Antipsychotic Drugs, Mood Stabilizers, and Risk of Pneumonia in Bipolar Disorder: A Nationwide Case-Control Study

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ABSTRACT

Objective: Like mood stabilizers, most second-generation antipsychotics are widely used to treat patients with bipolar disorder, yet their safety is still a concern. This study explored the association between antipsychotics and mood stabilizers and the risk of pneumonia, and it provides evidence-based information for clinical practice.

Method: In a nationwide cohort of bipolar patients (*ICD-9* codes 296.0 to 296.16, 296.4 to 296.81, and 296.89) derived from the National Health Insurance Research Database in Taiwan, who were admitted between July 1, 1998, and December 31, 2006 (N = 9,999), we identified 571 patients who developed pneumonia (*ICD-9* codes 480 to 486 and 507) requiring hospitalization defined as *cases*. On the basis of risk-set sampling in a 1:4 ratio, 2,277 matched controls were selected from the same cohort. We used conditional logistic regression to assess the association between drug exposure and pneumonia and sensitivity analyses to validate the association.

Results: Current use of several antipsychotics separately, including olanzapine (adjusted risk ratio [RR] = 2.97, $P < .001$), clozapine (RR = 2.59, $P < .01$), and haloperidol (RR = 3.68, $P < .001$), is associated with a dose-dependent increase in the risk of pneumonia. Interestingly, lithium has a dose-dependent protective effect from pneumonia. Among certain drug combinations, olanzapine plus carbamazepine had the highest risk (RR = 11.88, $P < .01$), followed by clozapine plus valproic acid (RR = 4.80, $P < .001$).

Conclusions: Several antipsychotics, but not mood stabilizers, were associated with the risk of pneumonia, which deserves our concern regarding patient safety. Some of the combinations of therapy resulted in synergy of risk.

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Bipolar disorder is a recurring mental illness that is complicated by high comorbidity and risk of poor health outcomes.[1] In addition to lithium, valproic acid, and carbamazepine, the US Food and Drug Administration has approved most of the second-generation antipsychotics for treating bipolar disorder.[2] Recent treatment guidelines for bipolar disorder[3] recommend that several second-generation antipsychotics be used for first-line monotherapy, including olanzapine, quetiapine, and risperidone. A recent meta-analysis[4] demonstrated that several antipsychotic drugs were superior to mood stabilizers in efficacy for acute mania, including olanzapine, risperidone, and haloperidol. However, the safety of antipsychotic drugs used in bipolar disorder could be underestimated, including the risk of pneumonia. An emerging body of literature shows that antipsychotic agents are associated with the risk of pneumonia in the elderly population[5,6] and in patients with schizophrenia,[7] but few studies of pneumonia risk in bipolar disorder exist.[8] An open adjunctive ziprasidone study[8] showed that 1 of 22 bipolar patients discontinued the trial because of pneumonia. Studies regarding individual antipsychotic agents and the risk of pneumonia in bipolar patients are lacking.

Clinical guidelines have long recommended lithium and valproic acid as the first-line treatment for bipolar disorder.[9,10] Risks of both drugs regarding the development of pneumonia are not yet established. Furthermore, many patients do not respond to monotherapy, and combination therapy is often recommended despite little evidence of its effectiveness.[10–12] Lithium or valproic acid with a second-generation antipsychotic is usually suggested as the second-line therapy choice and sometimes as the first-choice treatment for severe mania.[3] As for safety concerns, the question of whether the combination therapies are more likely to induce pneumonia than monotherapy deserves evidence-based information.

This study investigated the association between antipsychotics and mood stabilizers and the risk of pneumonia in a nested case-control study derived from a large nationwide bipolar cohort in Taiwan. Using multivariate and propensity-scoring methods, we focused on the risk of developing pneumonia with the most commonly used individual agents for treatment of bipolar patients in Taiwan. This study explored several dimensions of the risk for pneumonia associated with these agents, including temporal relationships, duration and dose of use, and combination therapies.

METHOD

Data Sources

The single-payer National Health Insurance program was implemented in Taiwan in 1995, and coverage of the 23,000,000 Taiwanese population had reached 98% by the end of 2007. The National Health Insurance Research Database (NHIRD) was used to collect standard claim documents of the beneficiaries, such as demographic data, prescriptions, and expenditures for health-care services. Data in the NHIRD that could be used to identify enrollees or care providers are scrambled by the National Health Research Institutes and then made available for the application of researchers (http://w3.nhri.org.tw/nhird/en/Data_Protection.html). All investigators signed

Clinical Points

- Clinicians should be aware that certain second-generation antipsychotics (olanzapine, quetiapine, and risperidone) recommended for first-line monotherapy in bipolar disorder are associated with risk of pneumonia.
- Lithium has a dose-dependent protective effect against pneumonia and valproic acid shows no risk, which provides evidence for use of both drugs as first-line treatments.
- Patients with bipolar disorder on combination therapy deserve special clinical attention, particularly those receiving olanzapine plus carbamazepine, or clozapine plus valproic acid, as their risks for pneumonia are high.

an agreement guaranteeing patient confidentiality before using the database. Details of the data source are described elsewhere.[7]

Bipolar Cohort

The Psychiatric Inpatient Medical Claims database is a subset of the NHIRD that includes patients whose admitting department was psychiatric and whose diagnoses were coded according to *International Classification of Diseases*, *Ninth Revision* (*ICD-9*), codes that ranged from 290 to 319 between January 1, 1996, and December 31, 2008 (N = 187,117). Additionally, this database has been used for research purposes other than pneumonia and psychiatric conditions.[13,14] Each hospital that provides psychiatric hospitalization in Taiwan is accredited periodically by an independent nongovernmental organization, ie, the Taiwan Joint Commission on Hospital Accreditation. The requirements for qualified accreditation include the diagnoses of inpatients made by board-certified psychiatrists.

We conducted a cohort study of patients identified from the Psychiatric Inpatient Medical Claims database who had been hospitalized between July 1, 1998, and December 31, 2006, with a stable diagnosis of bipolar disorder (*ICD-9* codes 296.0 to 296.16, 296.4 to 296.81, and 296.89) (N = 14,169), excluding schizophrenic patients (*ICD-9* code 295). The diagnosis of bipolar disorder for each patient was checked until December 31, 2008, and was based on the medical claims data to verify the consistency of the diagnosis. Therefore, each subject had a stable diagnosis for at least 2 years. We also limited eligible patients to those who were newly diagnosed between July 1, 1998, and December 31, 2006, and with more than 2 years of prior claims for inpatient and outpatient services. Their ages at first psychiatric admission ranged from 15 to 65 years. The final cohort of 9,999 patients was included. All of their medical claims during 1996 and 2008 were retrieved (see Supplementary eFigure 1), which included patient demographic characteristics, diagnoses, medical expenditures, and prescription data. Each prescription record contained the type of medication, dosage, time of prescription, and duration of drug regimen.

Nested Case-Control Study

Patients with subsequent pneumonia requiring hospitalization (*ICD-9* codes 480 to 486 and 507) after their first psychiatric admissions were identified as cases (n = 572), and the mean (SD) duration between first psychiatric admission and subsequent pneumonia was 2.84 (2.38) years.

The date of hospitalization for pneumonia was defined as the *index date*. Four controls or fewer (ie, no hospitalization for pneumonia) were selected for each case randomly from the cohort based on risk-set sampling, with matching by sex, age (± 5 years), and the year of the first psychiatric admission. Controls were assigned the same index date as their corresponding case. In addition, each control had at least 1 claim record after the corresponding index date to confirm that they were covered by the National Health Insurance program. Thus, the study included a total of 571 case-control pairs (ie, 571 cases and 2,277 controls) due to unavailability of controls for 1 case.

Exposure Measurement of Antipsychotics and Mood Stabilizers

We obtained data on the use of antipsychotic and mood stabilizers from prescription files and calculated the duration of treatment on the basis of the dispensed number of units and the dosing regimen for each patient. Antipsychotics and mood stabilizers are listed in the supplementary material (Supplementary eAppendix 1). Drug exposure in each case-control pair was measured by 3 approaches.

First, we defined patients taking a specified drug during the 30 days before the index date as current users; the remainder was defined as noncurrent users and served as the reference group in the analysis. We then estimated the risk of the specified drug on the development of pneumonia to demonstrate the temporal relationship of the association between drug exposure and pneumonia. Each specified drug was commonly used for treatment of bipolar disorder in Taiwan.

Second, we estimated the association between the duration of the drug used in the current period and pneumonia, along with the association between the cumulative defined daily dose and pneumonia. The defined daily dose was based on the dose information obtained from the Anatomic Therapeutic Chemical classification system.[15,16] For example, 10 mg of olanzapine or 300 mg of clozapine was equivalent to 1 defined daily dose.

Third, the combined uses of second- and first-generation antipsychotics and mood stabilizers on the risk of pneumonia were studied. Furthermore, we studied specific combined sets of antipsychotic drugs and mood stabilizer (eg, clozapine plus valproic acid) on the risk of pneumonia.

Potential Confounders

Several potential confounders for adjustment in the analyses included the Charlson Comorbidity Index score[17,18] at first psychiatric admission; number of psychiatric admissions, substance use disorders (alcohol use disorders and nonalcohol substance use disorders considered separately),

physical illnesses, and concomitant medications prescribed within 180 days before the index date (listed in Table 1); and the numbers of mood stabilizers and second- and first-generation antipsychotics. The numbers for mood stabilizers and antipsychotics excluded the specified drug(s) analyzed in the statistical model. For example, olanzapine was not calculated in the number of second-generation antipsychotics, while the risk of olanzapine was analyzed. Substance use disorders, physical illnesses, and concomitant medications served as covariates in the adjusted regression models due to their potential associations with and risk of pneumonia.[5–7,19]

Table 1. Characteristics of Pneumonia Cases and Controls Derived From a Nationwide Cohort With Bipolar Disorder (N = 9,999)

Characteristic	Cases (n = 571)	Controls (n = 2,277)	*P* Value[a]
At first admission			
Age, mean (SD), y	44.2 (13.4)	44.1 (13.3)	.0563
Men, n (%)	349 (61.1)	1,390 (61.1)	—
Charlson Comorbidity Index score, n (%)			
0	246 (43.1)	1,163 (51.1)	Reference
1	192 (33.6)	761 (33.4)	.0798
2	78 (13.7)	249 (10.9)	.0039
≥ 3	55 (9.6)	104 (4.6)	.0001
Within 180 days before the index date			
No. of psychiatric hospital admissions, mean (SD)	0.7 (1.0)	0.4 (0.7)	.0001
Substance use disorders, n (%)[b]			
Alcohol use disorder	55 (9.6)	130 (5.7)	.0006
Nonalcohol substance use disorder	25 (4.4)	53 (2.3)	.0081
Physical illness, n (%)			
Cardiovascular disease	244 (42.7)	641 (28.2)	.0001
Diabetes mellitus	127 (22.2)	296 (13.0)	.0001
Cerebrovascular disease	57 (10.0)	69 (3.0)	.0001
Chronic hepatic disease	125 (21.9)	244 (10.7)	.0001
Cancer	47 (8.2)	77 (3.4)	.0001
Asthma	63 (11.0)	63 (2.8)	.0001
Upper respiratory tract infection	273 (47.8)	865 (38.0)	.0001
Delirium	10 (1.8)	14 (0.6)	.0115
Concomitant drugs			
Cardiovascular drugs, n (%)			
Antihypertensive agents	41 (7.2)	68 (3.0)	.0001
β-blocking agents	257 (45.0)	803 (35.3)	.0001
Calcium channel blockers	159 (27.9)	388 (17.0)	.0001
Agents acting on the renin-angiotensin system	98 (17.2)	219 (9.6)	.0001
Lipid-modifying agents	60 (10.5)	129 (5.7)	.0001
Drugs used in diabetes	127 (22.2)	272 (12.0)	.0001
Antithrombotic agents	131 (22.9)	252 (11.1)	.0001
Corticosteroids for systemic use	240 (42.0)	348 (15.3)	.0001
Antiparkinson drugs	298 (52.2)	945 (41.5)	.0001
Respiratory drugs	556 (97.4)	1,399 (61.4)	.0001
Benzodiazepines	500 (87.6)	1,642 (72.1)	.0001

[a]Estimated using univariate conditional logistic regression.
[b]Alcohol use disorder: *ICD-9* codes 291.xx, 303.xx, and 305.0x; nonalcohol substance use disorder: *ICD-9* codes 292.xx, 304.xx, and 305.1x to 305.9x.

Statistical Analysis

Conditional logistic regression analysis was performed with SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina), and used to estimate the risk of pneumonia in relation to current use of individual antipsychotics or mood stabilizers. Covariates with reasonable associations with pneumonia ($P < .05$) were entered into the multivariate regression. The multivariate model was used to estimate the associations between pneumonia and duration of use and daily dose. A *P* value of .01 was considered significant.

Sensitivity Analysis

Because of the nonrandomized study design, the assignment of drugs was determined based on the presence of comorbid physical illnesses and concomitant medications (Table 1), a choice that introduces protopathic bias.[20] For example, doctors could be more likely to prescribe certain antipsychotics instead of mood stabilizers when a subject had comorbid medical conditions. We conducted a propensity score–adjusted regression to verify the associations between pneumonia and antipsychotics and mood stabilizers.

In this study, we assumed the effect period of the drug on the risk of pneumonia was 30 days before the index date. We further analyzed the risk of second-generation antipsychotics based on an alternative categorization of drug exposure adopted in prior studies[6,7]: ie, current, recent, past, or no use. *Current use* was defined as the prescription duration covered the 30 days before the index date, *recent use* was defined as usage ending 31 to 180 days before the index date, and *past use* was defined as the last prescription ended more than 180 days before the index date.

RESULTS

Incidence of Pneumonia

The crude incidence of subsequent pneumonia was calculated as the number of incident cases divided by the contributed person-years of each individual in the cohort. Their incidence of pneumonia was 1.09 cases per 100 person-years (95% CI, 1.01–1.17, based on the Poisson distribution).

Characteristics of Cases and Controls

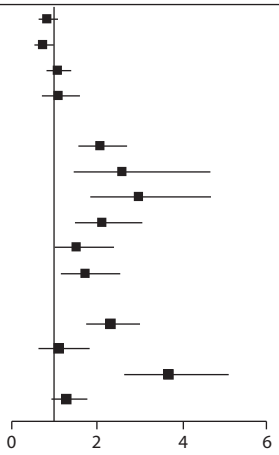
Case subjects had a greater proportion of substance use disorders, physical illnesses, and concomitant medication use than did controls (Table 1).

Effects of Antipsychotics and Mood Stabilizers on the Risk of Pneumonia

Figure 1 shows that current use of any second-generation antipsychotic was associated with the risk of pneumonia (adjusted risk ratio = 2.07, $P < .001$); the results for any first-generation antipsychotic were similar (adjusted risk ratio = 2.32, $P < .001$). Current use of any mood stabilizer was not associated with the risk of pneumonia.

As for the individual antipsychotics studied here, haloperidol had the highest risk for pneumonia, followed by olanzapine, clozapine, and quetiapine. Current use of lithium, valproic acid, or carbamazepine was not associated with the risk of pneumonia.

Figure 1. Association Between Pneumonia and Each of the Mood Stabilizers and Second- and First-Generation Antipsychotics (SGAs and FGAs) Among Pneumonia Cases and Controls Stratified by Current Use and Noncurrent Use (reference group)



Agent	Adjusted Risk Ratio (95% CI)[a]	Current Use, n (%) Cases (n = 571)	Controls (n = 2,277)
Any mood stabilizer	0.83 (0.63–1.08)	361 (63.2)	1,328 (58.3)
Lithium	0.75 (0.56–0.99)	151 (26.4)	658 (28.9)
Valproic acid	1.08 (0.83–1.41)	225 (39.4)	701 (30.8)
Carbamazepine	1.09 (0.75–1.59)	77 (13.5)	217 (9.5)
Any SGA	2.07 (1.58–2.71)**	258 (45.2)	657 (28.9)
Clozapine	2.59 (1.46–4.63)*	45 (7.9)	51 (2.2)
Olanzapine	2.97 (1.90–4.66)**	59 (10.3)	94 (4.1)
Quetiapine	2.12 (1.48–3.03)**	98 (17.2)	219 (9.6)
Zotepine	1.52 (0.98–2.38)	49 (8.6)	122 (5.4)
Risperidone	1.74 (1.21–2.50)*	83 (14.5)	212 (9.3)
Any FGA	2.32 (1.76–3.05)**	308 (53.9)	770 (33.8)
Chlorpromazine	1.10 (0.68–1.78)	39 (6.8)	125 (5.5)
Haloperidol	3.68 (2.66–5.09)**	203 (35.6)	316 (13.9)
Sulpiride	1.29 (0.94–1.76)	110 (19.3)	339 (14.9)

[a]Estimated using multivariate conditional logistic regression. Adjusted for Charlson Comorbidity Index at the first admission, and the following variables within 180 days before the index date, including the number of psychiatric hospital admissions, substance use disorders, physical illnesses, and concomitant medications (listed in Table 1), and the numbers of mood stabilizers and second- and first-generation antipsychotics, respectively.
*$P < .01$, **$P < .001$.

Table 2. Duration of Therapy and Dose of Individual Mood Stabilizers and Antipsychotic Agents Stratified by Pneumonia and Control Groups of Patients With Bipolar Disorder Currently on Therapy

Characteristic	Cases (n = 571), Mean (SD)	Controls (n = 2,277), Mean (SD)	Adjusted Risk Ratio[a]	95% CI
Duration of use within 30 days before index date, d				
Lithium	4.8 (9.3)	6.2 (10.6)	0.98*	0.97–0.99
Valproic acid	7.0 (10.4)	6.1 (10.4)	1.00	0.98–1.01
Carbamazepine	2.2 (6.6)	2.1 (6.9)	1.00	0.98–1.01
Clozapine	1.3 (5.2)	0.5 (3.3)	1.05*	1.02–1.08
Olanzapine	1.5 (5.3)	0.8 (4.3)	1.04*	1.01–1.06
Quetiapine	2.9 (7.2)	1.9 (6.5)	1.03*	1.01–1.04
Zotepine	1.3 (4.9)	1.0 (4.7)	1.00	0.98–1.03
Risperidone	2.5 (6.8)	1.8 (6.2)	1.02*	1.01–1.04
Chlorpromazine	1.1 (4.8)	1.0 (4.7)	1.00	0.98–1.03
Haloperidol	3.5 (6.5)	1.6 (5.3)	1.05**	1.03–1.07
Sulpiride	3.1 (7.6)	2.8 (7.5)	1.01	0.99–1.02
Cumulative dose within 30 days before index date, defined daily dose[b]				
Lithium	1.5 (3.9)	2.5 (5.0)	0.95**	0.92–0.98
Valproic acid	2.6 (5.6)	3.0 (6.5)	0.98	0.96–1.00
Carbamazepine	0.7 (2.7)	0.9 (3.5)	0.97	0.94–1.01
Clozapine	0.3 (1.7)	0.1 (1.2)	1.11*	1.03–1.19
Olanzapine	0.9 (5.1)	0.6 (4.5)	1.02	1.00–1.05
Quetiapine	0.8 (3.5)	0.9 (4.8)	1.00	0.97–1.03
Zotepine	0.2 (1.4)	0.3 (1.9)	0.96	0.90–1.03
Risperidone	0.6 (2.4)	0.7 (3.4)	1.00	0.96–1.04
Chlorpromazine	0.4 (3.2)	0.4 (2.7)	1.02	0.98–1.07
Haloperidol	0.8 (4.0)	0.8 (4.8)	1.00	0.98–1.03
Sulpiride	1.1 (5.0)	1.1 (4.6)	1.01	0.98–1.03

[a]Adjusted for Charlson Comorbidity Index at the first admission and the following variables within 180 days before the index date, including the number of psychiatric hospital admissions, substance use disorders, physical illnesses, and concomitant medications (listed in Table 1), and the numbers of mood stabilizers and second- and first-generation antipsychotics, respectively.
[b]The dose information of defined daily dose was obtained from the Anatomic Therapeutic Chemical classification system. For example, 10 mg of olanzapine or 300 mg of clozapine was equivalent to 1 defined daily dose.
*$P < .01$, **$P < .001$.

Dose-Dependent Relationship

Table 2 shows that, within 30 days before the index date, both the duration of dose and the cumulative defined daily dose were inversely correlated to the risk of pneumonia, with a clear dose-dependent relationship of the protective effect from pneumonia.

In contrast to lithium, clozapine showed positive correlations between both the duration of use and cumulative dose and the risk of pneumonia. The duration of current use of several antipsychotics (olanzapine, quetiapine, risperidone, or haloperidol) was significantly associated with the risk of pneumonia as well.

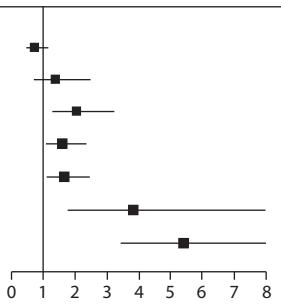
Combined Use on the Risk of Pneumonia

Figure 2 shows the analyses of the combination use of mood stabilizers and second- and first-generation antipsychotics and their association with the risk of pneumonia. The risk of pneumonia increased as more classes of drugs were used currently. Relative to noncurrent use, current use of all 3 classes of the drugs had the highest risk for pneumonia (adjusted risk ratio = 5.43, $P < .001$). Combination use of second- and first-generation antipsychotics had the second highest risk, followed by the use of first-generation antipsychotics only.

Figure 3 shows the estimations of the adjusted risk ratios of the specified drug combinations. Both olanzapine and haloperidol revealed significant risk for pneumonia while combined with each of the 3 mood stabilizers (lithium, valproic acid, and carbamazepine). Clozapine showed a significant risk for pneumonia while combined with valproic acid but not while combined with lithium or carbamazepine separately. Similar to clozapine, quetiapine combined with valproic acid was also associated with the risk (adjusted risk ratio = 2.26, $P < .001$). Other antipsychotics (zotepine, risperidone, chlorpromazine, and sulpiride) had no significant risk while combined with each of the mood stabilizers studied.

Among the drug combinations, olanzapine plus carbamazepine had the highest risk ratio (11.88, $P < .01$),

Figure 2. Analysis of the Combination Use of Mood Stabilizers and Second- and First-Generation Antipsychotics (SGAs and FGAs) and Their Association With Risk of Pneumonia in Cases and Controls Currently Receiving Therapy for Bipolar Disorder



Variable	Adjusted Risk Ratio (95% CI)[a]	Current Use, n (%) Cases (n = 571)	Controls (n = 2,277)
Noncurrent use	Reference	110 (19.3)	694 (30.5)
Mood stabilizer only	0.73 (0.46–1.15)	35 (6.1)	346 (15.2)
SGAs only	1.37 (0.75–2.50)	25 (4.4)	91 (4.0)
FGAs only	2.03 (1.27–3.23)*	56 (9.8)	144 (6.3)
Mood stabilizer and SGAs	1.61 (1.09–2.40)	93 (16.3)	376 (16.5)
Mood stabilizer and FGAs	1.66 (1.13–2.45)	112 (19.6)	436 (19.2)
SGAs and FGAs	3.85 (1.77–8.40)**	19 (3.3)	20 (0.9)
Mood stabilizer, SGAs, and FGAs	5.43 (3.42–8.62)**	121 (21.2)	170 (7.5)

[a]Estimated using multivariate regression. Adjusted for Charlson Comorbidity Index at the first admission, variables within 180 days before the index date listed in Table 1 (including the number of psychiatric hospital admissions, substance use disorders, physical illnesses, and concomitant medications), and the number of mood stabilizers and second- and first-generation antipsychotics, respectively.
*$P < .01$, **$P < .001$.

followed by clozapine plus valproic acid (risk ratio = 4.80, $P < .001$).

Sensitivity Analysis

The propensity score–adjusted model, which controlled the variables potentially related to the assignment of individual drugs of interest, showed no significant difference compared to the associations estimated based on the multivariate regression model. For instance, relative to noncurrent users, the adjusted risk ratios of clozapine were 2.69 (95% CI, 1.51–4.80; $P < .001$) in the propensity score–adjusted model and 2.59 (95% CI, 1.46–4.63; $P < .01$) in the multivariate adjusted model.

We further analyzed second-generation antipsychotics for the risk of pneumonia based on the 4 categories of current use, recent use, past use, and nonuse. The results were similar to the risk estimated based on the binary categories of current and noncurrent use. For instance, the adjusted risk ratio of current use of olanzapine was 2.81 ($P < .001$) in 4-category analysis, which was similar to that of binary category analysis (2.97, $P < .001$). Further details of sensitivity analyses are provided in the supplementary material (Supplementary eTables 1 and 2).

DISCUSSION

Strengths

We estimated the risk of pneumonia associated with antipsychotic and mood stabilizer therapies among a nationwide cohort with bipolar disorder. Our results revealed that the use of second-generation antipsychotics was significantly associated with the risk of pneumonia (adjusted risk ratio = 2.07); the use of first-generation antipsychotics was also associated with pneumonia risk (adjusted risk ratio = 2.32). Interestingly, mood stabilizers showed no risk for pneumonia. These findings provide evidence for safety concerns over antipsychotic therapy for bipolar disorder and impact the treatment guidelines for the disorder.

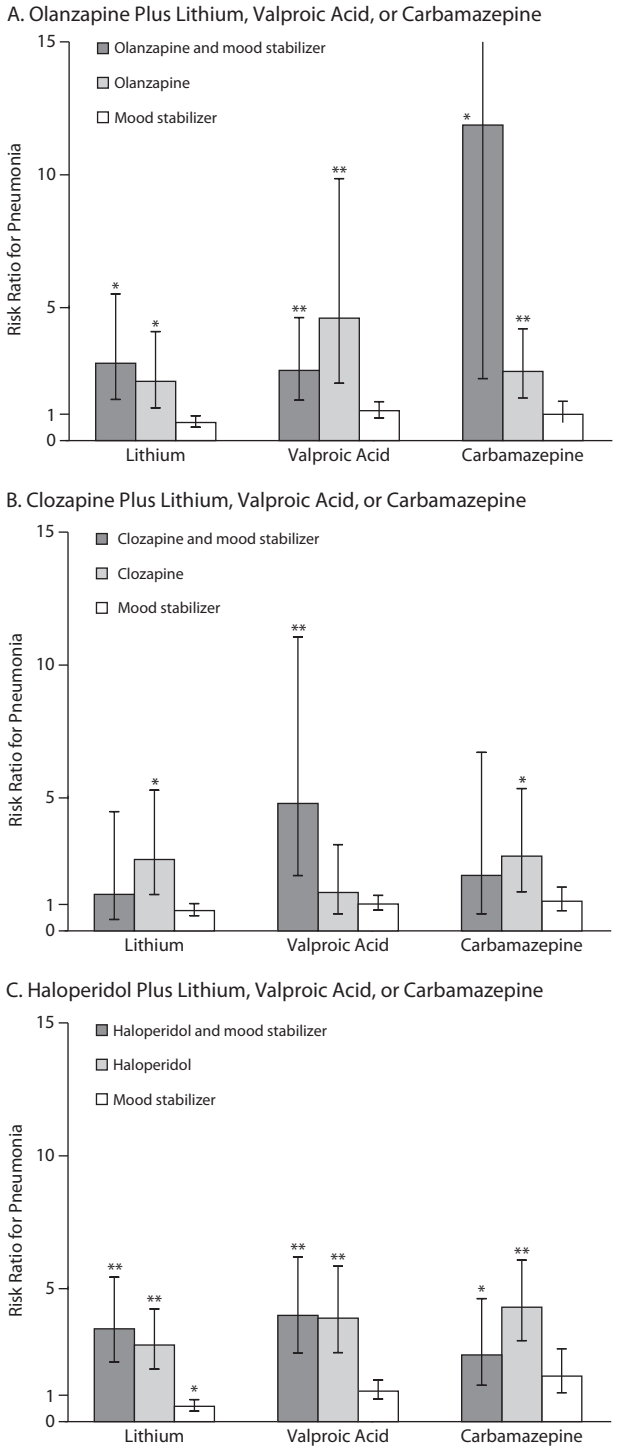
Antipsychotics and the Risk of Pneumonia

Consistent with prior studies,[5,6] we found that patients who received second-generation antipsychotics had a higher risk for pneumonia. Because of the large sample size, this study allowed investigation of the association between the individual antipsychotic drugs and the risk of pneumonia.

In this study, current use of each of 3 drugs separately (ie, olanzapine, clozapine, haloperidol) has risk ratios for pneumonia of greater than 2.50. Furthermore, pneumonia cases had a longer duration during the current use period with each of the 3 drugs, which added robust evidence for the risk for pneumonia.

The affinities for neurotransmitter receptors help explain the mechanism of how the antipsychotics induce pneumonia.[5–7] Both olanzapine and clozapine carry high risks for pneumonia and both have high affinities for histamine H_1 and muscarinic M_1 receptors. The anticholinergic effect of antipsychotic drugs with M_1 action contributes to aspiration pneumonia through dryness of the mouth, esophageal dilatation, and hypomotility.[21] Sedation[22] as a result of H_1-receptor blocking in the central nervous system might also facilitate aspiration pneumonia. Nonetheless, the risk of pneumonia could not be fully explained based on H_1 and M_1 receptors. For instance, chlorpromazine was without risk for pneumonia in the present study, but its affinity for H_1 and M_1 receptors is moderate despite being slightly lower than that of olanzapine and chlorpromazine.[23] Further study to confirm H_1 and M_1 receptor affinities as a cause of pneumonia is needed. Additionally, the risk ratio of haloperidol (3.68) for pneumonia was 2-fold that of risperidone (1.74). The mechanism of this risk could be explained by haloperidol's stronger affinity for dopaminergic-2 receptors, which are involved in extrapyramidal syndrome, potentially contributing to the

Figure 3. Association Between Pneumonia and Individual Antipsychotic Drugs Plus a Mood Stabilizer, Stratified by Specified Antipsychotic, Mood Stabilizer, Antipsychotic and Mood Stabilizer Combination, and Noncurrent Use (reference group)[a]



[a]Risk ratio for pneumonia was estimated using multivariate regression with adjustments for Charlson Comorbidity Index at the first admission, and the following variables within 180 days before the index date, including the number of psychiatric hospital admissions, substance use disorders, physical illnesses, and concomitant medications (listed in Table 1), and the numbers of mood stabilizers and second- and first-generation antipsychotics.
*$P < .01$, **$P < .001$.

development of pneumonia.[23,24] Sulpiride was also without risk for pneumonia, and haloperidol has greater extrapyramidal side effects than sulpiride.[25]

Risk of Pneumonia With Mood Stabilizers

One of the key findings in this study was that there was no significant association between mood stabilizers and pneumonia. Additionally, lithium had a dose-dependent protective effect from pneumonia that was rarely reported. Some in vitro studies help to shed light on the anti-infection effect of lithium in humans. Cell culture studies showed that lithium inhibited the replication of several viruses, such as herpes simplex virus[26] and infectious bronchitis coronavirus.[27,28] In addition to these studies, our study provides evidence regarding the antipneumonia effect of lithium.

Lithium is a well-established glycogen synthase kinase-3 (GSK-3) inhibitor, which modulates immune function and plays a pivotal role in regulating the production of proinflammatory and anti-inflammatory cytokines.[29] This could also contribute to antipneumonia properties of lithium. Even though haloperidol and clozapine, which were identified with high risk for pneumonia, are also GSK-3 inhibitors,[30] they regulate GSK-3 through different mechanisms than lithium. The differences in GSK-3 signaling could explain, at least in part, why antipsychotics contribute to the risk of pneumonia, while lithium had a protective effect. Future studies exploring the mechanisms of protection against pneumonia and for development of pneumonia are necessary.

Combination Therapies

Combined use of olanzapine and carbamazepine has more metabolic side effects than carbamazepine monotherapy.[31] The current study provided evidence that the combination use of mood stabilizers and second- and first-generation antipsychotics was associated with the risk of pneumonia. The combined use of olanzapine plus carbamazepine had the highest risk for pneumonia, followed by clozapine plus valproic acid; both combinations had high adjusted risk ratios, which indicate a synergistic effect for risk. Thus, we recommend that, among patients with bipolar disorder, these combinations be used very cautiously. The mechanism explaining the synergistic effect of combined use remains speculative.

As for pharmacodynamic drug-drug interactions, olanzapine has strong affinity for H_1 and M_1 receptors and carbamazepine could have an additive sedating effect prompting difficulty swallowing olanzapine, which could increase the risk of aspiration pneumonia. The combined set of valproic acid plus clozapine provides a similar picture. Valproic acid has an additive sedating effect on clozapine for the synergistic risk of pneumonia.[32]

With regard to pharmacokinetic considerations, carbamazepine increases the clearance of olanzapine by 40%–50%,[31,33] in part due to the induction of the cytochrome P450 1A2 and glucuronidation pathways.[33,34] This interaction contradicts possible mechanisms of synergy between the 2 drugs for the risk for pneumonia due to the lowered

concentration of olanzapine. Valproic acid is an inhibitor of clozapine metabolism, which increases sedation and affects swallowing ability.[35] The interaction between valproic acid and clozapine is confounded by cigarette smoking. Valproic acid inhibits clozapine metabolism in nonsmokers, whereas it induces clozapine metabolism in smokers.[35]

The drug combinations with significant risk for pneumonia (risk ratios between 2.0 and 4.0), which evoke a moderate warning in clinical practice, comprise lithium plus olanzapine (2.92), lithium plus haloperidol (3.50), valproic acid plus olanzapine (2.65), valproic acid plus haloperidol (4.00), and carbamazepine plus haloperidol (2.52). Other drug combinations show low risk for pneumonia, indicating safe use, such as a mood stabilizer plus risperidone.

Other Possible Causes of Pneumonia

In this study, other possible causes of pneumonia could contribute to the risk of pneumonia. The case group had a higher proportion of inherent physical illnesses than did the control group, which was in line with prior studies[5,6] reporting that physical illnesses predisposed the development of pneumonia. Furthermore, some of physical illnesses could have interaction with antipsychotic drug levels. Upper respiratory infection elevates the concentration of clozapine, which could increase the risk for pneumonia.[36]

Limitations

Several limitations of this study should be considered when interpreting the results. First, we could not determine the mental state (mania, depression, or remission) of a subject shortly before the development of pneumonia from the dataset; thus, cases might be more likely than controls to have received antipsychotics and not mood stabilizers because they were more likely to be in an acute phase of their illness rather than in a remission phase. Nonetheless, mental state is reflected by the severity of the illness, and a measure of severity in this study was the frequency of psychiatric hospitalizations (Table 1). We included the frequency of psychiatric hospitalizations in the regression model to diminish this bias. Furthermore, the class of drug use could reflect higher severity of illness; therefore, we controlled for the numbers of mood stabilizers, and second- and first-generation antipsychotics, while estimating the risk of pneumonia for each antipsychotic agent and mood stabilizer. Further research is needed to clarify whether the mental state or the severity of the bipolar disorder predisposes the development of pneumonia.

Second, body weight, behavioral profile, and laboratory data were unavailable in the claims database. Potential unmeasured confounders or mediators included obesity, falls, and neutropenia. It is necessary to consider whether obesity confounds the association between drug exposure and pneumonia. A component related to metabolic syndrome available in our study was diabetes mellitus, which was controlled in the adjusted regression analysis. Falls are implicated as a consequence more likely to happen in patients with mental disorders who receive psychiatric drugs[37] and are also related to pneumonia.[38] In a prior study of schizophrenic patients treated with clozapine associated with pneumonia,[39] we found that all 6 patients had no neutropenia during their hospitalizations for pneumonia. Further research is needed to clarify the role of neutropenia or immune deficiency as a mediator to pneumonia in patients with bipolar disorder.

Third, we conducted this study by using claims databases, so adherence to the prescribed medication could not be assessed. Nonadherence would lead to the underestimation of actual risk due to nondifferentiated misclassification of exposure.

Fourth, this study did not include the long-acting antipsychotics. This condition would not likely change the direction of the estimates due to the small fraction of patients with bipolar disorder using the long-acting antipsychotics.

CONCLUSIONS

Certain second-generation antipsychotics (olanzapine, quetiapine, and risperidone) recommended for first-line monotherapy in the guidelines are associated with risk of pneumonia. In contrast, lithium has a dose-dependent protective effect against pneumonia and valproic acid shows no risk, which provides evidence for both drugs to be used as first-line treatment. Patients on combination therapy deserve extra clinical vigilance, particularly those receiving olanzapine plus carbamazepine, or clozapine plus valproic acid, as their risk of pneumonia is highest.

Drug names: carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lithium (Lithobid and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), valproic acid (Stavzor, Depakene, and others), ziprasidone (Geodon and others).

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Author contributions: Drs Yang, Kuo, and Liao conceived and designed the study; Dr Yang acquired the data; Dr Liao performed the statistical analysis; Drs W. J. Chen and C. C. Chen provided administrative and material support; Drs Yang and Kuo drafted the manuscript; Drs Liu and W. J. Chen made critical revisions to the manuscript for important intellectual content; and Drs Kuo and C. C. Chen supervised the study.

Potential conflicts of interest: The authors declare that they have no competing interests.

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Supplementary material: See accompanying pages.

REFERENCES

1. Müller-Oerlinghausen B, Berghöfer A, Bauer M. Bipolar disorder. *Lancet*. 2002;359(9302):241–247.
2. Connolly KR, Thase ME. The clinical management of bipolar disorder: a review of evidence-based guidelines. *Prim Care Companion CNS Disord* 2011;13(4):pii: PCC.10r01097.
3. Nivoli AM, Murru A, Goikolea JM, et al. New treatment guidelines for acute bipolar mania: a critical review. *J Affect Disord*. 2012;140(2):125–141.
4. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011;378(9799):1306–1315.
5. Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic drug use and risk of pneumonia in elderly people. *J Am Geriatr Soc*. 2008;56(4):661–666.
6. Trifirò G, Gambassi G, Sen EF, et al. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. *Ann Intern Med*. 2010;152(7):418–425, W139–40.
7. Kuo CJ, Yang SY, Liao YT, et al. Second-generation antipsychotic medications and risk of pneumonia in schizophrenia [published online ahead of print Jan 26, 2012]. *Schizophr Bull*.
8. Wang PW, Hill SJ, Childers ME, et al. Open adjunctive ziprasidone associated with weight loss in obese and overweight bipolar disorder patients. *J Psychiatr Res*. 2011;45(8):1128–1132.
9. McKnight RF, Adida M, Budge K, et al. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet*. 2012;379(9817):721–728.
10. Geddes JR, Goodwin GM, Rendell J, et al; BALANCE investigators and collaborators. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet*. 2010;375(9712):385–395.
11. Freeman MP, Stoll AL. Mood stabilizer combinations: a review of safety and efficacy. *Am J Psychiatry*. 1998;155(1):12–21.
12. Goodwin GM. Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder: revised second edition–recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2009;23:346–388.
13. Gau SS, Chao PF, Lin YJ, et al. The association between carbamazepine and valproate and adverse cutaneous drug reactions in patients with bipolar disorder: a nested matched case-control study. *J Clin Psychopharmacol*. 2008;28(5):509–517.
14. Gau SS, Chung CH, Gau CS. A pharmacoeconomic analysis of atypical antipsychotics and haloperidol in first-episode schizophrenic patients in Taiwan. *J Clin Psychopharmacol*. 2008;28(3):271–278.
15. ATC/DDD Index 2012. WHO Collaborating Centre for Drug Statistics Methodology. http://www.whocc.no/atc_ddd_index/. Updated December 19, 2011. Accessed October 24, 2012.
16. WHO Collaborating Centre for Drug Statistic Methodology. *ATC Index With DDDs*. Oslo: WHO; 2009.
17. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in *ICD-9-CM* and *ICD-10* administrative data. *Med Care*. 2005;43(11):1130–1139.
18. Quail JM, Lix LM, Osman BA, et al. Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts. *BMC Health Serv Res*. 2011;11(1):146.
19. Mehta AJ, Guidot DM. Alcohol abuse, the alveolar macrophage and pneumonia. *Am J Med Sci*. 2012;343(3):244–247.
20. Feinstein AR. *Clinical Epidemiology: The Architecture of Clinical Research*. Philadelphia, PA: WB Saunders; 1985.
21. Maddalena AS, Fox M, Hofmann M, et al. Esophageal dysfunction on psychotropic medication: a case report and literature review. *Pharmacopsychiatry*. 2004;37(3):134–138.
22. Hinkes R, Quesada TV, Currier MB, et al. Aspiration pneumonia possibly secondary to clozapine-induced sialorrhea. *J Clin Psychopharmacol*. 1996;16(6):462–463.
23. Virani A, Bezchlibnyk-Butler KZ, Jeffries JJ. *Clinical Handbook of Psychotropic Drugs*. 18th ed. Cambridge, MA: Hogrefe & Huber; 2009.
24. Yang SY, Kao Yang YH, Chong MY, et al. Risk of extrapyramidal syndrome in schizophrenic patients treated with antipsychotics: a population-based study. *Clin Pharmacol Ther*. 2007;81(4):586–594.
25. Gerlach J, Behnke K, Heltberg J, et al. Sulpiride and haloperidol in schizophrenia: a double-blind cross-over study of therapeutic effect, side effects and plasma concentrations. *Br J Psychiatry*. 1985;147(3):283–288.
26. Ziaie Z, Kefalides NA. Lithium chloride restores host protein synthesis in herpes simplex virus-infected endothelial cells. *Biochem Biophys Res Commun*. 1989;160(3):1073–1078.
27. Li J, Yin J, Sui X, et al. Comparative analysis of the effect of glycyrrhizin diammonium and lithium chloride on infectious bronchitis virus infection in vitro. *Avian Pathol*. 2009;38(3):215–221.
28. Ren X, Meng F, Yin J, et al. Action mechanisms of lithium chloride on cell infection by transmissible gastroenteritis coronavirus. *PLoS ONE*. 2011;6(5):e18669.
29. Wang H, Brown J, Martin M. Glycogen synthase kinase 3: a point of convergence for the host inflammatory response. *Cytokine*. 2011;53(2):130–140.
30. Sutton LP, Rushlow WJ. The effects of neuropsychiatric drugs on glycogen synthase kinase-3 signaling. *Neuroscience*. 2011;199:116–124.
31. Tohen M, Bowden CL, Smulevich AB, et al. Olanzapine plus carbamazepine v carbamazepine alone in treating manic episodes. *Br J Psychiatry*. 2008;192(2):135–143.
32. Costello LE, Suppes T. A clinically significant interaction between clozapine and valproate. *J Clin Psychopharmacol*. 1995;15(2):139–141.
33. Lucas RA, Gilfillan DJ, Bergstrom RF. A pharmacokinetic interaction between carbamazepine and olanzapine: observations on possible mechanism. *Eur J Clin Pharmacol*. 1998;54(8):639–643.
34. de Leon J, Santoro V, D'Arrigo C, et al. Interactions between antiepileptics and second-generation antipsychotics. *Expert Opin Drug Metab Toxicol*. 2012;8(3):311–334.
35. Diaz FJ, Santoro V, Spina E, et al. Estimating the size of the effects of co-medications on plasma clozapine concentrations using a model that controls for clozapine doses and confounding variables. *Pharmacopsychiatry*. 2008;41(3):81–91.
36. de Leon J, Diaz FJ. Serious respiratory infections can increase clozapine levels and contribute to side effects: a case report. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(6):1059–1063.
37. Lavsa SM, Fabian TJ, Saul MI, et al. Influence of medications and diagnoses on fall risk in psychiatric inpatients. *Am J Health Syst Pharm*. 2010;67(15):1274–1280.
38. Siracuse JJ, Odell DD, Gondek SP, et al. Health care and socioeconomic impact of falls in the elderly. *Am J Surg*. 2012;203(3):335–338, discussion 338.
39. Chang YT, Kuo CJ, Chen WJ, et al. Risk factors associated with pneumonia among schizophrenia patients. *Taipei City Med J*. 2012;9:11–20.

Supplementary material follows this article.

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Supplementary Material

Article Title: Antipsychotic Drugs, Mood Stabilizers, and Risk of Pneumonia in Bipolar Disorder: A Nationwide Case-Control Study

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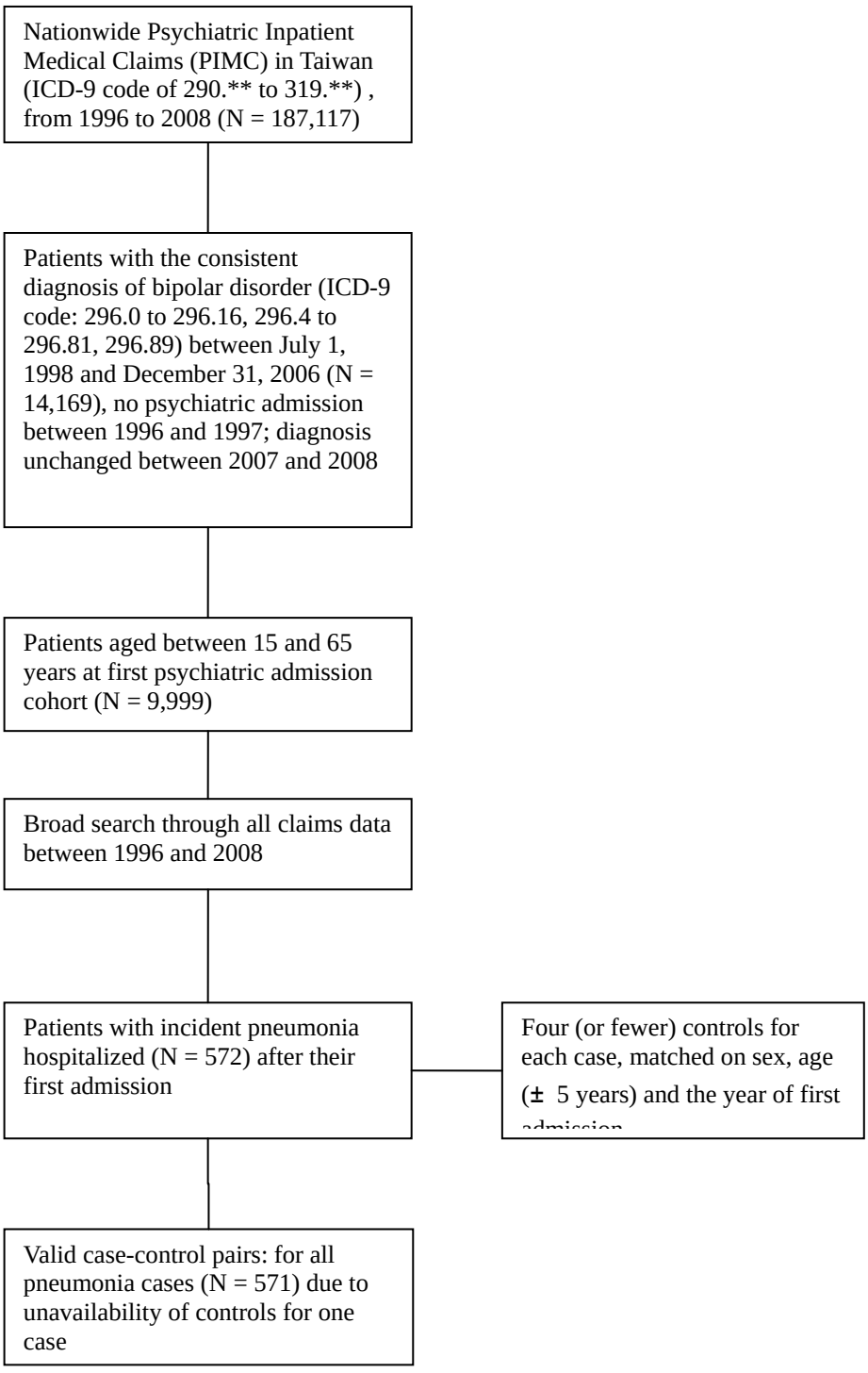
List of Supplementary Material for the article

Disclaimer

Supplementary eFigure 1. Study flow diagram



Supplementary eTable 1. The distribution of mood stabilizers, second-generation and first-generation antipsychotics between the all of pneumonia cases and controls among patients with bipolar disorder (noncurrent use as the reference)

	Pneumonia Cases (N = 571)	Controls (N = 2,277)	Propensity score-adjusted model		Multivariate adjusted model	
Characteristic	N (%)	N (%)	Risk Ratio[a]	95% CI	Risk Ratio[b]	95% CI
Lithium						
Current use	151 (26.4)	658 (28.9)	0.75	0.57–1.00	0.75	0.56–0.99
Valproate						
Current use	225 (39.4)	701 (30.8)	1.08	0.83–1.40	1.08	0.83–1.41
Carbamazepine						
Current use	77 (13.5)	217 (9.5)	1.09	0.75–1.59	1.09	0.75–1.59
Clozapine						
Current use	45 (7.9)	51 (2.2)	2.69**	1.51–4.80	2.59*	1.46–4.63
Olanzapine						
Current use	59 (10.3)	94 (4.1)	2.97**	1.90–4.66	2.97**	1.90–4.66
Quetiapine						
Current use	98 (17.2)	219 (9.6)	2.16**	1.51–3.11	2.12**	1.48–3.03
Zotepine						
Current use	49 (8.6)	122 (5.4)	1.53	0.98–2.39	1.52	0.97–2.38
Risperidone						
Current use	83 (14.5)	212 (9.3)	1.77*	1.23–2.55	1.74*	1.21–2.50
Chlorpromazine						
Current use	39 (6.8)	125 (5.5)	1.11	0.68–1.79	1.10	0.68–1.78
Haloperidol						
Current use	203 (35.6)	316 (13.9)	3.69**	2.67–5.10	3.68**	2.66–5.09
Sulpiride						
Current use	110 (19.3)	339 (14.9)	1.28	0.94–1.75	1.29	0.94–1.76

*$P < .01$, **$P < .001$.

[a]Adjusted with the propensity score, described in the Methods.

[b]Adjusted for Charlson Comorbidity Index at the first admission, variables within 180 days before the index date listed in Table 1 (including the number of psychiatric hospital admissions, substance use disorders, physical illnesses, and concomitant medications), and the number of mood stabilizers, second- and first-generation antipsychotics.

Supplemenatry eTable 2. The distribution of second-generation antipsychotics between the pneumonia cases and controls among patients with bipolar disorder

Characteristic, N (%)	Pneumonia Cases (N = 571)	Controls (N = 2,277)	Adjusted Risk Ratio[a]	95% CI
Clozapine				
No use	476 (83.4)	2101 (92.3)	Reference	-
Past use	41 (7.2)	102 (4.5)	1.62	0.98–2.67
Recent use	9 (1.6)	23 (1.0)	1.10	0.42–2.90
Current use	45 (7.9)	51 (2.2)	2.72**	1.52–4.86
Olanzapine				
No use	436 (76.4)	1831 (80.4)	Reference	-
Past use	67 (11.7)	273 (12.0)	0.91	0.62–1.34
Recent use	9 (1.6)	79 (3.5)	0.30*	0.13–0.71
Current use	59 (10.3)	94 (4.1)	2.81**	1.78–4.44
Quetiapine				
No use	386 (67.6)	1707 (75.0)	Reference	-
Past use	63 (11.0)	247 (10.9)	1.05	0.71–1.57
Recent use	24 (4.2)	104 (4.6)	0.83	0.47–1.48
Current use	98 (17.2)	219 (9.6)	2.09**	1.43–3.06
Zotepine				
No use	434 (76.0)	1789 (78.6)	Reference	-
Past use	64 (11.2)	286 (12.6)	0.74	0.51–1.07
Recent use	24 (4.2)	80 (3.5)	1.09	0.60–1.97
Current use	49 (8.6)	122 (5.4)	1.46	0.93–2.30
Risperidone				
No use	353 (61.8)	1511 (66.4)	Reference	-
Past use	105 (18.4)	415 (18.2)	0.88	0.63–1.24
Recent use	30 (5.3)	139 (6.1)	0.87	0.52–1.47
Current use	83 (14.5)	212 (9.3)	1.67*	1.15–2.43

*$P < .01$, **$P < .001$.

[a]Adjusted for Charlson Comorbidity Index at the first admission, variables within 180 days before the index date listed in Table 1 (including the number of psychiatric hospital admissions, substance use disorders, physical illnesses, and concomitant medications), and the number of mood stabilizers, second- and first-generation antipsychotics.

Supplementary eAppendix 1. List of first- and second-generation antipsychotics and mood stabilizers included in this study

1. Antipsychotics

   a. First-generation (FGAs): haloperidol, sulpiride, chlorpromazine, flupentixol, clotiapine, zuclopenthixol, thioridazine, trifluoperazine, loxapine, levomepromazine, chlorprothixene, tiotixene, perphenazine, fluphenazine, pipotiazine, pimozide, clopenthixol, moperone
   b. Second-generation (SGAs): olanzapine, clozapine, risperidone, zotepine, quetiapine, amisulpride

2. Mood stabilizers: lithium, valproic acid, carbamazepine, topiramate, valpromide, lamotrigine, gabapentin, vigabatrin