Antipsychotic Treatment and the Occurrence of Venous Thromboembolism: A 10-Year Nationwide Registry Study

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ABSTRACT

Objective: To examine the association between antipsychotic use and venous thromboembolism (VTE) in a Taiwan population.

Method: We conducted a nested case-control study using the National Health Insurance Research Database in Taiwan. A total of 2,162 cases with VTE (defined as pulmonary embolism and infarction [*ICD-9-CM*-code: 415.1] or deep vein thrombosis [*ICD-9-CM*-codes: 451.1x, 451.81, or 453.8]) and 12,966 matched controls were identified from 2001 to 2010. Antipsychotic exposure status was measured, and potential confounding factors were adjusted for in the analyses. Conditional logistic regressions were applied to determine the effect of antipsychotic use on VTE.

Results: Current antipsychotic use was associated with an increased risk for VTE (adjusted odds ratio [AOR] = 1.52; 95% CI, 1.19–1.93). Among current antipsychotic users, new users had a higher risk of VTE (AOR = 3.26; 95% CI, 2.06–5.17), whereas the risk among continuous users was modest but not statistically significant (AOR = 1.18; 95% CI, 0.89–1.56).

Conclusions: The results demonstrated an increased risk of VTE among subjects with current antipsychotic use. Antipsychotic drugs should be prescribed with caution and attention to the increased risk of VTE. The underlying mechanisms related to the effect of antipsychotics on VTE development warrant further investigation.

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Venous thromboembolism (VTE) is a serious and life-threatening disease.[1,2] The incidence of VTE among white individuals ranges from 0.70–1.17 per 1,000 person-years,[3,4] while the incidence appears to be 2.5- to 4-fold lower among Asians.[4,5] Known risk factors include age, immobilization, malignancy, trauma, pregnancy, superficial vein thrombosis, and estrogen-related medications.[6]

It has been suspected that antipsychotic drug use may be one of the factors leading to increased VTE risk. Since 1953, case reports and case series studies of VTE after antipsychotic use have been published in the medical literature.[7] However, the association between antipsychotic use and VTE risk has remained inconclusive. First, most studies have indicated a positive association between antipsychotic use and VTE risk, but the estimated risk ranged widely from 1.3 to 13.3.[7–17] Negative findings were reported by 2 recent studies.[18,19] Second, most previous studies were conducted in white populations[8–14,16,18–22]; only 1 small-scale study was conducted in Japan.[17] As a result, the effect of antipsychotics on VTE among Asian populations still has not been fully investigated. Third, factors that modify the effect of antipsychotics on VTE risk such as age and gender were explored in only a few studies.[11,12,16] Finally, the underlying mechanisms remain unclear. The various side effects of antipsychotics have been associated with the neurotransmitter receptor–binding profiles of antipsychotics[23]; however, their role in the pathophysiologic pathway for VTE remains unknown.

We conducted a nested case-control study to examine the association between antipsychotic use and VTE using nationwide population-based medical claims data in Taiwan. We hypothesized that antipsychotic use would increase the risk of VTE. In addition, we further explored the modifying effect of age, sex, and physical conditions on the association between antipsychotics and VTE and the relationship between VTE risk and the 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 datasets that are part of the National Health Insurance Research Database (NHIRD) in Taiwan. In brief, almost all residents in Taiwan have participated in the National Health Insurance (NHI) program. The data derived from the reimbursement claims of the NHI program include patients' demographic characteristics, disease diagnoses, and prescription records. More specifically, each prescription record includes types of medication, date of prescription, duration of drug supply, and dosage. The NHIRD has been used to examine a wide spectrum of diseases including stroke,[24] VTE,[3] and neurodevelopmental disorders.[25] This study used the Longitudinal Health Insurance Database 2005, which included 1,000,000 individuals (roughly 5% of the total population of Taiwan) randomly sampled from the 2005 NHI Registry for Beneficiaries and was representative of the original NHIRD.

Study Sample

This matched case-control study cohort comprised participants 16 years and older in 2001, and the study duration was from January 1, 2001, to December 31, 2010. Cases with a diagnosis of VTE before December 31, 2000, were excluded from the subsequent analyses. We followed participants from their entry date (January 1, 2001) until the end of the study period (December 31, 2010), the date that they exited the NHI program, or the date that they had a diagnosis of VTE.

VTE Cases and Controls

The potential incident VTE cases were defined as those who had an *International Classification of Diseases*, *Ninth Revision*, Clinical Modification (*ICD-9-CM*) diagnosis of pulmonary embolism and infarction (*ICD-9-CM* code: 415.1) or deep vein thrombosis (*ICD-9-CM* codes: 451.1x, 451.81, or 453.8). To ensure the accuracy of diagnosis, a subject must have had at least 1 hospitalization VTE claim record or at least 1 outpatient VTE claim record with subcutaneous or intravenous anticoagulant therapy. The date of the first VTE claim was defined as the index date.

For each VTE case, we randomly selected 6 controls who did not have a VTE diagnosis at the time that the matched case had a diagnosis of VTE. The controls were individually matched with the case by age (the same birth year) and gender. If there were fewer than 6 eligible controls, then all controls were selected. Controls were then assigned an index date, which was defined as the same onset date of the matched VTE case. Of note, subjects were excluded if they were younger than 16 years of age in 2001 or if they had participated in the NHI program for less than 1 year before the index date (both cases and controls).

Antipsychotics Exposure

We defined antipsychotics (N05A) according to the Anatomic Therapeutic Chemical (ATC) classification system, which was developed by the WHO Collaborating Centre[26] to improve the quality of drug use. This system classified medications according to their target organ system and therapeutic, pharmacologic, and chemical properties. We classified antipsychotics into either first-generation antipsychotics (FGAs: chlorpromazine, clopenthixol, clothiapine, flupenthixol, fluphenazine, haloperidol, levomepromazine, loxapine, methotrimeprazine, perphenazine, pimozide, pipotiazine, prochlorperazine, sulpiride, trifluoperazine, and thioridazine) or second-generation antipsychotics (SGAs: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and zotepine). Although lithium was coded as N05AN01 in the ATC system, we classified it as a mood stabilizer rather than an antipsychotic drug.

We further categorized the status of antipsychotic use based on the date of prescription plus the duration of the drug supply. First, participants were classified with regard to antipsychotic exposure as users (defined as at least 1 day of antipsychotic drug supply within the 12 months prior to the index date) or nonusers. Next, we classified the antipsychotic users as current users (defined as at least 1 day of antipsychotic drug supply during the 1 month before the index date) or past users (defined as at least 1 day of antipsychotic drug supply 2–12 months, but not during 1 month, before the index date). Finally, we further divided the current users into new users (defined as the first antipsychotic prescription during 1 month before the index date and no exposure to antipsychotics 2–12 months before the index date) and continuous users (defined as exposure to antipsychotics during both 1 and 2–12 months before the index date).

Clinical Points

- Use of antipsychotic medication is associated with an increased risk of venous thromboembolism, especially among new users of antipsychotics.
- While prescribing antipsychotic medication, physicians should use caution and closely monitor for the symptoms and signs of venous thromboembolism, even among patients who previously had no clinical risk factors.

In addition to the status of antipsychotic use, we further explored the relationship between the various neurotransmitter receptor–binding profiles of antipsychotics and VTE risk. According to the Psychoactive Drug Screening Program's K_i Database,[27] the binding affinity of antipsychotics is grouped as a variety of neurotransmitter receptors, including serotonin 5-HT_{2A}, dopamine D_2, and histamine H_1 receptors (see Supplementary eTable 1 at PSYCHIATRIST.COM). Patients taking an antipsychotic drug with an unknown K_i value of binding affinity were excluded. As such, we only included 14 frequently prescribed antipsychotics (amisulpride, chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, perphenazine, prochlorperazine, quetiapine, risperidone, sulpiride, trifluoperazine, thioridazine, and zotepine) in the analyses of the antipsychotic binding profiles versus the VTE risk. We subsequently classified the examined antipsychotic drugs as having either a high or low binding affinity according to the median K_i value of the binding affinity for each neurotransmitter receptor. Moreover, we examined the dose-response effect of antipsychotics on the VTE risk by using the chlorpromazine-equivalent dose, which was derived from a survey for the consensus of international clinical and research experts.[28]

Potential Confounding Factors

The confounding variables included comorbid medical and psychiatric illnesses, medication use, and health care utilization within 1 year before the index date. In detail, comorbid medical and psychiatric illnesses that could increase the risk of VTE included coronary heart disease, cardiac failure, peripheral vascular disease, mood disorders, and psychotic disorders.[29] Medications that could increase the VTE risk included antidepressants, female hormone–related drugs, lipid modifying agents, mood stabilizers, antithrombotic agents, and benzodiazepines.[16,29] Health care system utilization was computed by the number of clinic visits and hospitalizations within 1 year before the index date.

Data Analysis

Descriptive statistics of the VTE cases and controls were reported as counts with corresponding percentages or as means with corresponding standard deviations (SDs) for demographic characteristics, clinical characteristics, psychiatric comorbidity, medication use, and health care system utilization. To examine the differences in demographic and clinical data between VTE cases and controls, the Student *t* test was performed for continuous variables, and the χ^2 test was performed for discrete variables. We conducted a

conditional logistic regression to estimate the effect of antipsychotics on VTE risk. In considering the small case number, to retain a certain degree of statistical power, we calculated a disease risk score (DRS) for each subject to capture and adjust for the potential confounding effect of the above risk factors.[30,31] We then treated DRS deciles as a categorical variable to control for the confounding effect in a separate conditional logistic regression with the study outcome.

Next, we applied separate conditional logistic regression models to investigate the effect of new antipsychotic use on VTE risk, based on antipsychotic exposure status, antipsychotic class (low-potency FGA, high-potency FGA, and SGA), binding affinity, and chlorpromazine-equivalent dose. In particular, new users taking 2 or more classes of antipsychotics at the same time were defined as multiple antipsychotic users. In terms of binding affinity, new users taking both high and low binding affinity antipsychotics within 1 month before the index date were classified into the high binding affinity group.

To examine the antipsychotic effect modified by the demographic characteristics of the study subjects, we performed subgroup analyses with adjustment of DRS stratified by age (18–44, 45–64, ≥65 years) and gender, separately. We further performed another 2 subgroup analyses to evaluate the effect of various medical conditions, specifically DRS (low vs high) and presence of any major medical risk factor (idiopathic vs nonidiopathic). In detail, we grouped patients into low- and high-risk groups on the basis of the median value of the cases' DRS. Cases with idiopathic VTE were defined as those without major medical risk factors, including fracture of lower limb, pregnancy, malignancy, coronary heart disease, cardiac failure, cerebrovascular disease, and hospitalization during the preceding year. Of note, since cases and controls were not matched by DRS or a major medical risk factor, unconditional logistic regression models with adjustment for age and gender were performed to evaluate the influence of clinical variation among the study subjects. To investigate the modifying effect of subject characteristics such as age and gender, we further examined the interaction between antipsychotic use and subject characteristics by adding a product term of antipsychotic use and subject characteristics in the analysis.

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

Table 1. Demographic and Clinical Characteristics of the Study Sample (2001–2010)[a]

	Cases (n = 2,162)		Controls (n = 12,966)		
Characteristic	n	%	n	%	*P* Value[b]
Sex					…[c]
Male	1,043	48.24	6,252	48.22	
Female	1,119	51.76	6,714	51.78	
No. of ambulatory visits					<.01
0	31	1.43	829	6.39	
1–10	287	13.27	3,456	26.65	
11–20	370	17.11	3,061	23.61	
≥21	1,474	68.18	5,620	43.34	
No. of inpatient visits					<.01
0	1,042	48.20	11,094	85.56	
1	551	25.49	1,250	9.64	
≥2	569	26.32	622	4.79	
Medical comorbidity					
Coronary heart disease	33	1.53	82	0.63	<.01
Cardiac failure	314	14.52	579	4.47	<.01
Peripheral vascular disease	52	2.41	171	1.32	<.01
Cerebrovascular disease	328	15.17	1,169	9.02	<.01
Chronic obstructive pulmonary disease	428	19.80	1,514	11.68	<.01
Peptic ulcer	473	21.88	1,762	13.59	<.01
Liver disease	243	11.24	896	6.91	<.01
Diabetes mellitus	547	25.30	1,907	14.71	<.01
Hemiplegia	39	1.80	94	0.72	<.01
Rheumatologic disease	64	2.96	134	1.03	<.01
Renal failure	250	11.56	259	2.00	<.01
Malignancy	383	17.72	641	4.94	<.01
Hypertension	1,023	47.32	4,640	35.79	<.01
Dyslipidemia	374	17.30	1,782	13.74	<.01
Fracture of lower limb	97	4.49	274	2.11	<.01
Parkinsonism	69	3.19	210	1.62	<.01
Pregnancy	14	0.65	33	0.25	<.01
Varicose veins	62	2.87	38	0.29	<.01
Psychiatric comorbidity					
Mood disorder	125	5.78	385	2.97	<.01
Schizophrenia or other psychotic disorder	40	1.85	92	0.71	<.01
Anxiety disorder	303	14.01	1,162	8.96	<.01
Sleep disorder	406	18.78	1,762	13.59	<.01
Alcohol-related disorder	48	2.22	60	0.46	<.01
Substance use disorder	16	0.74	57	0.44	.06
Dementia	108	5.00	361	2.78	<.01
Medication use					
Anticoagulants	163	7.54	50	0.39	<.01
Female hormone–related drugs	138	6.38	576	4.44	<.01
Mood stabilizers	98	4.53	236	1.82	<.01
Statins	672	31.08	2,767	21.34	<.01
Aspirin	638	29.51	2,076	16.01	<.01
Tamoxifen	15	0.69	22	0.17	<.01
Antidepressants	391	18.09	1,229	9.48	<.01
	Mean ± SD	Median, IQR	Mean ± SD	Median, IQR	
Disease risk score	0.30 ± 0.26	0.19, 0.11–0.42	0.12 ± 0.11	0.09, 0.06–0.12	<.01

[a]Mean ± SD age was 63.98 ± 17.12 years for the cases and 63.96 ± 17.10 years for the controls.
[b]*P* values are obtained from univariate analysis; Student *t* test was used for continuous variables, and χ^2 test was used for discrete variables.
[c]No *P* value provided for sex because controls were matched to cases on age and sex.
Abbreviations: IQR = interquartile range, SD = standard deviation.

Table 2. Association Between Antipsychotic Use and Venous Thromboembolism, Grouped by Exposure Status of Antipsychotic Use

	Cases		Controls		Model 1		Model 2	
	n	%	n	%	Crude OR[a]	95% CI	AOR[a,b]	95% CI
Nonusers	1,797	83.12	11,797	90.98	…	…	…	…
Users	365	16.88	1,169	9.02	**2.07**	1.82–2.35	1.06	0.92–1.23
Current users	132	6.11	290	2.24	**3.01**	2.43–3.72	**1.52**	1.19–1.93
New users	42	1.94	59	0.46	**4.73**	3.17–7.05	**3.26**	2.06–5.17
Continuous users	90	4.16	231	1.78	**2.57**	2.00–3.29	1.18	0.89–1.56
Past users	233	10.78	879	6.78	**1.76**	1.51–2.05	0.91	0.76–1.08

[a]Significant results are in bold; statistical significance was determined in conditional logistic regression by Wald χ^2 test with $df = 1$.
[b]Adjusted for disease risk score deciles.
Abbreviations: AOR = adjusted odds ratio, OR = odds ratio.

Table 3. Association Between New Use of Antipsychotics and Venous Thromboembolism by Class, Various Receptors of Binding Affinity, and Chlorpromazine-Equivalent Dose

	Cases		Controls		Model 1		Model 2	
	n	%	n	%	Crude OR[a]	95% CI	AOR[a,b]	95% CI
Class of antipsychotic received								
None or past user	2,030	97.97	12,676	99.54	…	…	…	…
Low-potency FGAs	25	1.21	42	0.33	**3.72**	2.26–6.12	**2.92**	1.64–5.19
High-potency FGAs	7	0.34	9	0.07	**4.80**	1.78–12.91	**3.38**	1.11–10.29
SGAs only	7	0.34	8	0.06	**5.44**	1.96–15.07	**3.96**	1.22–12.93
Multiple antipsychotics	3	0.14	…	0.00	…	…	…	…
Serotonin 5-HT_{2A} receptor								
None or past user	2,030	97.97	12,676	99.54	…	…	…	…
Low binding affinity	6	0.29	4	0.03	**9.48**	2.67–33.64	**7.32**	1.45–36.89
High binding affinity	36	1.74	55	0.43	**4.06**	2.66–6.21	**3.07**	1.89–4.98
Histamine H_1 receptor								
None or past user	2,030	97.97	12,676	99.54	…	…	…	…
Low binding affinity	9	0.43	13	0.10	**4.23**	1.80–9.94	2.28	0.88–5.93
High binding affinity	33	1.59	46	0.36	**4.48**	2.86–7.03	**3.69**	2.19–6.23
Dopamine D_2 receptor								
None or past user	2,030	97.97	12,676	99.54	…	…	…	…
Low binding affinity	26	1.25	32	0.25	**5.06**	3.00–8.52	**3.21**	1.76–5.88
High binding affinity	16	0.77	27	0.21	**3.69**	1.98–6.87	**3.43**	1.68–6.97
Chlorpromazine-equivalent dose								
None or past user	2,030	97.97	12,676	99.54	…	…	…	…
Low dose (< 100 mg)	21	1.01	24	0.19	**5.32**	2.95–9.59	**3.11**	1.57–6.14
High dose (≥ 100 mg)	21	1.01	35	0.27	**3.80**	2.21–6.55	**3.47**	1.87–6.45

[a]Significant results are in bold; statistical significance was determined in conditional logistic regression by Wald χ^2 test with $df = 1$.
[b]Adjusted for disease risk score deciles.
Abbreviations: AOR = adjusted odds ratio, FGA = first-generation antipsychotic, OR = odds ratio, SGA = second-generation antipsychotic.

RESULTS

A total of 2,162 cases were included and examined in subsequent analyses. In detail, we initially identified 2,535 cases with a diagnosis of VTE between 2001 and 2010; however, 373 cases were excluded from the study due to a prior diagnosis of VTE in 2000 (n = 202), age younger than 16 years in 2001 (n = 16), or use of warfarin within 30–365 days before the index date (n = 155). As a result, a total of 2,162 cases were included in the study and examined in subsequent analyses. The distributions of demographic characteristics, comorbid medical and psychiatric disorders, medication use, and health care utilization are presented in Table 1. Mean age and the corresponding standard deviation (SD) of the VTE cases was 64.0 ± 17.1 years, and 51.8% of the VTE cases were women. Compared to the 12,966 controls, the VTE cases had a higher prevalence of all examined diseases, a higher prevalence of use of various examined types of medication, and a greater number of outpatient visits and hospitalizations (Table 1).

Next, we investigated the association between antipsychotic use and VTE. As shown in Table 2, compared to nonusers, current antipsychotic users had a 52% increased risk of VTE (adjusted odds ratio [AOR] = 1.52; 95% CI, 1.19–1.93). Past antipsychotic use was not associated with VTE risk (AOR = 0.91; 95% CI, 0.76–1.08). Interestingly, new antipsychotic users had a higher risk of VTE (AOR = 3.26; 95% CI, 2.06–5.17), whereas the risk among continuous antipsychotic users was modest but not statistically significant (AOR = 1.18; 95% CI, 0.89–1.56).

Table 3 shows the associations between new use of antipsychotics and VTE risk in relation to various antipsychotic classes, potency, various receptors of binding affinity, and chlorpromazine-equivalent dose, separately. When examining various antipsychotic classes and potency, we found that all classes of antipsychotics were associated with increased

Table 4. Association Between Continuous Use of Antipsychotics and Venous Thromboembolism by Class, Various Receptors of Binding Affinity, and Chlorpromazine-Equivalent Dose

	Cases		Controls		Model 1		Model 2	
	n	%	n	%	Crude OR[a]	95% CI	AOR[a,b]	95% CI
Class of antipsychotic received								
None or past users	2,030	95.75	12,676	98.21	…	…	…	…
Low-potency FGAs	28	1.32	82	0.64	**2.14**	1.39–3.30	1.05	0.65–1.71
High-potency FGAs	15	0.71	57	0.44	1.68	0.95–2.97	1.00	0.53–1.88
SGAs only	33	1.56	68	0.53	**3.01**	1.98–4.57	1.53	0.96–2.45
Multiple antipsychotics	14	0.66	24	0.19	**3.59**	1.85–6.95	1.21	0.58–2.51
Serotonin 5-HT_{2A} receptor								
None or past users	2,030	95.80	12,676	98.23	…	…	…	…
Low binding affinity	21	0.99	39	0.30	**3.36**	1.97–5.73	1.41	0.78–2.53
High binding affinity	68	3.21	190	1.47	**2.25**	1.70–2.98	1.17	0.85–1.61
Histamine H_1 receptor								
None or past users	2,030	95.80	12,676	98.24	…	…	…	…
Low binding affinity	37	1.75	94	0.73	**2.48**	1.69–3.64	**1.58**	1.03–2.43
High binding affinity	52	2.45	133	1.03	**2.45**	1.77–3.38	1.05	0.73–1.51
Dopamine D_2 receptor								
None or past users	2,030	95.75	12,676	98.23	…	…	…	…
Low binding affinity	33	1.56	93	0.72	**2.26**	1.51–3.37	1.23	0.78–1.92
High binding affinity	57	2.69	135	1.05	**2.62**	1.92–3.58	1.25	0.88–1.78
Chlorpromazine-equivalent dose								
None or past users	2,030	95.75	12,676	98.21	…	…	…	…
Low dose (< 100 mg)	33	1.56	95	0.74	**2.16**	1.45–3.21	1.31	0.84–2.06
High dose (≥ 100 mg)	57	2.69	136	1.05	**2.65**	1.93–3.62	1.15	0.81–1.63

[a]Significant results are in bold; statistical significance was determined in conditional logistic regression by Wald χ^2 test with $df = 1$.
[b]Adjusted for disease risk score deciles.
Abbreviations: AOR = adjusted odds ratio, FGA = first-generation antipsychotic, OR = odds ratio, SGA = second-generation antipsychotic.

Table 5. Association Between Antipsychotic Use and Venous Thromboembolism Stratified by Age, Gender, Disease Risk Score, and Presence of Major Medical Risk Factors

	Cases		Controls		Model 1			
	Current Users	Nonusers or Past Users	Current Users	Nonusers or Past Users	Crude OR[a]	95% CI	Model 2 AOR[a–c]	Model 2 95% CI
Age								
16–44 y	17	307	26	1,918	**3.97**	2.15–7.35	0.92	0.44–1.94
45–64 y	30	615	77	3,793	**2.42**	1.57–3.74	0.92	0.56–1.51
≥ 65 y	85	1,108	187	6,965	**2.86**	2.19–3.72	**1.90**	1.42–2.54
Gender								
Male	72	1,047	176	6,538	**3.28**	2.39–4.52	**1.68**	1.17–2.42
Female	60	983	114	6,138	**2.56**	1.93–3.40	**1.45**	1.05–2.00
Disease risk score								
Low	46	1,035	215	11,342	**4.54**	3.01–6.86	**5.11**	3.47–7.53
High	86	995	75	1,334	**2.44**	1.85–3.20	**2.29**	1.76–2.96
Major medical risk factor[d]								
Nonidiopathic	100	1,299	132	3,219	**1.93**	1.45–2.58	**1.99**	1.51–2.61
Idiopathic	32	731	158	9,457	**2.90**	1.91–4.39	**2.69**	1.83–3.97

[a]Significant results are in bold; statistical significance was determined using logistic regression by Wald χ^2 test with $df = 1$.
[b]For age and gender, statistical significance was determined using conditional logistic regression with adjustment for disease risk score deciles.
[c]For disease risk score and major medical risk factor, statistical significance was determined using unconditional logistic regression with adjustment for age and gender.
[d]Included fracture of lower limb, pregnancy, malignancy, coronary heart disease, cardiac failure, cerebrovascular disease, and hospitalization in the preceding year.
Abbreviations: AOR = adjusted odds ratio, OR = odds ratio.

risk of VTE (Table 3). When examining the relationship between different receptors of binding affinity and VTE risk, we found no significant difference between low and high binding affinity for 5-HT_{2A}, histamine H_1, and dopamine D_2 receptors (Supplementary eTables 2 and 3). Additionally, no clear trend was observed for the dose-response relationship after adjusting for DRS (Tables 3 and 4). Likewise, similar results were observed when we examined the association between continuous use of antipsychotics and VTE risk in relation to various antipsychotic classes, potency, various receptors of binding affinity, and chlorpromazine-equivalent dose, separately, but most associations were not statistically significant (Table 4).

Table 5 shows the results of subgroup analyses. Among current antipsychotic users, subjects with low DRS had a higher VTE risk than those with high DRS. Although the 95% confidence interval overlapped, we found a significant interaction between DRS level and antipsychotic use ($P = .04$).

Similarly, among current antipsychotic users, subjects without major medical risk factors had a higher VTE risk compared with subjects with major medical risk factors, but the interaction between major medical risk factors and antipsychotic use was not statistically significant ($P = .12$). In addition, we did not find an interaction of antipsychotic use with gender ($P = .59$) or age ($P = .16$).

DISCUSSION

This study demonstrated that antipsychotics are associated with an increased VTE risk in a Taiwanese population. Current antipsychotic use was associated with a 52% increased risk of VTE (AOR = 1.52; 95% CI, 1.19–1.93). Among current users, new users had a higher risk of VTE than continuous users. In addition, patients with low DRS and those without major medical risk had a higher VTE risk among current antipsychotic users.

Our results were supported by most previous studies conducted among white subjects.[10–13,16,18,22] For example, one meta-analysis[15] included 7 case-control studies and found that the pooled estimated VTE risk of current and recent antipsychotic use was 2.39 (95% CI, 1.71–3.35). However, our estimated risk (AOR = 1.52; 95% CI, 1.19–1.93) was lower than that reported in this previous meta-analysis. Although our finding might imply that the VTE risk associated with antipsychotic use among Asian populations could be less severe, it should be noted that in the study by Zhang et al,[15] the pooled estimate was calculated directly according to the exposure status of cases and controls, without adjustment for any potential confounding factor. In addition, one large-scale study[12] using a representative database in the United Kingdom found a relatively small VTE risk of 1.56 (95% CI, 1.39–1.75), which was closer to our findings. Therefore, the difference of the estimated effect of antipsychotic use on the VTE risk might be attributed to sample size, as well as to controlling for various potential confounders, rather than ethnic differences. On the other hand, one observational study,[17] which surveyed 1,125 forensic autopsy records, reported an increased VTE risk of 10.49 (95% CI, 3.95–27.85) in a Japanese population. However, the estimated risk reported in this forensic autopsy study might be overestimated due to the method of control selection and a lack of adjustment for potential confounders.

Two studies[18,19] showed a lack of association between antipsychotic use and VTE risk. Ray et al[19] conducted a retrospective cohort study in Canada and compared the VTE risk of subjects with antipsychotic use to that of subjects receiving thyroid hormone therapy, as negative controls. No association was found for overall antipsychotic use and risk of VTE. Although no evidence indicated that thyroid hormone therapy was associated with VTE, patients with hypothyroidism might have lower physical activity levels and consequently an increased risk of developing VTE; thus, the findings would be confounded by hypothyroidism. Kleijer et al[18] used prescription drug data from the PHARMO database in the Netherlands to investigate the VTE risk of elderly patients treated with antipsychotics. They did not find an increased risk of VTE among antipsychotic users compared with nonusers. However, their study was based on a small sample size, and they did not adjust for psychiatric diagnosis. In addition, age might have been a potential effect modifier in these 2 studies conducted in the elderly. Therefore, the effect of antipsychotics on VTE risk among patients with more comorbid disorders might be less significant. Consistently, we found that the magnitude of the VTE risk was smaller among those with either a high DRS or nonidiopathic status, although the age effect in our study was not significant.

Several plausible hypotheses might explain the observed association between antipsychotic use and VTE.[9] The sedative effect of antipsychotics would decrease physical activity; as a consequence, it may cause venous stasis and increase the occurrence of VTE. In addition, the function of platelet aggregation might be directly enhanced by antipsychotics or secondary to hyperprolactinemia. However, we could not draw conclusions regarding the above stated hypotheses (ie, sedative effect [histamine H_1 receptors], directly enhanced platelet aggregation [serotonin 5-HT_{2A} receptor], and hyperprolactinemia [dopamine D_2 receptor]) based on our nonsignificant results with respect to the effect of binding affinity for various neurotransmitter receptors. One potential reason for the nonsignificant results is that the sample size might not have been large enough, especially after stratification into low and high binding affinity for various kinds of receptors. In addition, it is likely that the pathophysiologic pathway for the link between VTE and antipsychotic use might not be through the receptor binding affinity. Moreover, other possible mechanisms such as elevation of antiphospholipid antibodies should be also considered.[14,32] As such, further investigation to explore the underlying mechanisms linking antipsychotic use and the development of VTE is merited.

Several limitations of the study should be noted. First, the accuracy of VTE was not validated by medical chart review. However, we defined VTE cases based not only on the *ICD-9-CM* codes (415.1, 451.1x, 451.81, or 453.8) but also on VTE hospitalization claim records or at least 1 outpatient VTE claim record with subcutaneous or intravenous anticoagulant therapy, to ensure the accuracy of diagnosis. Second, data on adherence to antipsychotic drug therapy were not available in the NHIRD. However, misclassification of diagnosis or medication adherence might be undifferentiated and would reduce the estimated risk. Third, the indications for antipsychotic use might have biased our findings. Most indications for antipsychotic treatment are acute psychotic or behavioral disturbances, which would generally increase patient activity levels. Although patients with a psychotic state might have catatonic symptoms or be physically restrained, the proportion would be small. Therefore, the treatment indications were unlikely to bias our findings. Fourth, a number of potential confounding factors that might affect the association between antipsychotic use and VTE, such as body mass index and smoking, are not available in the NHIRD. Therefore, we used proxy measures, such as chronic obstructive pulmonary diseases for smoking and hyperlipidemia and diabetes for obesity, to control for those unmeasured

confounders. However, it is likely that the observed increased risk with antipsychotic use might still be partially explained by unmeasured confounders.

In conclusion, we found that current antipsychotic use increased the risk of VTE in an Asian population. The highest VTE risk associated with antipsychotic use was observed among new antipsychotic users. Although there seems to be a lower VTE incidence in Asian populations, physicians should take caution when prescribing antipsychotics, particularly for first-time prescriptions, and closely monitor any symptom of VTE, including chest pain, dyspnea, or lower extremity edema. Preventive strategies such as sufficient hydration and regular physical exercise should be considered among patients taking antipsychotics.[33]

Regarding research implications, further investigation would be warranted to shed more light on the underlying mechanisms related to the effect of antipsychotic use on VTE risk.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lithium (Lithobid and others), loxapine (Loxitane and others), olanzapine (Zyprexa), pimozide (Orap), prochlorperazine (Procomp and others), quetiapine (Seroquel), risperidone (Risperdal and others), warfarin (Coumadin, Jantoven, and others), ziprasidone (Geodon.

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Supplementary material: Supplementary material available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Antipsychotic Treatment and the Occurrence of Venous Thromboembolism: A 10-Year Nationwide Registry Study

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List of Supplementary Material for the article

Disclaimer

Supplementary eTable 1. Receptor binding affinity (pK_i)[a] for antipsychotic drugs

Antipsychotic drug	$5HT_{2A}$	D_2	H_1
Amisulpride	5.08	8.89	5.00
Chlorpromazine	7.96	8.29	8.51
Clozapine	7.80	7.27	8.95
Fluphenazine	7.42	9.27	7.85
Haloperidol	6.81	8.92	5.77
Olanzapine	8.62	7.28	8.66
Perphenazine	8.25	9.04	8.10
Prochlorperazine	7.82	9.40	7.72
Quetiapine	6.04	6.39	8.16
Risperidone	9.23	8.24	7.70
Sulpiride	5.00	7.84	5.00
Thioridazine	7.56	7.98	7.78
Trifluoperazine	7.13	8.89	7.20
Zotepine	8.57	7.60	8.49

Abbreviations: $5HT_{2A}$=serotonin 5-HT_{2A} receptor; D_2=dopamine D_2 receptor; H_1= histamine H_1 receptor.

[a] A minimal (pK_i) value of 5.0 was used for low biding affinity.

Supplementary eTable 2. Association between new use of antipsychotics and VTE by various receptors of binding affinity (using low binding affinity as the reference group).

	Case		Control		Model 1		Model 2	
	n	**%**	**n**	**%**	**Crude OR[a]**	**95% CI**	**AOR[a,b]**	**95% CI**
Serotonin 5-HT_{2A} receptor								
None or past users	2,030	(97.97)	12,676	(99.54)	**0.11**	(0.03-0.37)	**0.14**	(0.03-0.69)
Low binding affinity	6	(0.29)	4	(0.03)	-	-	-	-
High binding affinity	36	(1.74)	55	(0.43)	0.43	(0.11-1.63)	0.42	(0.08-2.26)
Histamine H_1 receptor								
None or past users	2,030	(97.97)	12,676	(99.54)	**0.24**	(0.10-0.56)	0.44	(0.17-1.14)
Low binding affinity	9	(0.43)	13	(0.10)	-	-	-	-
High binding affinity	33	(1.59)	46	(0.36)	1.06	(0.40-2.78)	1.62	(0.55-4.79)
Dopamine D_2 receptor								
None or past users	2,030	(97.97)	12,676	(99.54)	**0.20**	(0.12-0.33)	**0.31**	(0.17-0.57)
Low binding affinity	26	(1.25)	32	(0.25)	-	-	-	-
High binding affinity	16	(0.77)	27	(0.21)	0.73	(0.33-1.64)	1.07	(0.42-2.70)

Abbreviations: OR=odds ratio; AOR=adjusted odds ratio.

[a] Significant results are in bold; statistical significance was determined in conditional logistic regression by Wald χ^2 test with df = 1.

[b] Adjusted for disease risk score deciles.

Supplementary eTable 3. Association between continuous use of antipsychotics and VTE by various receptors of binding affinity (using low binding affinity as the reference group).

	Case		Control		Model 1		Model 2	
	n	**%**	**n**	**%**	**Crude OR[a]**	**95% CI**	**AOR[a,b]**	**95% CI**
Serotonin 5-HT_{2A} receptor								
None or past users	2,030	(95.80)	12,676	(98.23)	**0.30**	(0.18-0.51)	0.71	(0.40-1.27)
Low binding affinity	21	(0.99)	39	(0.30)	-	-	-	-
High binding affinity	68	(3.21)	190	(1.47)	0.67	(0.37-1.22)	0.83	(0.43-1.61)
Histamine H_1 receptor								
None or past users	2,030	(95.80)	12,676	(98.24)	**0.40**	(0.28-0.59)	**0.63**	(0.41-0.97)
Low binding affinity	37	(1.75)	94	(0.73)	-	-	-	-
High binding affinity	52	(2.45)	133	(1.03)	0.99	(0.60-1.63)	0.67	(0.38-1.16)
Dopamine D_2 receptor								
None or past users	2,030	(95.75)	12,676	(98.23)	**0.44**	(0.30-0.66)	0.81	(0.52-1.28)
Low binding affinity	33	(1.56)	93	(0.72)	-	-	-	-
High binding affinity	57	(2.69)	135	(1.05)	1.16	(0.70-1.92)	1.02	(0.58-1.79)

Abbreviations: OR=odds ratio; AOR=adjusted odds ratio.

[a] Significant results are in bold; statistical significance was determined in conditional logistic regression by Wald χ^2 test with df = 1.

[b] Adjusted for disease risk score deciles.