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Antipsychotic Treatment and the Risk of Hip Fracture in Subjects With Schizophrenia:
A 10-Year Population-Based Case-Control Study

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ABSTRACT

Background: To investigate the association between antipsychotic treatment and risk of hip fracture in subjects with schizophrenia.

Method: Among patients with schizophrenia (*ICD-9-CM* code 295), 605 cases with hip fracture and 2,828 matched controls were identified from 2002 to 2011 using the National Health Insurance Research Database in Taiwan. The authors conducted a nested case-control study to investigate the association between antipsychotic treatment and risk of hip fracture in subjects with schizophrenia. The modifiable effects of age and gender were evaluated by stratified analysis. In addition, the effects of antipsychotic use, antipsychotic classes, and receptor-binding profiles of antipsychotics, individually, on hip fracture were estimated, and potential confounding factors were adjusted in subsequent analysis. Conditional logistic regressions were applied to determine the effect of antipsychotic treatment on hip fracture.

Results: Current antipsychotic use was associated with an increased risk for hip fracture (adjusted odds ratio [AOR] = 1.61; 95% CI, 1.24–2.10). Among current users, new users had a higher risk of hip fracture (AOR = 4.28; 95% CI, 1.76–10.36) than past users (AOR = 1.11; 95% CI, 0.79–1.56). In addition, a significant increased risk of hip fracture was noted in schizophrenia subjects with first-generation antipsychotic use (AOR = 1.59; 95%CI, 1.15–2.20) but not in those with second-generation antipsychotic use (AOR = 1.16; 95% CI, 0.91–1.48).

Conclusions: These results extend previous findings and demonstrate an increased risk of hip fracture associated with antipsychotic use in schizophrenia subjects. Further investigation is needed to dissect the underlying mechanisms related to the effect of antipsychotic use on hip fracture in subjects at risk.

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Hip fracture is an important public health issue that leads to substantial morbidity and mortality and consequently reduces quality of life and increases health care costs.[1,2] A number of independent risk factors related to hip fracture have been reported by several observational studies, including falls,[3] vitamin D deficiency,[4] low bone mineral density (BMD),[5] and low body mass index (BMI).[6]

Schizophrenia is a devastating neuropsychiatric illness that imposes considerable societal burden.[7,8] A systematic review[9] of epidemiologic studies reports that the estimated lifetime prevalence ranges from 0.30% to 0.66% per 100,000 person-years. It has been well documented that antipsychotic drugs are commonly used in clinical practice to treat subjects with schizophrenia.[10] Previous observational studies[11–13] have reported an increased risk of hip fracture among antipsychotic users. For example, the short-term side effects of antipsychotics include sedation, extrapyramidal symptoms, somnolence, and orthostatic hypotension, all of which may potentially lead to an elevated risk of hip fracture.[14–16] In addition, the long-term effect of antipsychotic use on elevated serum levels of prolactin, which in turn may reduce BMD, has also been noted and considered to be one of the causal risk factors for hip fracture.[17–19] Although a certain number of studies[20–22] have reported decreased BMD in subjects with schizophrenia compared to healthy controls, limited studies have been designed and conducted to examine the association between hip fracture and antipsychotic medication use, particularly in subjects with schizophrenia.[23]

We conducted a nested case-control study to investigate association between antipsychotic use and hip fracture in subjects with schizophrenia using nationwide population-based medical claims data in Taiwan. We hypothesized that antipsychotic use would be associated with an increased risk of hip fracture in subjects with schizophrenia. We first examined whether there was positive association between antipsychotic use and hip fracture in subjects with schizophrenia. Next, we evaluated the modifiable effects of age and sex on the association between antipsychotics and hip fracture. Furthermore, we assessed association of hip fracture with various characteristics of antipsychotics, including classes, dose, and neurotransmitter receptor-binding affinity.

METHOD

Data Source

Data used for this study were obtained from ambulatory and inpatient claims data that are part of the National Health Insurance Research Database (NHIRD) in Taiwan. Briefly, the NHIRD is derived from the National Health Insurance Program (NHIP), which was launched in 1995. The NHIP provides mandatory comprehensive medical care services to residents of Taiwan. Since 1995, the NHIRD derived from the reimbursement claims of the NHIP has collected subjects' demographic characteristics, disease diagnoses, ambulatory care and inpatient claims data, and prescription

records from NHIP enrollees, who represent approximately 98% of the total population in Taiwan.[24] Additional information of the NHIRD can be found at http://nhird.nhri.org.tw/en/index.htm. The data, maintained by the National Health Research Institutes, Taiwan, are provided to scientists for research purposes.

In this study, we used a subset derived from the NHIRD: Psychiatric Inpatient Medical Claim Dataset, which contains inpatient and outpatient medical claims data for subjects with psychiatric disorders, specifically, *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 290–319. This study protocol was approved by the institutional review board at the National Health Research Institutes, Taiwan.

Study Sample

The matched case-control study sample was composed of subjects with an inpatient diagnosis of schizophrenia spectrum disorder (*ICD-9-CM* code 295), aged 20 years and older in 2002. Subjects with a diagnosis of hip fracture before December 31, 2001, were considered to be prevalence cases and excluded from subsequent analyses. The 10-year study duration was from January 1, 2002, to December 31, 2011. Participants were followed from their entry date (January 1, 2002) till the end of the study period (December 31, 2011), the date that they exited the NHI program, or the date that they had a diagnosis of hip fracture.

Cases of Hip Fracture and Controls

The incident cases of hip fracture were defined as subjects aged 20 years and older in 2002 with a medical claim record (either inpatient or outpatient) of hip fracture (*ICD-9-CM* codes 820.0–820.9) during the study period. The date of the first claim record of hip fracture was defined as the index date.

For each case, we randomly selected 5 controls that did not have any hip fracture diagnosis at the time that the matched case had a diagnosis of hip fracture. The controls were individually matched with the case by age (the same birth year), gender, and index year. If there were less than 5 eligible controls, then all controls were selected. Controls were assigned the same index date as their matched case. Of note, subjects were excluded if they participated in the NHI program less than 1 year before the index date (both cases and controls).

Antipsychotic Utilization

Information from prescription records regarding antipsychotic use (N05A) were defined according to the Anatomic Therapeutic Chemical (ATC) classification system, which was developed by the WHO Collaborating Centre.[25] We investigated the effect of antipsychotic use on risk of hip fracture in subjects with schizophrenia based on the status of antipsychotic use (nonusers vs users), antipsychotic classification (first-generation antipsychotics [FGAs] vs second-generation antipsychotics [SGAs]), and various neurotransmitter receptor-binding profiles of antipsychotics

Clinical Points

- Antipsychotic use compared to nonuse of antipsychotics was associated with a 1.34-fold increased risk for hip fracture among patients with schizophrenia.
- First-generation antipsychotics demonstrated an increased risk for hip fracture.

(5-HT_{2A} serotonin, D_2 dopaminergic, α_1 adrenergic, and H_1 histaminergic receptors).

In terms of the status of antipsychotic use, each study subject was first clustered into 1 of 2 groups: users (at least 1 day of antipsychotic drug supply within the 6 months prior to the index date) or nonusers (no exposure to antipsychotics within the 6 months prior to the index date). Next, within the group of users, we classified the subjects as current users (at least 1 day of antipsychotic drug supply during the month before the index date) or past users (at least 1 day of antipsychotic drug supply between 2 and 6 months, but not during the month before the index date). Finally, within the group of current users, we further divided the subjects into new users (first antipsychotic prescription during the month before the index date and no exposure to antipsychotics between 2 and 6 months before the index date) or continuous users (exposure to antipsychotics during the half year before the index date).

In addition to the status of antipsychotic use, antipsychotics examined in this study were classified as either FGAs (chlorpromazine, clopenthixol, clothiapine, chlorprothixene, flupentixol, fluphenazine, haloperidol, levomepromazine, loxapine, methotrimeprazine, moperone, perphenazine, pimozide, pipotiazine, prochlorperazine, thiothixene, trifluoperazine, and thioridazine) or SGAs (amisulpiride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sulpiride, ziprasidone, and zotepine). Of note, although lithium is coded as N05AN01 in the ATC system, we classified lithium as a mood stabilizer rather than an antipsychotic drug and did not include it in this study.

Next, we explored the effect of various neurotransmitter receptor-binding profiles of antipsychotics on risk of hip fracture because the receptor-binding profiles of antipsychotics may be associated with the occurrence of side effects that are related to hip fracture. For example, D_2 dopaminergic antagonism would induce hyperprolactinemia and lead to osteoporosis.[17–19] Medications related to serotonin activation would affect bone formation.[26,27] Moreover, α_1 adrenergic and H_1 histaminergic effect would also increase the risk of falls due to side effects of orthostatic hypotension and oversedation, respectively.[28] According to the Psychoactive Drug Screening Program's K_i Database,[29] the binding affinity of antipsychotics is based on their response to a variety of neurotransmitter receptors, such as 5-HT_{2A} serotonin, D_2 dopaminergic, α_1 adrenergic, and H_1 histaminergic receptors. Patients taking an antipsychotic drug with an unknown K_i value for binding affinity were not included in the subsequent analyses. As such, we included only 15 frequently prescribed antipsychotics

Figure 1. Flow Diagram of Criteria for Inclusion and Exclusion in the Present Study, 2001–2011

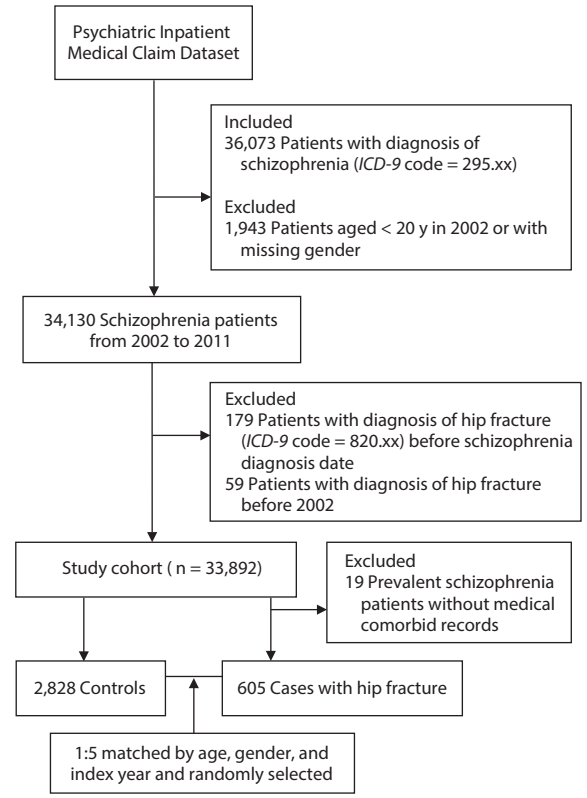


Table 1. Demographic and Clinical Characteristics of the Study Sample

Characteristic	Cases (n = 605) n	Cases (n = 605) %	Controls (n = 2,828) n	Controls (n = 2,828) %	*P* Value[a]
Age, mean ± SD, y	58.51 ± 17.22		56.80 ± 16.42		Not provided[b]
Sex					
Male	332	54.88	1,582	55.94	Not provided[b]
Female	273	45.12	1,246	44.06	
No. of ambulatory visits					
0	29	4.79	232	8.20	< .0001
1–10	92	15.21	533	18.85	
11–20	102	16.86	582	20.58	
≥ 21	382	63.14	1,481	52.37	
No. of inpatient visits					
0	264	43.64	1,764	62.38	< .0001
1	146	24.13	556	19.66	
≥ 2	195	32.23	508	17.96	
Medical comorbidity					
Anemia	35	5.79	122	4.31	.12
Coronary heart disease	3	0.50	15	0.53	.92
Hypertension	168	27.77	643	22.74	.01
Cerebrovascular disease	66	10.91	223	7.89	.02
Chronic pulmonary disease	95	15.70	344	12.16	.02
Diabetes mellitus	81	13.39	356	12.59	.59
Malignant neoplasm	13	2.15	63	2.23	.90
Peripheral vascular disease	10	1.65	37	1.31	.51
Parkinson's disease	47	7.77	155	5.48	.03
Rheumatoid arthritis	5	0.83	11	0.39	.15
Renal failure	16	2.64	31	1.10	.01
Psychiatry comorbidity					
Sleep disorder	137	22.64	531	18.78	.03
Alcohol-related disorder	32	5.29	87	3.08	.01
Substance use disorder	16	2.64	50	1.77	.15
Dementia	89	14.71	267	9.44	< .0001
Medication use					
Antidepressants	214	35.37	739	26.13	< .0001
Anticonvulsants	172	28.43	587	20.76	< .0001
Anxiolytics	359	59.34	1,338	47.31	< .0001
Benzodiazepines	351	58.02	1,408	49.79	< .0001
Oral glucocorticosteroids	70	11.57	290	10.25	.34
Hormone replacement therapy	28	4.63	84	2.97	.04

[a]*P* values were obtained from univariate analysis; Student *t* test was used for continuous variables and χ^2 test was used for discrete variables.
[b]Not provided since the controls were matched to cases on age and sex.

(amisulpiride, chlorpromazine, clothiapine, clozapine, fluphenazine, flupentixol, haloperidol, olanzapine, perphenazine, quetiapine, risperidone, sulpiride, thioridazine, trifluoperazine, and zotepine) in the analyses of antipsychotic binding affinity profiles versus risk of hip fracture (see Supplementary eTable 1 at PSYCHIATRIST.COM). Among those, we examined 15 antipsychotic drugs with either a high or low binding affinity according to the median K_i value for the binding affinity of each neurotransmitter receptor (Supplementary eTable 1).

Potential Confounding Factors

The confounding variables taken into account in this study were comorbid medical and psychiatric illnesses, medication use, and health care utilization in 2000 and 2001. Comorbid medical and psychiatric illnesses that could potentially cause an increased risk of hip fracture included a recent history of anemia, coronary heart disease, hypertension, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, malignant neoplasm, peripheral vascular disease, Parkinson's disease, rheumatoid arthritis, renal failure, sleep disorder, alcohol-related disorder, substance use disorder, and dementia.[30] In addition, medication use in 2000 and 2001 that could increase the occurrence of hip fracture included antidepressants, anticonvulsants, anxiolytics, benzodiazepines, oral glucocorticosteroids, and hormone replacement therapy.[31] Health care system utilization was computed using the number of ambulatory visits and hospitalizations within 2000 and 2001.

Data Analysis

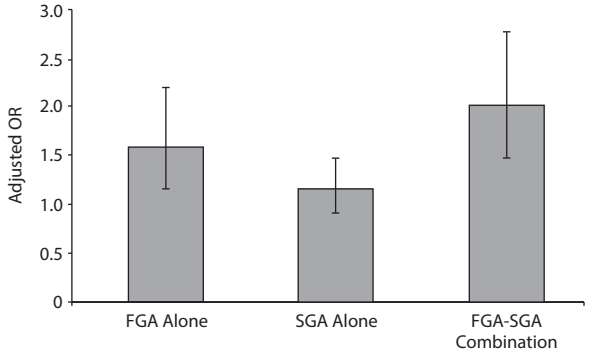
Descriptive statistics of the hip fracture cases and matched controls were reported as counts and the corresponding percentages or by mean and the corresponding standard deviation (SD) for demographic and clinical characteristics, psychiatric comorbidity, medication use, and health care system utilization. We used the Student *t* test for continuous variables and χ^2 test for discrete variables, separately, to compare demographic and clinical characteristics between cases and controls. We performed conditional logistic regression models (with and without covariates adjustment) to estimate the effect of antipsychotics on risk of hip fracture, according to antipsychotic exposure status, classes (FGAs versus SGAs), binding affinity, and daily dose. If subjects took 2 or more classes of antipsychotics at the same time, we defined those subjects as concomitant antipsychotic users. In

Table 2. The Association Between Antipsychotic Use and Hip Fracture, Grouped by Different Exposure Status, and Average Daily Dose of Antipsychotics[a]

Variable, n	Cases (n = 605) n	Cases (n = 605) %	Controls (n = 2,828) n	Controls (n = 2,828) %	Model 1[b,c]	95% CI	Model 2[c,d]	95% CI	Model 3[c,e]	95% CI
Nonusers[f]	164	27.11	1,043	36.88	Reference		Reference		Reference	
Different exposure status of antipsychotic use										
Users	441	72.89	1,785	63.12	**1.61**	1.31–1.97	**1.34**	1.07–1.69	**1.34**	1.07–1.69
Current users	320	52.89	1,273	45.01	**1.72**	1.38–2.14	**1.61**	1.24–2.10	**1.63**	1.25–2.12
New users	27	4.46	51	1.80	**5.17**	2.45–10.88	**4.28**	1.76–10.36	**4.36**	1.84–10.34
Continuous users	293	48.43	1,222	43.21	**1.64**	1.31–2.05	**1.53**	1.17–2.01	**1.55**	1.18–2.03
Past users	121	20.00	512	18.10	**1.41**	1.06–1.87	1.11	0.79–1.56	1.12	0.80–1.56
Type of antipsychotics										
FGA alone	78	12.89	297	10.50	**1.74**	1.28–2.36	**1.59**	1.15–2.20	**1.59**	1.15–2.20
SGA alone	243	40.17	1,172	41.44	**1.31**	1.05–1.64	1.16	0.90–1.48	1.16	0.91–1.48
Combination	120	19.83	316	11.17	**2.62**	1.99–3.45	**2.02**	1.47–2.77	**2.02**	1.48–2.77
Different average daily antipsychotics[g]										
FGAs										
Low (0 ≤ DDD < 0.5)	25	10.50	115	8.61	1.33	0.78–2.26	1.07	0.57–2.00	1.05	0.56–1.94
Medium (0.5 ≤ DDD < 1)	16	6.72	75	5.72	1.26	0.66–2.41	1.13	0.57–2.27	1.01	0.56–2.18
High (1 ≤ DDD)	33	13.87	102	7.64	**2.43**	1.47–4.02	**2.30**	1.30–4.07	**2.36**	1.35–2.18
SGAs										
Low (0 ≤ DDD < 0.5)	98	24.08	425	19.19	1.34	0.99–1.81	1.19	0.85–1.67	1.21	0.86–1.69
Medium (0.5 ≤ DDD < 1)	76	18.67	396	17.88	1.24	0.91–1.70	1.17	0.83–1.66	1.18	0.83–1.67
High (1 ≤ DDD)	69	16.95	351	15.85	1.33	0.96–1.84	1.26	0.88–1.80	1.28	0.90–1.82
Combination										
Low (0 ≤ DDD < 0.5)	39	13.73	91	6.70	**3.58**	2.19–5.86	**2.46**	1.36–4.42	**2.46**	1.37–4.43
Medium (0.5 ≤ DDD < 1)	45	15.85	109	8.02	**2.98**	1.91–4.65	**2.36**	1.36–4.10	**2.48**	1.43–4.29
High (1 ≤ DDD)	36	12.68	116	8.54	**2.06**	1.29–3.31	**1.79**	1.01–3.18	**1.80**	1.02–3.17

[a]Antipsychotic use is defined as at least 1 day of antipsychotic drug supply within the 6 months prior to the index date.
[b]Crude analysis.
[c]Significant results ($P < .05$) are in bold.
[d]Adjusted analysis including all covariates listed in Table 1.
[e]Adjusted analysis including the covariates listed in Table 1 and $P < .15$ after stepwise selection (anemia, hypertension, cerebrovascular disease, chronic pulmonary disease, Parkinson's disease, renal failure, sleep disorder, alcohol-related disorder, dementia, antidepressants, anticonvulsants, anxiolytics, benzodiazepines, hormone replacement therapy, ambulatory visits, and inpatient visits).
[f]Subjects without antipsychotic use were used as the reference group.
[g]Percentages are derived by dividing the number in each cell by total number of nonusers plus number of FGA, SGA, or combination users.
Abbreviations: DDD = defined daily dose, FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

Figure 2. Effect of Different Types of Antipsychotics on Risk of Hip Fracture[a]



[a]The error bar is defined as 95% CI for each corresponding group.
Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

terms of binding affinity, if subjects took both high and low binding affinity antipsychotics within 1 month before the index date, we included them in the high binding affinity group. In addition, we further carried out subgroup analyses with covariates adjustment to examine the modifying effect of subject characteristics, specifically age and sex. Of note, the adjusted covariates included the potential confounding factors listed above. We also applied stepwise selection procedures and identified a set of covariates with P value < .15 for entry or removal in model. All the analyses were carried out with and without adjusting all the potential confounding factors and the covariates with P value < .15.

Statistical significance was assessed using 95% confidence intervals (CIs) or a P value < .05. All of the analyses were performed using SAS version 9.2 for Windows (SAS Institute; Cary, North Carolina).

RESULTS

A total of 3,433 subjects with schizophrenia (605 subjects with hip fracture and 2,828 matched controls) were included in this study. A detailed flowchart for identifying the study cohort is depicted in Figure 1. The distributions of demographic characteristics, comorbid medical and psychiatric disorders, medication use, and health care utilization are presented in Table 1. In detail, the mean ± SD age of schizophrenia subjects with hip fracture was 58.51 ± 17.22 years; and 45.12% were female. Schizophrenia subjects with hip fracture tended to have a higher prevalence of most of the examined diseases than the matched controls, except for malignant neoplasm and coronary heart disease. In addition, compared to the matched controls, they also had

Table 3. Association Between Use of Antipsychotics[a] and Risk of Hip Fracture, Stratified by Patients' Characteristics

Variable	Cases		Controls		Model 1[b,c]		Model 2[c,d]		Model 3[c,e]	
	Users	Nonusers	Users	Nonusers		95% CI		95% CI		95% CI
Patients (N = 3,433)[f]	441 (72.89)	164 (27.11)	1,785 (63.12)	1,043 (36.88)	**1.61**	1.31–1.97	**1.34**	1.07–1.69	**1.34**	1.07–1.69
Subgroup analyses										
Age group, n (%) y										
< 35 (n = 444)	61 (82.43)	13 (17.57)	236 (63.78)	134 (36.22)	**2.68**	1.42–5.08	1.25	0.56–2.82	1.24	0.55–2.77
35–64 (n = 1,686)	200 (71.17)	81 (28.83)	903 (64.27)	502 (35.73)	**1.37**	1.04–1.82	1.09	0.78–1.52	1.09	0.78–1.53
≥ 65 (n = 1,303)	180 (72.00)	70 (28.00)	646 (61.35)	407 (38.65)	**1.70**	1.23–2.36	**1.65**	1.14–2.37	**1.64**	1.14–2.35
Sex, n (%)										
Female (n = 1,519)	214 (78.39)	59 (21.61)	814 (65.33)	432 (34.67)	**2.03**	1.46–2.81	**1.78**	1.23–2.58	**1.76**	1.21–2.54
Male (n = 1,914)	227 (68.37)	105 (31.63)	971 (61.38)	611 (38.62)	**1.38**	1.06–1.78	1.12	0.82–1.51	1.11	0.82–1.49
Charlson Comorbidity Index score, n (%)										
0–1 (n = 2,126)	273 (75.62)	88 (24.38)	1,199 (67.93)	566 (32.07)	**1.53**	1.15–2.02	1.21	0.88–1.68	1.21	0.88–1.67
2–3 (n = 693)	106 (79.70)	27 (20.30)	393 (70.18)	167 (29.82)	1.43	0.78–2.62	1.52	0.74–3.12	1.50	0.73–3.05
≥ 4 (n = 353)	62 (75.61)	20 (24.39)	193 (71.22)	78 (28.78)	1.31	0.53–3.25	0.57	0.06–5.14	0.93	0.23–3.82
Concomitant use of antidepressants, n (%)										
Yes (n = 953)	184 (85.98)	30 (14.02)	595 (80.51)	144 (19.49)	1.46	0.84–2.56	1.57	0.85–2.91	1.60	0.87–2.93
No (n = 2,480)	257 (65.73)	134 (34.27)	1,190 (56.97)	899 (43.03)	**1.44**	1.13–1.83	1.25	0.93–1.67	1.24	0.93–1.66
Concomitant use of anticonvulsants, n (%)										
Yes (n = 759)	141 (81.98)	31 (18.02)	484 (82.45)	103 (17.55)	0.85	0.46–1.57	0.67	0.32–1.43	0.81	0.40–1.65
No (n = 2,674)	300 (69.28)	133 (30.72)	1,301 (58.05)	940 (41.95)	**1.62**	1.29–2.04	**1.41**	1.07–1.84	**1.41**	1.08–1.84
Concomitant use of anxiolytics/ benzodiazepines, n (%)										
Yes (n = 2,322)	384 (83.12)	78 (16.88)	1,456 (78.28)	404 (21.72)	**1.40**	1.05–1.87	**1.43**	1.06–1.94	**1.44**	1.06–1.95
No (n = 1,111)	57 (39.86)	86 (60.14)	329 (33.99)	639 (66.01)	1.24	0.79–1.96	0.79	0.43–1.44	0.76	0.42–1.37

[a]Antipsychotic use is defined as at least 1 day of antipsychotic drug supply within the 6 months prior to the index date.
[b]Crude analysis.
[c]Significant results ($P < .05$) are in bold.
[d]Adjusted analysis including all covariates listed in Table 1.
[e]Adjusted analysis including the covariates listed in Table 1 and $P < .15$ after stepwise selection (anemia, hypertension, cerebrovascular disease, chronic pulmonary disease, Parkinson's disease, renal failure, sleep disorder, alcohol-related disorder, dementia, antidepressants, anticonvulsants, anxiolytics, benzodiazepines, hormone replacement therapy, ambulatory visits, and inpatient visits).
[f]Subjects without antipsychotic use were used as the reference group.

a higher percentage use of the most examined medications and a greater number of outpatient visits, separately (Table 1). We also compared clinical characteristics between FGA and SGA users and found similar distribution of most examined medical comorbidity and medication use in FGA and SGA users, but prevalence of comorbid psychiatric disorders, including sleep disorder, alcohol-related disorder, and substance use disorder, was higher in FGA users than SGA users (Supplementary eTable 2).

We first examined the association between the effect of antipsychotic use and hip fracture. The results in Table 2 suggest that antipsychotic users had a 34% increased risk of hip fracture compared to nonusers (adjusted odds ratio [AOR] = 1.34; 95% CI, 1.07–1.69). When classifying antipsychotic users into current, new, continuous, and past users, separately, a significant increased risk of hip fracture was found among current, new, and continuous users but not past users (current users: AOR = 1.61; 95% CI, 1.24–2.10; new users: AOR = 4.28; 95% CI, 1.76–10.36; continuous users: AOR = 1.53; 95% CI, 1.17–2.01; and past users: AOR = 1.11; 95% CI, 0.79–1.56).

Of note, when data were stratified by different generations of antipsychotics, a significant effect was observed in subjects taking FGAs but not SGAs (both current and past users). Figure 2 indicates a significant effect of FGAs and concomitant use of both FGAs and SGAs on risk of hip fracture, but not SGAs (AOR = 1.59 [95% CI, 1.15–2.20] for subjects taking FGAs, AOR = 1.16 [95% CI, 0.90–1.48] for subjects taking SGAs, AOR = 2.02 [95% CI, 1.47–2.77] for subjects taking both FGAs and SGAs). A dose-response relationship was found between nonusers and subjects taking FGAs (AOR = 1.07 [95% CI, 0.57–2.00] for low-dose users, AOR = 1.13 [95% CI, 0.57–2.27] for medium-dose users, and AOR = 2.30 [95% CI, 1.30–4.07] for high-dose users), but not between nonusers and subjects taking SGAs or between nonusers and subjects taking FGAs and SGAs concomitantly (Table 2).

We further estimated the relationship between current use of individual antipsychotics and risk of hip fracture. Among the examined antipsychotics, we found a positive association between the use of sulpiride (AOR = 1.59 [95% CI, 1.13–2.25] for current users), haloperidol (AOR = 1.47 [95% CI, 1.02–2.13] for current users) and thioridazine (AOR = 2.56 [95% CI, 1.04–6.31] for current users) and the occurrence of hip fracture (Supplementary eTable 3).

Table 3 presents the results of subgroup analyses (stratified by age, sex, Charlson Comorbidity Index score, and concomitant use). We found that among antipsychotic users the risk of hip fracture was slightly higher in young and middle-aged adults than in the elderly (AOR = 1.25 [95% CI, 0.56–2.82] in subjects aged less than 35 years, AOR = 1.09 [95% CI, 0.78–1.52] in subjects aged less than 65 years, AOR = 1.65 [95% CI,

Table 4. Association Between Use of Antipsychotics[a] and Risk of Hip Fracture, Grouped by Various Receptors of Binding Affinity[b]

Classification by receptor biding affinity	Cases		Controls		Model 1[c,d]	95% CI	Model 2[d,e]	95% CI	Model 3[d,f]	95% CI
	n	%	n	%						
5-HT_{2A} serotonin										
Low binding affinity	297	49.83	1,034	37.67	**1.89**	1.52–2.36	**1.62**	1.24–2.10	**1.60**	1.23–2.09
High binding affinity	135	22.65	668	24.34	1.19	0.90–1.58	1.08	0.78–1.51	1.09	0.79–1.01
D_2 dopaminergic										
Low binding affinity	344	58.11	1,387	50.64	**1.61**	1.30–1.99	**1.31**	1.02–1.68	**1.32**	1.03–1.70
High binding affinity	84	14.19	309	11.28	**1.67**	1.20–2.32	**1.52**	1.02–2.26	1.48	0.99–2.19
α_1 Adrenergic										
Low binding affinity	242	42.91	841	31.62	**1.98**	1.57–2.51	**1.59**	1.19–2.13	**1.61**	1.20–2.14
High binding affinity	158	28.01	776	29.17	1.21	0.93–1.58	1.07	0.78–1.47	1.09	0.79–1.49
H_1 histaminergic										
Low binding affinity	314	53.04	1,174	42.86	**1.74**	1.40–2.16	**1.43**	1.10–1.85	**1.43**	1.11–1.85
High binding affinity	114	19.26	522	19.06	1.33	0.99–1.79	1.21	0.85–1.73	1.21	0.85–1.73

[a]Antipsychotic use is defined as at least one day of antipsychotic drug supply within the 6 months prior to the index date.
[b]Subjects without antipsychotic use were used as the reference group. Subjects who used antipsychotics with unknown binding affinity were excluded.
[c]Crude analysis.
[d]Significant results ($P < .05$) are in bold.
[e]Adjusted analysis including all covariates listed in Table 1.
[f]Adjusted analysis including the covariates listed in Table 1 and $P < .15$ after stepwise selection (anemia, hypertension, cerebrovascular disease, chronic pulmonary disease, Parkinson's disease, renal failure, sleep disorder, alcohol-related disorder, dementia, antidepressants, anticonvulsants, anxiolytics, benzodiazepines, hormone replacement therapy, ambulatory visits, and inpatient visits).

1.14–2.37] in subjects aged ≥65 years), but the interactive effect between age and antipsychotic use on hip fracture was not statistically significant (P for interaction = .72). In addition, a significant increased risk of hip fracture was found among women, and borderline significance was found among men (AOR = 1.12 [95% CI, 0.82–1.51] in men and AOR = 1.78 [95% CI, 1.23–2.58] in women; P for interaction = .07). When we examined potential synergistic effect of other psychotropic medications (including antidepressants, anticonvulsants and anxiolytics/benzodiazepines), no significant synergistic effect was found (Table 3).

We next explored the relationship of various neurotransmitter receptor-binding profiles with risk of hip fracture in schizophrenia subjects. The binding affinity of 15 examined antipsychotics was based on their response to a variety of neurotransmitter receptors including 5-HT_{2A} serotonin, D_2 dopaminergic, α_1 adrenergic, and H_1 histaminergic receptors (Supplementary eTable 1). When the relationship between these different receptors of binding affinity and the risk of hip fracture was examined, an increased risk of hip fracture was observed for antipsychotics with low binding affinity for 5-HT_{2A}, H_1 histaminergic, and α_1 adrenergic receptors. In addition, antipsychotics with low or high binding affinity for the dopamine D_2 receptor were associated with the risk of hip fracture (Table 4).

DISCUSSION

To date, limited observational studies have examined the effect of antipsychotics on occurrence of hip fracture in schizophrenia subjects. Consistent with previous studies, our results have demonstrated that antipsychotics are associated with an increased risk of hip fracture in schizophrenia subjects.[13,32,33] Moreover, in subgroup analysis, we observed that schizophrenia subjects taking FGAs had a higher risk of hip fracture compared to those taking SGAs.

The findings from this study are in line with other studies[23,34] showing positive association between antipsychotic use and the risk of hip fracture among patients with schizophrenia. In particular, Howard et al[23] conducted a case-control study using data from a representative database in the United Kingdom and found an elevated risk of antipsychotic-induced hip fracture in patients with a history of schizophrenia. In addition, a recent study conducted by Sørensen et al[34] also found a dose-response relationship between lifetime antipsychotic drug consumption and hip fracture in a Danish population.

In this study, we found a 1.34-fold increased risk of hip fracture in schizophrenia subjects using antipsychotics compared to antipsychotic nonusers, which was comparable to findings reported in previous studies.[11–13,35] For example, Liperoti et al[12] found a 1.4-fold increased risk of hospitalization for femur fracture among elderly patients taking either typical or atypical antipsychotic drugs in comparison to antipsychotic nonusers. In addition, Ray et al[35] reported a 2.0-fold adjusted risk of hip fracture in current antipsychotic users. Interestingly, when further classifying antipsychotics into FGAs and SGAs, we found that schizophrenia subjects using FGAs were at a significantly increased risk for hip fracture, but not those using SGAs. These findings were partially in line with a recent meta-analysis[36] which also showed that FGA users had a higher risk of hip fracture than SGA users, even though we observed insignificant results for SGA users in the present study. In addition, another meta-analysis[37] showed that SGAs were not associated with the risk of falls and fractures in dementia patients in randomized clinical trials.

In this study, we did not observe that age modified the association between antipsychotic use and hip fracture.

However, we found that female schizophrenia patients tended to have a higher risk of hip fracture associated with antipsychotic use than their male counterparts. It should be noted that osteoporosis is more common in women than men[38]; therefore, antipsychotic use might have had a synergistic effect on increased risk of hip fracture in the female schizophrenia subjects.

The underlying mechanisms for the association between hip fracture and antipsychotics would be multifactorial. Antipsychotic drugs were associated with falls due to the adverse effect of oversedation, postural hypotension, or extrapyramidal symptoms, thereby causing hip fracture.[16,28] In addition, the long-term effect of antipsychotic treatment would induce osteoporosis and further increase the risk of hip fracture. Our analysis for the relations of neurotransmitter receptor binding affinity supported the role of osteoporosis on the association between antipsychotics and hip fracture. Most antipsychotics are dopamine D_2 receptor antagonist and would block the prolactin secretion inhibiting function of the tuberoinfundibular system, and consequently cause hyperprolactinemia. Furthermore, hyperprolactinemia would reduce the level of estrogen and testosterone, which would further increase the turnover rate of bone mineral and thus the development of osteoporosis. We found that antipsychotics with both a high and low binding affinity for the dopaminergic D_2 receptor were associated with an elevated risk of hip fracture. Hyperprolactinemia would occur in most antipsychotic treatment, even in those with low D_2 receptor binding affinity.[18] Previous studies have also shown that antipsychotics with lesser prolactin-increasing side effects could increase the risk of hip fracture.[34] In addition, serotonin would inhibit bone formation and play a key role on osteoporosis.[26,27] We found that antipsychotics with a high serotonin receptor binding affinity were not associated with the risk of hip fracture. In contrast, the risk of hip fracture was markedly elevated among those who received low serotonin receptor binding affinity antipsychotics. Therefore, antipsychotics with a high potency serotonin antagonism might show some benefit in bone mineral density, thereby attenuating the risk of hip fracture.

Factors associated with falls had less impact on the occurrence of hip fracture. Although sedation induced by an antihistamine effect or orthostatic hypotension induced by antiadrenergic effect might be potential explanations for an increased risk of hip fracture in schizophrenia subjects with antipsychotic use,[10,13,39] the associations between a high binding affinity for H_1 histaminergic or α_1 adrenergic receptors did not appear to be significant after adjustment was made for other confounding factors (Table 4). These findings were consistent with the work of Hugenholtz et al,[11] which found no association between the degree of antagonism of H_1 histaminergic or α_1 adrenergic receptors and the risk of fracture.

Several limitations should be noted when interpreting the results of this study. First, information regarding adherence to antipsychotic drug therapy was not available in the NHIRD. However, medication adherence would most likely result in nondifferentiated misclassification of diagnosis and would be in favor of a null hypothesis and would reduce the estimated risk. Second, detailed information on clinical variables such as severity of schizophrenia, physical activity, or body weight were not available in the NHIRD. It would be of interest to explore whether antipsychotic treatment is associated with a range in severity of hip fractures. Third, we assumed that patients would always use as-needed medications and categorized them as users. Given that the study populations are patients with schizophrenia, most antipsychotics were prescribed for daily use. The proportion of as-needed antipsychotics would be small. In addition, as-needed antipsychotics were often prescribed for psychiatric indications, which would not be related to hip fracture; therefore, the category would most likely result in nondifferentiated misclassification of antipsychotic use. Fourth, a number of potential confounding factors that might affect risk of hip fracture, such as BMI or physical activity, were not available in the NHIRD. Therefore, we used proxy measures (for example, diabetes and hypertension for obesity) to control for those unmeasured confounders. However, it is likely that the observed increased risk of fracture associated with antipsychotic use might be still partially explained by residual confounding effects due to those unmeasured factors. Fifth, the study sample included only an Asian population; our findings may or may not be generalized to other ethnic populations. Last, the actual pathophysiology of antipsychotic side effects remained unclear; therefore, further investigations will be needed.

In summary, we found that current antipsychotic use increased the risk of hip fracture in subjects with schizophrenia. The highest risk of hip fracture associated with antipsychotic use was observed among new antipsychotic users. The results indicate that antipsychotic use, especially FGAs, may be one of the explanations for the observed association between hip fracture and schizophrenia. Therefore, physicians should pay more caution when prescribing antipsychotics and monitor any potential side effects leading to hip fracture, osteoporosis, or falls. Further investigation would be warranted to facilitate our understanding of the underlying mechanisms related to the effect of antipsychotic drugs on elevated risk of hip fracture.

Drug names: aripiprazole (Abilify and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lithium (Lithobid and others), olanzapine (Zyprexa and others), 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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Author contributions: Drs. Wu and Tsai conceptualized, designed, and supervised the study; raised funding for the study; interpreted the results; and drafted the manuscript. Mss Tsai and Huang performed data analysis, assisted

in data collection, interpreted the results, and participated in drafting and critically revising the manuscript. Dr Chang provided intellectual input, assisted in data analysis and interpretation, and participated in drafting and critically revising the manuscript.

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Supplementary Material

Article Title: Antipsychotic Treatment and the Risk of Hip Fracture in Subjects With Schizophrenia: A 10-Year Population-Based Case-Control Study

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List of Supplementary Material for the article

1. **eTable 1** Receptor binding affinity (pK_i) for antipsychotic drugs
2. **eTable 2** Demographic and clinical characteristics of the FGAs, SGAs and combination drug users
3. **eTable 3** Association of the use of each antipsychotic drug with risk of hip fracture

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Supplementary eTable 1. Receptor binding affinity (pK_i)* for antipsychotic drugs

Drug name	$5HT_{2A}$	D_2	α_1	H_1
First-generation antipsychotics				
Chlorpromazine	7.96	8.29	8.59	8.51
Clothiapine	8.46	-	-	-
Flupentixol	7.06	8.82	-	9.07
Fluphenazine	7.42	9.27	8.20	7.85
Haloperidol	6.81	8.92	7.77	5.77
Perphenazine	8.25	9.04	8.00	8.10
Thioridazine	7.56	7.98	8.30	7.78
Trifluoperazine	7.13	8.89	7.62	7.20
Second-generation antipsychotics				
Amisulpride	5.08	8.89	5.00	5.00
Clozapine	7.80	7.27	8.17	8.95
Olanzapine	8.62	7.28	7.36	8.66
Quetiapine	6.04	6.39	8.09	8.16
Risperidone	9.23	8.24	8.57	7.70
Sulpiride	5.00	7.84	5.00	5.00
Zotepine	8.57	7.60	8.14	8.49

Note:
Abbreviations: $5HT_{2A}$=serotonin 5-HT_{2A} receptor; D_2=dopamine D_2 receptor; α_1 adrenergic receptor; H_1= H_1 histaminergic receptor.
* A minimal (pK_i) value of 5.0 was used for low biding affinity.

Supplementary eTable 2. Demographic and clinical characteristics of the FGAs, SGAs and combination drug users.

	FGAs (*n*=375)		SGAs (*n*=1,415)		combination (*n*=436)		***P-value***[a]
	n	%	n	%	n	%	
Age (mean ± SD)	55.22±15.55		58.38±16.75		52.28±15.90		NP[b]
Sex							
Male	219	58.40	750	53.00	229	52.52	NP[b]
Female	156	41.60	665	47.00	207	47.48	
No. of ambulatory visits							
0	0	0	0	0	0	0	0.02
1-10	47	12.53	139	9.82	35	8.03	
11-20	94	25.07	326	23.04	81	18.58	
≧21	234	62.40	950	67.14	320	73.39	
No. of inpatient visits							
0	225	60.00	819	57.88	186	42.66	<0.0001
1	77	20.53	289	20.42	126	28.9	
≧2	73	19.47	307	21.70	124	28.44	
Medical comorbidity							
Anemia	16	4.27	87	6.15	19	4.36	0.19
Coronary Heart Disease	1	0.27	10	0.71	3	0.69	0.62
Hypertension	100	26.67	370	26.15	109	25.00	0.85
Cerebrovascular disease	17	4.53	128	9.05	42	9.63	0.02
Chronic Pulmonary Disease	47	12.53	206	14.56	62	14.22	0.61
Diabetes mellitus	57	15.20	209	14.77	59	13.53	0.76
Malignant neoplasm	7	1.87	37	2.61	9	2.06	0.62
Peripheral Vascular Disease	7	1.87	21	1.48	5	1.15	0.70
Parkinson's disease	16	4.27	117	8.27	36	8.26	0.03
Rheumatoid arthritis	2	0.53	9	0.64	2	0.46	0.90
Renal failure	5	1.33	20	1.41	4	0.92	0.73
Psychiatry comorbidity							
Sleep disorder	92	24.53	287	20.28	134	30.73	<0.0001
Alcohol-related disorder	23	6.13	36	2.54	25	5.37	0.0003
Substance use disorder	12	3.20	22	1.55	21	4.82	0.0004
Dementia	28	7.47	214	15.12	34	7.80	0.87
Medication use							
Antidepressants	98	26.13	399	28.20	178	40.83	<0.0001
Anticonvulsants	75	20.00	289	20.42	125	28.67	0.0008
Anxiolytics	191	50.93	768	54.28	291	66.74	<0.0001
Benzodiazepines	196	52.27	737	52.08	280	64.22	<0.0001
Oral glucocorticosteroids	47	12.53	153	10.81	58	13.30	0.30
Hormone replacement therapy	13	3.47	61	4.31	24	5.50	0.36

Note:
Abbreviations: SD=standard deviation.
[a] *P* values were obtained from univariate analysis; Student's t test was used for continuous variables and chi-square test was used for discrete variables.
[b] NP=not-provided since the controls were matched to cases on age and sex.

Supplementary eTable 3. Association of the use of each antipsychotic drug* with risk of hip fracture.

	Cases (*n*=605)		Controls (*n*=2,828)		Model 1#,a	95% CI	Model 2#	95% CI	Model 3#	95%CI
	n	%	*n*	%						
Any use of FGAs										
PROCHLORPERAZINE[b]										
Current users	3	0.5	14	0.5	1.06	(0.30, 3.69)	0.78	(0.22, 2.78)	0.77	(0.22, 2.75)
Past users	9	1.49	32	1.13	1.27	(0.60, 2.73)	0.80	(0.36, 1.80)	0.78	(0.35, 1.75)
HALOPERIDOL[b]										
Current users	51	8.43	144	5.09	**1.88**	(1.34, 2.64)	**1.82**	(1.28, 2.58)	**1.84**	(1.30, 2.61)
Past users	47	7.77	134	4.74	**1.91**	(1.34, 2.72)	**1.47**	(1.02, 2.13)	**1.49**	(1.03, 2.16)
CHLORPROMAZINE[b]										
Current users	10	1.65	43	1.52	1.18	(0.59, 2.37)	1.03	(050, 2.10)	0.99	(0.49, 2.01)
Past users	12	1.98	29	1.03	**2.08**	(1.06, 4.11)	1.54	(0.75, 3.13)	1.54	(0.76, 3.13)
TRIFLUOPERAZINE[b]										
Current users	7	1.16	17	0.6	2.01	(0.83, 4.86)	1.90	(0.78, 4.64)	1.96	(0.81, 4.79)
Past users	3	0.5	10	0.35	1.00	(0.22, 4.56)	1.09	(0.24, 5.04)	1.09	(0.23, 5.03)
THIORIDAZINE[b]										
Current users	3	0.5	18	0.64	0.83	(0.25, 2.83)	0.78	(0.23, 2.72)	0.80	(0.23, 2.77)
Past users	8	1.32	14	0.5	**2.87**	(1.20, 6.87)	**2.56**	(1.04, 6.31)	**2.61**	(1.06, 6.42)
FLUPENTIXOL[b]										
Current users	32	5.29	104	3.68	1.51	(0.99, 2.29)	1.45	(0.94, 2.22)	1.43	(0.93, 2.20)
Past users	25	4.13	78	2.76	1.57	(0.99, 2.49)	1.19	(0.73, 1.93)	1.18	(0.73, 1.91)
CLOTHIAPINE[b]										
Current users	12	1.98	25	0.88	**2.47**	(1.23, 4.97)	**2.22**	(1.08, 4.56)	**2.27**	(1.11, 4.65)
Past users	4	0.66	15	0.53	1.39	(0.46, 4.18)	1.01	(0.33, 3.11)	0.99	(0.32, 3.04)

Any use of SGAs										
RISPERIDONE[b]										
Current users	81	13.39	343	12.13	1.18	(0.91, 1.54)	1.15	(0.87, 1.51)	1.16	(0.88, 1.52)
Past users	57	9.42	200	7.07	**1.40**	(1.01, 1.93)	1.22	(0.87, 1.70)	1.21	(0.87, 1.69)
QUETIAPINE[b]										
Current users	55	9.09	177	6.26	1.38	(0.99, 1.92)	1.15	(0.81, 1.63)	1.14	(0.81, 1.62)
Past users	25	4.13	109	3.85	1.11	(0.71, 1.74)	0.80	(0.50, 1.28)	0.81	(0.51, 1.29)
OLANZAPINE[b]										
Current users	29	4.79	106	3.75	1.38	(0.90, 2.12)	1.24	(0.80, 1.91)	1.24	(0.81, 1.92)
Past users	22	3.64	70	2.48	1.53	(0.93, 2.53)	1.20	(0.72, 2.01)	1.19	(0.71, 1.99)
ZOTEPINE[b]										
Current users	13	2.15	55	1.94	1.10	(0.58, 2.09)	0.94	(0.49, 1.82)	0.94	(0.48, 1.81)
Past users	13	2.15	36	1.27	1.66	(0.86, 3.19)	1.29	(0.65, 2.56)	1.31	(0.67, 2.59)
AMISULPRIDE[b]										
Current users	13	2.15	53	1.87	1.23	(0.66, 2.28)	1.06	(0.56, 1.99)	1.04	(0.55, 1.96)
Past users	10	1.65	51	1.8	0.98	(0.49, 1.94)	0.88	(0.44, 1.78)	0.88	(0.44, 1.76)
SULPIRIDE[b]										
Current users	60	9.92	223	7.89	**1.43**	(1.06, 1.94)	1.30	(0.95, 1.79)	1.31	(0.96, 1.79)
Past users	58	9.59	149	5.27	**2.06**	(1.48, 2.86)	**1.59**	(1.13, 2.25)	**1.60**	(1.14, 2.26)
CLOZAPINE[b]										
Current users	12	1.98	91	3.22	0.59	(0.31, 1.12)	0.59	(0.31, 1.12)	0.60	(0.31, 1.13)
Past users	9	1.49	35	1.24	1.10	(0.51, 2.39)	0.98	(0.44, 2.17)	0.99	(0.45, 2.19)
ARIPIPRAZOLE[b]										

Current users	9	1.49	43	1.52	NA	NA	NA
Past users	1	0.17	32	1.13			

Note:
[#] Model 1: crude analysis; Model 2: adjusted analysis including all covariates listed in Table 1; Model 3: adjusted analysis including the covariates listed in Table 1 and p<0.15 after stepwise selection (anemia, hypertension, cerebrovascular disease, chronic pulmonary disease, Parkinson's disease, renal failure, sleep disorder, alcohol-related disorder, dementia, antidepressants, anticonvulsants, anxiolytics, benzodiazepines, hormone replacement therapy, ambulatory visits and inpatient visits).
[*] Antipsychotic use is defined as at least one day of antipsychotic drug supply within the 6 months prior to the index date.
[a] Significant results (p <0.05) are in bold.
[b] Subjects without antipsychotic use were used as the reference group.