a new user design and a high-dimensional propensity score stratification approach, were employed to capture important proxies for unmeasured confounders. We demonstrate the robustness of our findings by several sensitivity analyses.

Of the individual risk factors, younger age, male gender, and the diagnosis of schizophrenia were associated with higher dosages of antipsychotics, thereby increasing ARS risk. Both autism spectrum disorder and mental retardation were associated with a higher risk of seizure, which might reflect their intrinsic seizure-proneness as neurodevelopmental disorders.[17] Renal insufficiency can be associated with a higher risk of seizures as a result of the decreased renal clearance of active antipsychotic metabolites. It is not surprising that alcohol use should be associated with a higher risk of ARS, since chronic use of alcohol might incur organic brain damage, and alcohol withdrawal itself is associated with withdrawal seizures. Although the current study found associations between the use of adjunctive medications and increased ARS risk, any causal inference needs to be further scrutinized. For example, use of antiepileptics, especially those not used as a mood stabilizer, likely reflected the clinician's concerns about possible medical or neurologic conditions that might predispose the individual to seizure. Whether the relationship between selective serotonin reuptake inhibitors and seizure risk is causal warrants further investigation.

The finding that the overall ARS risk of the FGAs was marginally higher than that of the SGAs was contrary to previous results from a study using adverse drug reaction reports in the Spanish Pharmacovigilance System.[10] Such a discrepancy likely arose from the disparity in the definition of relative risk as the ratio of convulsion to all adverse events, rather than true incidence rates among new users of individual antipsychotics. Another cross-sectional study that assessed EEG recordings from 323 hospitalized psychiatric patients indicated that SGA users were more likely to have severe EEG abnormalities (spike discharges or spike-and-wave activities) than FGA users.[18] Likewise, the results were subject to sampling bias and unclear temporality of the development of EEG abnormality and drug exposure.

We found that clozapine, chlorprothixene, haloperidol, and thioridazine were associated with higher seizure risks, but aripiprazole might carry a lower risk than risperidone. Such findings were consistent with the widely recognized fact that clozapine has a high seizure-inducing propensity.[8,19,20] In addition, chlorprothixene was one of the most common antipsychotics reported to be associated with convulsion.[9] Few studies have explored the effect of thioridazine on seizure risk. One study[21] reported the cases of 4 patients on lithium treatment who developed delirium, seizure, and grossly abnormal EEG readings after thioridazine was added.

Despite the common understanding that haloperidol is associated with a low ARS risk, so it has been recommended in different organic brain syndromes,[1,2] we found that haloperidol carried a 2.34-fold greater seizure risk than risperidone. No prior study has compared the seizure risk of haloperidol directly with that of risperidone. One study[9] using the WHO adverse drug reaction database found that the ratio of convulsions to total adverse event reports was 3.27% for haloperidol and 3.68% for risperidone. Of note, the metabolism of haloperidol in Han Chinese populations differs from that in other ethnicities[22]; the higher reduced plasma haloperidol concentration in Han Chinese populations might be associated with an increased risk of neurologic adverse events.[23] The potential modifying effect of ethnicity on the seizure risk of haloperidol warrants further investigation.

The finding that aripiprazole was marginally associated with a lower seizure risk than risperidone is consistent with the reported low rate of new-onset seizure of 0.1% with the use of aripiprazole in clinical trials.[24] As there were no other systematic studies or data to support the superiority of aripiprazole over other antipsychotics in terms of ARS, the finding was encouraging but preliminary. Nevertheless, it could be of significant clinical importance, considering the fact that aripiprazole now has been approved and is widely used for both schizophrenia and mood disorder—it can provide a wider safety margin in clinical practice.

Limitations

Despite the methodological improvements, the current study still has several important limitations. First, the validity of the diagnosis of seizure in the NHIRD was not verified by strict clinical assessments. We found the diagnosis of seizure had good internal validity: approximately 90.1% of patients with seizure events had undergone EEG examination and/or received antiepileptic drugs. However, the results of EEG examination were not available. In addition, we could not fully exclude psychogenic seizure. External validation for the definition of drug-induced seizure warrants further investigation. Second, although we employed a new user design, used high-dimensional propensity score analysis, and

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included most measured confounding factors, there are still unmeasured confounding factors that could have influenced the current results. As an example, we included comorbid alcohol and substance use disorders in our primary analyses and excluded these patients from sensibility analyses. However, the information in the claims records might not reflect the actual exposure status in the real world. Third, we did not adjust for multiple comparisons in this study. Correction with multiple comparisons could reduce type I errors, but also increase type II errors.[25] Given that the aim of this study was to explore the variation of ARS risk across antipsychotics and provide information for clinical decision making, we did not adjust with multiple comparisons in order to avoid missing signals of drug safety. Finally, our results may not be generalizable to the population outside Taiwan, as the common prescription knowledge base and clinical practice might be different in other contexts. Also, pharmacokinetic factors across ethnic groups might potentially impact the risks.

Implications

Pending systematic studies, the current study provides empirical information about the comparative ARS risks of antipsychotics in psychiatric populations and supplements the knowledge base for making judicious choices in prescribing antipsychotics. ARS was of particular concern in the context of alcohol use, renal insufficiency, and certain concurrent medications. Clozapine, chlorprothixene, haloperidol, and thioridazine were associated with significantly higher seizure risks; hence, treatment should be started carefully with low doses and titrated slowly, with the use of the lowest maintenance dose.[26] In contrast, the low seizure-propensity associated with aripiprazole remains to be confirmed by larger-scale systematic studies. If aripiprazole is indeed associated with a lower ARS risk, it might provide a window for delving into the specific receptor-binding profile and neurophysiologic mechanisms underlying the differential seizure-inducing propensity of antipsychotics associated with ARS.

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Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa and others), paliperidone (Invega), pimozide (Orap), prochlorperazine (Procomp and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), thiothixene (Navane and others), ziprasidone (Geodon and others).

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Additional information: This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance of the Department of Health, Taiwan, and managed by the National Health Research Institutes, Taiwan. Information on how to access the data can be found at http://nhird.nhri.org.tw/en/index.html.

Supplementary material: See accompanying pages.

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Supplementary Material

Article Title: Comparative Risk of Seizure With Use of First- and Second-Generation Antipsychotics in Patients With Schizophrenia and Mood Disorders

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List of Supplementary Material for the article

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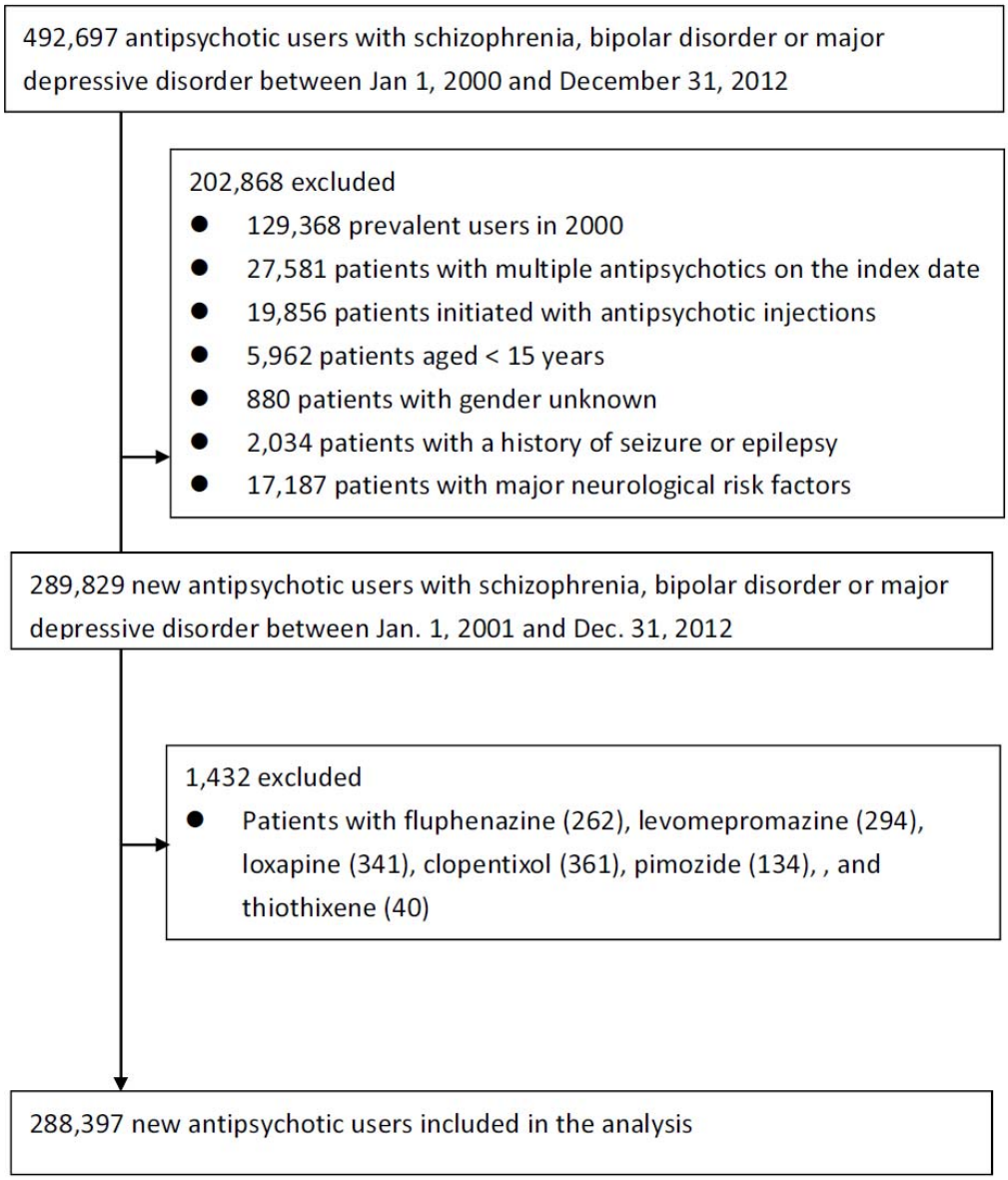
Supplementary eFigure 1. Selection of study population



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Supplementary eTable 1. Risk of seizure with antipsychotic use within 365 days, using as-treated analysis with conventional covariate adjustment approaches

	Multivariate Cox regression model	
	HR	95%CI
Class (SGAs as reference)		
FGAs	**1.37**	**(1.13 , 1.66)**
Drug (risperidone as reference)		
Amisulpride	**1.92**	**(1.06 , 3.47)**
Aripiprazole	0.72	(0.29 , 1.78)
Chlorpromazine	1.20	(0.63 , 2.28)
Chlorprothixene	**3.99**	**(1.58 , 10.04)**
Clothiapine	0.62	(0.23 , 1.65)
Clozapine	**2.50**	**(1.32 , 4.77)**
Flupentixol	1.04	(0.42 , 2.54)
Haloperidol	**1.76**	**(1.13 , 2.74)**
Olanzapine	0.75	(0.39 , 1.43)
Paliperidone	0.96	(0.12 , 7.74)
Perphenazine	1.51	(0.17 , 13.02)
Prochlorperazine	1.22	(0.70 , 2.13)
Quetiapine	1.45	(0.94 , 2.25)
Sulpiride	1.20	(0.87 , 1.67)
Thioridazine	**3.73**	**(2.09 , 6.63)**
Trifluoperazine	0.93	(0.39 , 2.24)
Ziprasidone	0.75	(0.10 , 5.48)
Zotepine	**2.03**	**(1.09 , 3.78)**

Abbreviation: FGAs=first-generation antipsychotics; SGAs=second-generation antipsychotics

Bold indicates a statistically significant difference ($p<0.05$)

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Supplementary eTable 2A Incidence rate of seizure by antipsychotic drug, using first exposure carried forward analysis

Drug	Number of patient	Person-year	Number of event	Incidence rate[a]	95% Confidence Interval
Overall	288397	266089	1772	6.7	(6.4, 7.0)
Class					
FGAs	82104	75991	612	8.1	(7.4, 8.7)
SGAs	206293	190099	1160	6.1	(5.8, 6.5)
Drug					
Amisulpride	5653	5183	34	6.6	(4.5, 9.2)
Aripiprazole	7118	6089	19	3.1	(1.9, 4.9)
Chlorpromazine	8922	8345	55	6.6	(5.0, 8.6)
Chlorprothixene	782	726	15	20.7	(11.6, 34.1)
Clothiapine	3580	3361	19	5.7	(3.4, 8.8)
Clozapine	2536	2410	23	9.5	(6.0, 14.3)
Flupentixol	3329	3145	23	7.3	(4.6, 11.0)
Haloperidol	16656	15280	163	10.7	(9.1, 12.4)
Olanzapine	9126	8418	46	5.5	(4.0, 7.3)
Paliperidone	748	650	5	7.7	(2.5, 17.9)
Perphenazine	455	426	2	4.7	(0.6, 17.0)
Prochlorperazine	37627	34577	257	7.4	(6.6, 8.4)
Quetiapine	35446	30848	218	7.1	(6.2, 8.1)
Risperidone	31089	28939	158	5.5	(4.6, 6.4)
Sulpiride	109571	102854	617	6.0	(5.5, 6.5)
Thioridazine	4743	4411	57	12.9	(9.8, 16.7)
Trifluoperazine	6010	5721	21	3.7	(2.3, 5.6)
Ziprasidone	891	814	5	6.1	(2.0, 14.3)
Zotepine	4115	3893	35	9.0	(6.3, 12.5)

[a] per 1,000 person-years

Abbreviation: FGAs=first-generation antipsychotics; SGAs=second-generation antipsychotics

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Supplementary eTable 2B Risk of Seizure with Antipsychotic Use within 365 Days, using first exposure carried forward analysis

	Unadjusted model		High-dimension propensity score stratification	
	HR	95%CI	HR	95%CI
Class (SGAs as reference)				
FGAs	**1.33**	**(1.20 , 1.46)**	**1.19**	**(1.00 , 1.41)**
Drug (risperidone as reference)				
Amisulpride	1.17	(0.81 , 1.71)	1.33	(0.84 , 2.09)
Aripiprazole	**0.55**	**(0.34 , 0.90)**	**0.53**	**(0.30 , 0.95)**
Chlorpromazine	1.21	(0.89 , 1.64)	1.04	(0.69 , 1.58)
Chlorprothixene	**3.79**	**(2.23 , 6.43)**	**3.22**	**(1.77 , 5.87)**
Clothiapine	1.04	(0.64 , 1.67)	0.89	(0.50 , 1.59)
Clozapine	**1.76**	**(1.13 , 2.72)**	**2.37**	**(1.32 , 4.27)**
Flupentixol	1.34	(0.87 , 2.08)	1.47	(0.87 , 2.50)
Haloperidol	**1.95**	**(1.57 , 2.43)**	**1.96**	**(1.48 , 2.59)**
Olanzapine	1.00	(0.72 , 1.39)	1.21	(0.79 , 1.85)
Paliperidone	1.45	(0.58 , 3.63)	1.17	(0.40 , 3.39)
Perphenazine	0.86	(0.21 , 3.48)	0.78	(0.19 , 3.23)
Prochlorperazine	**1.36**	**(1.12 , 1.66)**	**1.46**	**(1.09 , 1.95)**
Quetiapine	**1.28**	**(1.04 , 1.57)**	1.16	(0.88 , 1.52)
Sulpiride	1.10	(0.92 , 1.31)	**1.24**	**(1.02 , 1.52)**
Thioridazine	**2.37**	**(1.75 , 3.21)**	**2.41**	**(1.66 , 3.50)**
Trifluoperazine	0.68	(0.43 , 1.07)	0.76	(0.42 , 1.35)
Ziprasidone	1.10	(0.45 , 2.68)	1.01	(0.39 , 2.58)
Zotepine	**1.65**	**(1.15 , 2.38)**	1.40	(0.89 , 2.20)

Abbreviation: FGAs=first-generation antipsychotics; SGAs=second-generation antipsychotics

Bold indicates a statistically significant difference ($p<0.05$)

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Supplementary eTable 3A Incidence rate of seizure by antipsychotic drug, excluding patients with mental retardation, autism-spectrum disorder, and alcohol and substance-related disorders, using as-treated analysis

Drug	Number of patient	Person-year	Number of event	Incidence rate[a]	95% Confidence Interval
Overall	263278	52496	433	8.2	(7.5 , 9.1)
Class					
FGAs	74992	10795	128	11.9	(9.9 , 14.1)
SGAs	188286	42433	305	7.2	(6.4 , 8.0)
Drug					
Amisulpride	5156	1219	13	10.7	(5.7 , 18.2)
Aripiprazole	6558	1641	6	3.7	(1.3 , 8.0)
Chlorpromazine	7708	1315	13	9.9	(5.3 , 16.9)
Chlorprothixene	678	155	3	19.4	(4.0 , 56.6)
Clothiapine	2795	655	4	6.1	(1.7 , 15.6)
Clozapine	2367	931	12	12.9	(6.7 , 22.5)
Flupentixol	3027	716	6	8.4	(3.1 , 18.2)
Haloperidol	14650	2793	40	14.3	(10.2 , 19.5)
Olanzapine	8481	2059	7	3.4	(1.4 , 7.0)
Paliperidone	691	176	1	5.7	(0.1 , 31.7)
Perphenazine	447	51	1	19.6	(0.5 , 109.3)
Prochlorperazine	35789	3486	36	10.3	(7.2 , 14.3)
Quetiapine	31524	8570	65	7.6	(5.9 , 9.7)
Risperidone	28117	7091	47	6.6	(4.9 , 8.8)
Sulpiride	101220	19850	144	7.3	(6.1 , 8.5)
Thioridazine	4076	844	19	22.5	(13.6 , 35.2)
Trifluoperazine	5822	780	6	7.7	(2.8 , 16.7)
Ziprasidone	796	163	0	0.0	(0.0 , 22.7)
Zotepine	3376	732	10	13.7	(6.5 , 25.1)

[a] per 1,000 person-years

Abbreviation: FGAs=first-generation antipsychotics; SGAs=second-generation antipsychotics

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Supplementary eTable 3B Risk of seizure with antipsychotic use within 365 days, excluding patients with mental retardation, autism-spectrum disorder, and alcohol and substance-related disorders, using as-treated analysis

	Unadjusted model		High-dimension propensity score stratification	
	HR	95%CI	HR	95%CI
Class (SGAs as reference)				
FGAs	**1.34**	**(1.11 , 1.62)**	**1.37**	**(1.11 , 1.69)**
Drug (risperidone as reference)				
Amisulpride	1.48	(0.80 , 2.76)	1.39	(0.69 , 2.79)
Aripiprazole	0.57	(0.24 , 1.37)	0.44	(0.17 , 1.14)
Chlorpromazine	1.16	(0.56 , 2.40)	1.09	(0.51 , 2.36)
Chlorprothixene	2.77	(0.86 , 8.89)	2.02	(0.58 , 7.03)
Clothiapine	0.88	(0.32 , 2.45)	0.60	(0.20 , 1.80)
Clozapine	**2.43**	**(1.28 , 4.61)**	**2.58**	**(1.16 , 5.73)**
Flupentixol	1.23	(0.53 , 2.88)	1.30	(0.51 , 3.30)
Haloperidol	**1.88**	**(1.23 , 2.88)**	**2.13**	**(1.25 , 3.63)**
Olanzapine	0.50	(0.23 , 1.11)	0.45	(0.19 , 1.08)
Paliperidone	1.08	(0.14 , 8.18)	0.67	(0.08 , 5.45)
Perphenazine	1.95	(0.27 , 14.20)	2.38	(0.31 , 18.56)
Prochlorperazine	1.00	(0.62 , 1.61)	1.41	(0.71 , 2.80)
Quetiapine	1.17	(0.81 , 1.71)	1.34	(0.79 , 2.28)
Sulpiride	0.98	(0.70 , 1.36)	1.22	(0.84 , 1.78)
Thioridazine	**3.02**	**(1.77 , 5.14)**	**3.06**	**(1.61 , 5.84)**
Trifluoperazine	0.82	(0.35 , 1.94)	1.13	(0.40 , 3.18)
Ziprasidone	N/A		N/A	
Zotepine	1.94	(0.98 , 3.83)	1.75	(0.81 , 3.79)

Abbreviation: FGAs=first-generation antipsychotics; SGAs=second-generation antipsychotics

Bold indicates a statistically significant difference ($p<0.05$)

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