Antipsychotic Reexposure and Recurrent Pneumonia in Schizophrenia: A Nested Case-Control Study

Galen Chin-Lun Hung, MD, MS[a,b]; Hsing-Cheng Liu, MD, PhD[a,c,d]; Shu-Yu Yang, PhD[a,e]; Chun-Hung Pan, MD, MS[a,f]; Ya-Tang Liao, PhD[g]; Chiao-Chicy Chen, MD, PhD[a,c,d,h,i]; and Chian-Jue Kuo, MD, PhD[a,c,d,j,*]

ABSTRACT

Objective: Few studies have used systematic datasets to assess the safety of antipsychotic rechallenge after an adverse event. This nested case-control study estimated the risk for recurrent pneumonia after reexposure to antipsychotic treatment.

Method: In a nationwide schizophrenia (*ICD-9-CM* code 295) cohort (derived from the National Health Insurance Research Database in Taiwan) who were hospitalized for pneumonia (*ICD-9-CM* codes 480–486, 507) between 2000 and 2008 (N = 2,201), we identified 494 subjects that developed recurrent pneumonia after a baseline pneumonia episode. Based on risk-set sampling in a 1:3 ratio, 1,438 matched controls were selected from the cohort. Exposures to antipsychotics were categorized by type, duration, and defined daily dose. Using propensity score–adjusted analysis, we assessed individual antipsychotics for the risk of recurrent pneumonia; we furthermore assessed the effect of reexposure to these antipsychotics on the risk of recurrent pneumonia.

Results: Of the antipsychotics studied, current use of clozapine was the only one associated with a clear dose-dependent increase in the risk for recurrent pneumonia (adjusted risk ratio = 1.40, *P* = .024). Intriguingly, patients reexposed to clozapine had a higher risk for recurrent pneumonia (adjusted risk ratio = 1.99, *P* = .023) than those receiving clozapine only prior to the baseline pneumonia, and this risk was associated with gender. Women reexposed to clozapine were more susceptible to recurrent pneumonia (adjusted risk ratio = 4.93, *P* = .050).

Conclusions: In patients experiencing pneumonia while undergoing clozapine treatment, physicians should carefully consider the increased risk of pneumonia recurrence when clozapine is reintroduced. Future studies should try to quantify the risk of other medical conditions associated with clozapine reexposure.

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[a]Taipei City Psychiatric Center, Taipei City Hospital, Taipei, Taiwan
[b]Department of Public Health, School of Medicine, National Yang Ming University, Taipei, Taiwan
[c]Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[d]Psychiatric Research Center, Taipei Medical University Hospital, Taipei, Taiwan
[e]Graduate Institute of Clinical Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan
[f]Department of Psychology, National Chengchi University, Taipei, Taiwan
[g]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
[h]Department of Psychiatry, Mackay Memorial Hospital, Taipei, Taiwan
[i]Department of Psychiatry, Mackay Medical College, Taipei, Taiwan
[j]Department of Education and Research, Taipei City Hospital, Taipei, Taiwan
**Corresponding author:* Chian-Jue Kuo, MD, PhD, Department of General Psychiatry, Taipei City Psychiatric Center, 309 Sung-Te Rd, Taipei, 110, Taiwan (tcpckuo@seed.net.tw).

Over the past decade, the superior efficacy and safety of second-generation antipsychotics (SGAs) have been closely scrutinized; in fact, SGAs are associated with a wide range of adverse effects such as weight gain, metabolic syndrome,[1,2] and pneumonia.[3–6] In 2005, the US Food and Drug Administration (FDA) issued a warning against the use of SGAs for the treatment of elderly patients with behavioral disturbances because use of those agents was associated with increased mortality.[7] In the FDA report, the specific causes of death were due to either heart-related events or infections (mostly pneumonia). Thereafter, in elderly patients, studies have reported that the use of SGAs was associated with a greater risk of pneumonia.[3,5] Similarly, in patients with schizophrenia, we have demonstrated that the use of SGAs was associated with a 69% increased risk of pneumonia.[4]

Pneumonia in schizophrenic patients has an extremely unfavorable course, with greater risk of admission to the intensive care unit, acute respiratory failure, need for mechanical ventilation,[8] and mortality.[3,9] Patients who survived an episode of pneumonia constitute a high-risk population in which pneumonia is likely to recur.[10] Currently, few data are available regarding the incidence of recurrent pneumonia among schizophrenic patients and which antipsychotics are associated with a higher risk of such recurrence. Moreover, if a particular antipsychotic is discontinued due to the development of pneumonia, risk of pneumonia recurrence if this antipsychotic were to be reintroduced is unclear.

Among individual SGAs, the association of clozapine and pneumonia is most robust[4]; one may reasonably hypothesize that clozapine contributes to the risk of pneumonia recurrence. Moreover, the association of clozapine reexposure and recurrent pneumonia is of particular clinical significance. Discontinuation of clozapine after the first episode of pneumonia can have severe clinical consequences including relapse of psychotic symptoms[11] and suicidal behaviors.[12] Clozapine continues to be the only option to achieve optimal effectiveness in patients with refractory schizophrenia,[13] such that rechallenge with it is usually preferred. Nonetheless, research addressing the safety of clozapine rechallenge after an adverse event consists of case reports, case series, and clinical guidelines; randomized controlled trials or population-based registry studies are rare.[14–17]

Accordingly, we conducted a nested case-control study in a large schizophrenia cohort with a history of pneumonia

Clinical Points

- Among schizophrenic patients with a history of pneumonia, clozapine is the only antipsychotic associated with an elevated risk of recurrent pneumonia.
- In patients experiencing clozapine-related pneumonia, particularly among women, physicians are advised to balance the clinical benefits of clozapine reintroduction against the significantly increased risk of pneumonia recurrence.
- By adopting a nested case-control design in a population-based cohort, investigators may quantify the risk of other medical conditions associated with antipsychotic reexposure.

requiring hospitalization derived from a nationwide dataset in Taiwan. We examined exposure to different antipsychotics and their various dimensions of risk for recurrent pneumonia, including temporal relationships, duration, and dosage. If an antipsychotic was associated with the risk of recurrent pneumonia, we further assessed whether reexposure to this particular antipsychotic contributed to a greater risk of recurrent pneumonia.

METHOD

Data Sources

The source of the dataset has been described in more detail previously.[4] Briefly, the single-payer National Health Insurance program was launched in Taiwan in 1995, and by the end of 2007, coverage of the Taiwanese population of 23 million had reached 98%. The National Health Research Institute in Taiwan established the National Health Insurance Research Database (NHIRD). The database comprises patient demographics and medical claim files. Individual identification is decoded for protection of confidentiality (http://w3.nhri.org.tw/nhird/en/Data_Protection.html). All investigators signed an agreement guaranteeing patient confidentiality before using the database. This study was approved by the Institutional Review Board of the Committee on Human Subjects of Taipei City Hospital, Taipei, Taiwan.

Schizophrenia Inpatients With Pneumonia as the Study Cohort

The national Psychiatric Inpatient Medical Claims Dataset, a subset of the NHIRD comprising a cohort of patients hospitalized for any psychiatric disorder (*ICD-9-CM* codes 290.xx to 319.xx) between 1996 and 2008 (N = 187,117), was used in this study. We selected patients with at least 1 psychiatric hospital admission between 2000 and 2008 but no psychiatric admissions between 1996 and 1999 (N = 125,225) from the Psychiatric Inpatient Medical Claims Dataset.

The inclusion criteria for the study subjects were at least 1 discharge diagnosis of schizophrenia (*ICD-9-CM* code 295) and age at first psychiatric admission of 18 to 65 years (N = 35,627). If the subject had a diagnosis of pneumonia requiring hospitalization (*ICD-9-CM* codes 480–486 and 507) after their first psychiatric admission, then they were included in the study (N = 2,201), and this group was defined as the *study cohort*. We ensured sufficient follow-up to identify the incidence of recurrent pneumonia. Following an approach similar to that of Eurich and colleagues,[18] we excluded all patients who were readmitted to the hospital with pneumonia, died, or were otherwise censored within 30 days of discharge after their first admission. All of their prescription records during 1999 and 2010 were retrieved. A flow diagram and overview of the study design are provided in the supplementary material (Supplementary eFigures 1 and 2 at PSYCHIATRIST.COM).

Nested Case-Control Study

Among the study cohort, patients with subsequent recurrent pneumonia requiring hospitalization (*ICD-9-CM* codes 480–486 and 507) after their baseline pneumonia admissions were identified as cases (N = 494) and the mean (range) duration between the baseline pneumonia and recurrent pneumonia episodes was 655 (31–3,170) days. The date of hospitalization for recurrent pneumonia was defined as the *index date*. For each case, we randomly selected 3 or fewer controls (ie, no hospitalization for pneumonia) from the cohort based on risk-set sampling, matched by sex, age (± 5 years), and the year of the baseline pneumonia admission. Controls were then assigned the same index date as their matched case. In addition, each control subject had at least 1 claim record after the index date to confirm that they were covered by the National Health Insurance program.

Antipsychotic Exposure

We retrieved data on the use of antipsychotics from prescription files and calculated the durations and dosing regimens on the basis of the dispensed number of units for each patient. Second- and first-generation antipsychotics are listed in the eAppendix 1 of the supplementary material. Antipsychotic exposure in each case-control set was measured by the following approaches. First, on the basis of the temporal relationship, patients taking an antipsychotic during the 30 days before the recurrent pneumonia were defined as *current users*; the remaining patients were defined as *noncurrent users* and served as the reference group in the analysis. We then estimated the risk of an antipsychotic on the development of recurrent pneumonia. Antipsychotics used commonly in Taiwan were included in the individual drug analysis.

In addition, to demonstrate dose dependency, we estimated the effect of the duration of drug used in the current period on the risk of recurrent pneumonia as well as the effect of the cumulative defined daily dose on the risk of recurrent pneumonia. The defined daily dose (DDD) was based on the dose information obtained from the Anatomic Therapeutic Chemical (ATC) Classification System (ATC/DDD Index 2009. http://www.whocc.no/atc_ddd_index/ [accessed May 1, 2009]).[19] For example, 300 mg of clozapine was equal to 1 DDD.

Furthermore, for assessing the effects of drug reexposure on the risk of recurrent pneumonia, we defined the 30 days before the baseline pneumonia admission as the *prebaseline pneumonia period*, while the 30 days before the recurrent pneumonia admission was defined as the *prerecurrent pneumonia period*. We then categorized the patterns of individual antipsychotic exposure in the prebaseline and prerecurrent pneumonia periods into 4 subgroups: no reexposure (reference group), reexposure, new use, no use. Both the no reexposed and reexposed patients used a given antipsychotic drug in the prebaseline pneumonia period, but only the reexposed patients received this drug in the prerecurrent pneumonia period. Those who used this particular antipsychotic in the prerecurrent period but not in the prebaseline pneumonia period were defined as *new users*. Those who did not receive this drug in either of the 2 periods were defined as *nonusers*.

Potential Confounders

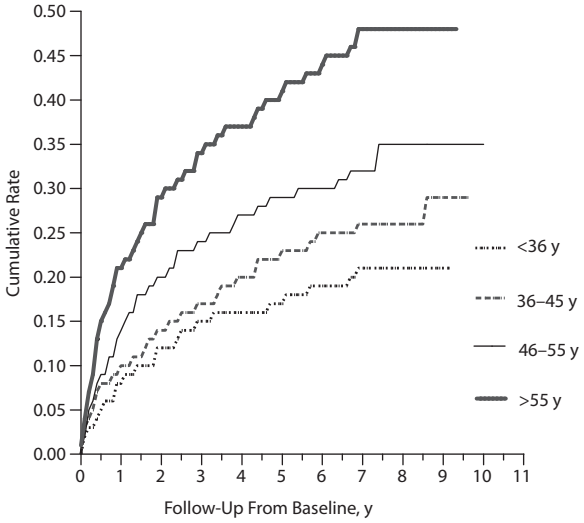
The potential confounders included comorbid physical illnesses and concomitant medications prescribed within the 30 days before the index date (see Table 1). Physical illnesses and concomitant medications served as potential covariates in the adjusted regression models due to their potential associations with the risk of pneumonia.[3–5,20]

Statistical Analysis

The crude incidence of recurrent pneumonia was calculated as the number of cases divided by the contributed person-years of each individual in the cohort. Differences in incidence of recurrent pneumonia among various age subgroups were investigated using the Gehan generalized Wilcoxon test[21] and life-table survival analysis.

Due to the nonrandomized study design, the choice of antipsychotics was determined based on the presence of comorbid physical illnesses and concomitant medications, introducing selection bias.[22] We conducted a propensity score–adjusted regression analysis[23] to estimate the associations between the specified antipsychotics and recurrent pneumonia. Among comorbid physical illnesses and concomitant medications (including the number of antipsychotics) (Table 1) and Charlson comorbidity index[24,25] and number of hospitalizations (Supplementary eTable 1), we included those with reasonable associations ($P < .1$) as covariates. With the selected covariates, we then formulated the regression equation by employing the multivariate logistic regression based on the use of each drug of interest as the dependent variable. The propensity score of each subject was obtained based on the formulated regression model for each drug of interest separately. Eventually, the propensity score was entered into the final regression model for adjustment to estimate the risk of recurrent pneumonia in relation to current use of individual antipsychotics, the duration of current drug use, and the DDD of the current drug. Furthermore, we conducted regression modeling to examine the effect of reexposure to antipsychotics on the risk of recurrent pneumonia. Regression modeling was conducted using SAS software, version 9.2 (SAS Institute, Cary, North Carolina). A P value of .05 was considered significant.

Figure 1. Cumulative Incidence of Recurrent Pneumonia Among Patients in the Schizophrenia With Pneumonia Cohort Stratified by Age



Sensitivity Analysis

To assess the robustness of the results, we conducted a sensitivity analysis. To ensure that the use of 3 controls was not deflating the statistical significance of our results, we repeated our analyses using 10 controls per case. The selection strategy of 10 controls per case was the same as the strategy of 3 controls per case, and both were based on risk-set sampling from the study cohort. In the main analyses, we did not use a case and control ratio of 1:10 because the summed number of cases and controls was larger than the number in the study cohort.

RESULTS

Incidence of Recurrent Pneumonia

The annual rate of recurrent pneumonia in the study cohort was 7.70 cases per 100 person-years (95% CI, 7.03–8.41, based on the Poisson distribution). The rates in men and women were 8.22 and 6.93, respectively, and did not differ significantly ($P = .126$, life-tables analysis). Figure 1 shows the cumulative incidence of recurrent pneumonia in different age subgroups; the incidence increased as age increased. Total incidence differed significantly ($P < .001$) among the 4 groups (Figure 1) (life-tables analysis). The results of any 2 compared groups differed significantly (all P values $< .005$), except for the comparison between the 2 youngest groups (age < 36 years and 36–45 years, $P = .144$).

Characteristics of Case and Control Patients

This study included 2,201 schizophrenia patients with pneumonia. Overall, 494 (22.4%) had recurrent pneumonia

more than 30 days after their initial pneumonia; the mean (SD) time to recurrence was 1.6 (1.7) years over 10 years of follow-up. We eventually matched 487 patients (487/494, 98.6%) with 1,438 controls (97.1% of patients having 3 controls). The patients had a similar distribution of Charlson comorbidity index at the baseline pneumonia episode compared to the controls (Supplementary eTable 1), but patients had greater numbers of physical illnesses and used greater numbers of concomitant drugs than did controls (Table 1).

Effect of Antipsychotics on the Risk of Recurrent Pneumonia

Table 2 shows that, by means of propensity score–adjusted analyses, among all the first-generation and second-generation antipsychotics examined, clozapine was the only one associated with the risk of recurrent pneumonia (adjusted risk ratio = 1.40, $P = .024$), and risperidone was inversely associated with such risk (adjusted risk ratio = 0.62, $P = .002$).

Results of adjusted analyses indicated that current use of clozapine was associated with an increased, dose-dependent risk of recurrent pneumonia (Table 3). Current clozapine use for 15 or more days resulted in a significantly greater risk of developing recurrent pneumonia (adjusted risk ratio = 1.41, $P = .027$) as did higher dosages (> 1 DDD) (adjusted risk ratio = 3.27, $P = .011$). In contrast, risperidone had no clear dose-dependent relationship with recurrent pneumonia. Risperidone taken for a shorter duration resulted in more risk reduction; similarly, the lowest dose used was associated with the greatest alleviation of recurrent pneumonia risk (data not shown).

Effect of Clozapine Reexposure on Risk of Recurrent Pneumonia

A substantial portion of subjects who received clozapine before the baseline hospitalization for pneumonia had used clozapine prior to the recurrent pneumonia. Among the cases (patients with recurrent pneumonia) of the 4 subgroups with different clozapine exposure (ie, no reexposure, reexposure, new use, no use), the mean (SD) age at the pneumonia recurrence by group was 53.7 (11.6), 48.8 (12.4), 46.4 (11.5), and 52.0 (11.9) years, respectively. There was no significant difference in age between any 2 subgroups based on the post hoc tests with the Scheffe method of analysis of variance.

For assessing the effect of clozapine reexposure on the risk of recurrent pneumonia, we used the no reexposure group as the reference group. We found that those with reexposure to clozapine had a higher risk for recurrent pneumonia (adjusted risk ratio = 1.99, $P = .023$), and the risk was associated with gender (Table 4). In the stratified analysis, women with clozapine reexposure were more susceptible to recurrent pneumonia (adjusted risk ratio = 4.93, $P = .050$) than

Table 1. Distribution of Physical Illnesses and Concomitant Medications Used Within 30 Days Before the Index Date Among Patients With Recurrent Pneumonia and Nonrecurrent-Pneumonia Controls (487 case-control pairs at a 1:3 ratio)

Characteristic	Cases (N = 487)	Controls (N = 1,438)	Crude Risk Ratio[a]	*P* Value[a]
Physical illnesses, n (%)				
Cardiovascular disease				
Hypertension	46 (9.4)	100 (7.0)	1.42	.069
Others	88 (18.1)	157 (10.9)	1.87**	< .001
Diabetes mellitus	50 (10.3)	101 (7.0)	1.51*	.025
Cancer	21 (4.3)	16 (1.1)	3.80**	< .001
Chronic hepatic disease	16 (3.3)	42 (2.9)	1.14	.661
Asthma	12 (2.5)	14 (1.0)	2.55*	.021
Upper respiratory tract infection	18 (3.7)	34 (2.4)	1.59	.117
Delirium	1 (0.2)	1 (0.1)	2.99	.438
Human immunodeficiency virus	0 (0.0)	2 (0.1)	0.00	.984
Chronic obstructive pulmonary disease	6 (1.2)	11 (0.7)	1.64	.331
Concomitant drugs, n (%)				
Cardiovascular drugs				
Antihypertensives	16 (3.3)	54 (3.8)	0.88	.658
β-Blocking agents	99 (20.3)	333 (23.2)	0.84	.188
Calcium channel blockers	68 (14.0)	173 (12.0)	1.20	.252
Agents acting on the renin-angiotensin system	41 (8.4)	125 (8.7)	0.96	.814
Lipid-modifying agents	14 (2.9)	52 (3.6)	0.80	.458
Drugs used in diabetes	68 (14.0)	160 (11.1)	1.31	.084
Antithrombotic agents	51 (10.5)	101 (7.0)	1.56*	.015
Corticosteroids for systemic use	55 (11.3)	91 (6.3)	1.90**	< .001
Nasal preparations	41 (8.4)	90 (6.3)	1.40	.094
Drugs for obstructive airway diseases	147 (30.2)	213 (14.8)	2.56**	< .001
Cough and cold preparations	266 (54.6)	442 (30.7)	2.76**	< .001
Antihistamines for systemic use	135 (27.7)	307 (21.3)	1.44*	.003
Antiparkinson drugs	247 (50.7)	776 (54.0)	0.88	.223
Respiratory drugs	318 (65.3)	571 (39.7)	2.96**	< .001
Psychotropics				
Benzodiazepines	335 (68.8)	910 (63.3)	1.29*	.025
Antidepressant	83 (17.0)	267 (18.6)	0.91	.512
Mood stabilizer	136 (27.9)	312 (21.7)	1.42*	.004
Number of antipsychotics, mean (SD)	1.10 (0.91)	1.10 (0.84)	1.01	.888

[a]Estimated using univariate conditional logistic regression.
*$P < .05$. **$P < .001$.

Table 2. Distribution of Antipsychotics Used in Recurrent Pneumonia Cases and Nonrecurrent-Pneumonia Controls

	Prerecurrent Pneumonia Period				
Antipsychotic	Cases (N = 487)	Controls (N = 1,438)	Adjusted Risk Ratio[a]	95% CI	*P* Value[a]
First-generation antipsychotics, n (%)	186 (38.2)	538 (37.4)	0.97	0.75–1.25	.805
Chlorpromazine	20 (4.1)	66 (4.6)	0.83	0.48–1.44	.507
Haloperidol	80 (16.4)	186 (12.9)	1.11	0.80–1.52	.540
Flupentixol	13 (2.7)	41 (2.9)	0.88	0.43–1.77	.717
Sulpiride	72 (14.8)	226 (15.7)	0.96	0.70–1.33	.808
Second-generation antipsychotics, n (%)	275 (56.5)	844 (58.7)	0.92	0.72–1.18	.521
Clozapine	96 (19.7)	226 (15.7)	1.40*	1.05–1.88	.024
Olanzapine	37 (7.6)	100 (7.0)	1.09	0.71–1.67	.690
Quetiapine	48 (9.9)	128 (8.9)	1.08	0.73–1.59	.703
Zotepine	19 (3.9)	73 (5.1)	0.79	0.46–1.37	.408
Risperidone	75 (15.4)	309 (21.5)	0.62*	0.46–0.84	.002
Amisulpride	19 (3.9)	45 (3.1)	1.11	0.61–2.01	.734
Aripiprazole	10 (2.1)	37 (2.6)	0.71	0.33–1.54	.390

[a]Estimated using propensity score–adjusted analysis.
*$P < .05$.

Table 3. Comparison of Dosage of Clozapine Used in the Prerecurrent Pneumonia Period Between Cases and Controls

Characteristic	Prerecurrent Pneumonia Period: Cases (N = 487)	Prerecurrent Pneumonia Period: Controls (N = 1,438)	Crude Risk Ratio[a]	*P* Value[a]	Adjusted Risk Ratio[b]	*P* Value[b]
Clozapine, n (%)						
Duration, d						
0	391 (80.3)	1,213 (84.4)	Reference	…	…	…
< 15	12 (2.5)	27 (1.9)	1.36	.3784	1.40	.374
15–30	84 (17.2)	198 (13.8)	1.30	.0638	1.41*	.027
Defined daily dose per day, n (%)						
0	391 (80.3)	1,212 (84.3)	Reference	…	…	…
0–1.0	84 (17.2)	212 (14.7)	1.21	.1743	1.31	.086
> 1.0	12 (2.5)	14 (1.0)	2.80*	.0127	3.27*	.011

[a]Estimated using univariate conditional logistic regression.
[b]Estimated using propensity score–adjusted analysis.
*$P < .05$.

Table 4. Reexposed Use of Clozapine and Risk of Recurrent Pneumonia

Characteristic	Cases, n (%)	Controls, n (%)	Adjusted Risk Ratio[a]	95% CI	*P* Value
All subjects	N = 487	N = 1,438			
No reexposure[b]	22 (4.5)	99 (6.3)	Reference	…	…
Reexposure[c]	68 (14.0)	156 (10.8)	1.99*	1.10–3.59	.023
New use[d]	28 (5.7)	70 (4.9)	2.02*	1.02–3.98	.044
No use[e]	369 (75.8)	1,113 (77.4)	1.47	0.88–2.45	.144
Stratified by gender					
Male	n = 316	n = 937			
No reexposure[b]	20 (6.3)	70 (7.5)	Reference	…	…
Reexposure[c]	46 (14.6)	106 (11.3)	1.73	0.88–3.39	.114
New use[d]	20 (6.3)	40 (4.3)	2.29*	1.03–5.09	.042
No use[e]	230 (72.8)	721 (76.9)	1.16	0.65–2.07	.617
Female	n = 171	n = 501			
No reexposure[b]	2 (1.2)	29 (5.8)	Reference	…	…
Reexposure[c]	22 (12.9)	50 (10.0)	4.93*	1.00–24.31	.050
New use[d]	8 (4.7)	30 (6.0)	3.68	0.66–20.41	.137
No use[e]	139 (81.3)	392 (78.2)	4.24	0.95–18.96	.059

[a]Estimated using propensity score–adjusted analysis.
[b]No reexposure: clozapine used in prebaseline pneumonia period but not used in prerecurrent pneumonia period.
[c]Reexposure: clozapine used in both prebaseline and prerecurrent pneumonia periods.
[d]New use: clozapine not used in prebaseline pneumonia period but used in prerecurrent pneumonia period.
[e]No use: clozapine not used in prebaseline or prerecurrent pneumonia periods.
*$P < .05$.

men, for whom such an association was not significant (adjusted risk ratio = 1.73, $P = .114$).

Sensitivity Analysis

In the sensitivity analysis, the results were almost identical using 10 controls per case (current clozapine use: adjusted risk ratio = 1.47; 95% CI, 1.14–1.90; $P = .0034$) compared to the 3 actually used.

DISCUSSION

Main Findings

To our knowledge, this study is the first to investigate the association between antipsychotic exposure and recurrent pneumonia. Using a nationwide, case-control study, we have shown that, in schizophrenic patients, clozapine is the only antipsychotic that has a dose-dependent relationship with recurrent pneumonia. Specifically, among patients with a history of clozapine-related pneumonia, reexposure to clozapine is associated with a higher risk of recurrent pneumonia.

Novel Investigational Methodology

One significant strength of this study is the use of a novel methodology to quantify the recurrence of an adverse effect after rechallenge with an antipsychotic, particularly clozapine. Clozapine is an irreplaceable resource for treatment-resistant schizophrenia, and many psychiatrists tend to either prematurely discontinue clozapine or feel reluctant to rechallenge with clozapine after an adverse event.[14,26] Therefore, delineating the course of clozapine-related side effects and the consequences of clozapine rechallenge is of paramount importance. Most prior studies include case reports and case series; consequently, clinical guidelines are based on insufficient evidence.[14] Identifying a population-based cohort with clozapine-related pneumonia and using a prospective, nested case-control design to assess the risk of recurrent pneumonia and its association with clozapine reexposure is a methodological innovation that has the potential to provide a more accurate estimate of risk.

Incidence of Recurrent Pneumonia

As demonstrated by Chen and colleagues,[8] among schizophrenic patients, hospitalization for pneumonia carries a poor prognosis. Therefore, elucidating the extent and predictors of pneumonia recurrence is essential for formulating a treatment plan after an initial episode of pneumonia. In our schizophrenic cohort, the annual incidence of recurrent pneumonia (7.70 cases per 100 person-years) was 7 times higher than that of the initial episode of pneumonia (1.12 cases per 100 person-years).[4] Factors contributing to recurrent pneumonia may include advanced age, comorbid physical illnesses, and concomitant medications.[10] Indeed, among the study patients, those older than 55 years had cumulative incidence of recurrent pneumonia over 45% after follow-up of 80 months; in contrast, fewer than 20% of individuals younger than 36 years experienced another episode of pneumonia in the identical period. Patients with recurrent pneumonia were more likely to have several medical disorders including cancer, cardiovascular disease, and asthma, which predisposed pneumonia recurrence. They also received anti-inflammatory and respiratory medications more often than those who did not develop recurrent pneumonia; such medications may be administered to deal with the emerging symptoms of pneumonia or chronic respiratory conditions, which are likely to

increase the risk of pneumonia recurrence. The propensity score–adjusted analysis used here was intended to address these confounders and enable us to estimate the net effect of antipsychotics on recurrent pneumonia.

Effect of Clozapine on the Risk of Recurrent Pneumonia

Clozapine stood out as the only antipsychotic drug associated with a 40% increased risk of pneumonia recurrence after accounting for the effects of physical condition and concomitant medications. Apart from clozapine, a number of SGAs including olanzapine, quetiapine, and zotepine have been linked to elevated risk of pneumonia occurrence[4]; however, they did not increase the risk of pneumonia recurrence. One possible explanation for these results is that, for recurrent pneumonia, concurrent medical conditions and their treatment agents could have exerted a more obscure role than the other antipsychotic agents, leaving only the effect of clozapine, the most robust one, observable. As for clozapine, sedation[27] as a result of histaminergic-1–receptor blocking in the central nervous system could facilitate aspiration pneumonia. The anticholinergic effect of clozapine with muscarinic-1 blockade contributes to aspiration pneumonia through swallowing problems such as esophageal dilatation and hypomotility.[28] Moreover, clozapine-induced hypersalivation induced by interruption of muscarinic receptor homeostasis leads to susceptibility to aspiration pneumonia.[29] Future research is needed to elucidate the pathogenesis of clozapine-associated recurrent pneumonia. Another line of explanation is that clozapine is known to cause agranulocytosis,[30] a severe side effect often requiring hospitalization. Pneumonia can potentially lead to discontinuation of clozapine. Nonetheless, clozapine is often the only option for patients with refractory schizophrenia, and discontinuation can have severe clinical consequences, which warrant hospitalization either for prevention or in response to the worsening of psychotic symptoms.

We unexpectedly found that risperidone exerted a protective effect against the risk of recurrent pneumonia. Absence of a dose-dependent relationship weakens the observed association; the protective effect of risperidone requires further investigation.

Effect of Reexposure to Clozapine on the Risk of Recurrent Pneumonia

Patients reexposed to clozapine had 2-fold greater risk of recurrent pneumonia compared to patients with clozapine exposure only prior to the first episode of pneumonia. Although reexposure is not identical to rechallenge, the present findings serve to inform clinicians that rechallenge of clozapine bears considerable risk of pneumonia recurrence. In the stratified analysis, such risk was evident only in women. A previous study[30] reporting a higher risk of clozapine-related agranulocytosis among women may shed light on the sex difference of the risk for recurrent pneumonia. From a pharmacokinetic perspective, one could speculate that, assuming an equal treatment dose, plasma levels of clozapine and its metabolite *N*-desmethylclozapine are significantly higher in women than men,[31] leading to the observed sex difference.

Limitations

The limitations of this study should be considered when interpreting the results. First, we could not capture data from patients with pneumonia not warranting hospitalization, and thus, we probably underestimated the true incidence. Second, in addition to physical conditions and concomitant medications, risk of recurrent pneumonia is confounded by unmeasured covariates such as obesity and alcohol and tobacco use. Residual confounding due to unmeasured covariates is, therefore, possible. Third, although the determination of current antipsychotic exposure (ie, agents used in the 30 days before the index date) is based on assumptions supported by previous studies,[3,4,6] we cannot rule out the effect of antipsychotics administered more than 30 days before the index date. Lastly, a substantial portion of subjects received more than 1 antipsychotic in this study. While polypharmacy of antipsychotics was accounted for in the analysis, more systematic studies are needed to tease apart the drug-specific effects.

Implications

Our study shows that, in patients with schizophrenia, clozapine is the only antipsychotic associated with recurrent pneumonia in a dose-dependent manner after the initial episode of pneumonia. In patients experiencing clozapine-related pneumonia, physicians must be aware of the significantly increased risk of pneumonia recurrence when reintroducing clozapine. Adapting a similar approach, investigators may examine the risk of other relevant medical conditions associated with clozapine reexposure. Such data could facilitate an evidence-based practice that balances the quantifiable harm and potential benefit of clozapine.

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Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).
Author contributions: Drs Hung, Liu, and Kuo conceived and designed the study. Dr Yang acquired the data. Ms Liao performed the statistical analysis. Dr Chen provided administrative and material support. Drs Hung and Kuo drafted the manuscript. Drs Liu and Pan made critical revisions to the manuscript for important intellectual content, and Drs Kuo and Chen supervised the study.
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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Antipsychotics Reexposure and Recurrent Pneumonia in Schizophrenia: A Nested Case-Control Study

Author(s): Galen Chin-Lun Hung, MD, MS; Hsing-Cheng Liu, MD, PhD; Shu-Yu Yang, PhD; Chun-Hung Pan, MD, MS; Ya-Tang Liao, PhD; Chiao-Chicy Chen, MD, PhD; and Chian-Jue Kuo MD, PhD

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List of Supplementary Material for the article

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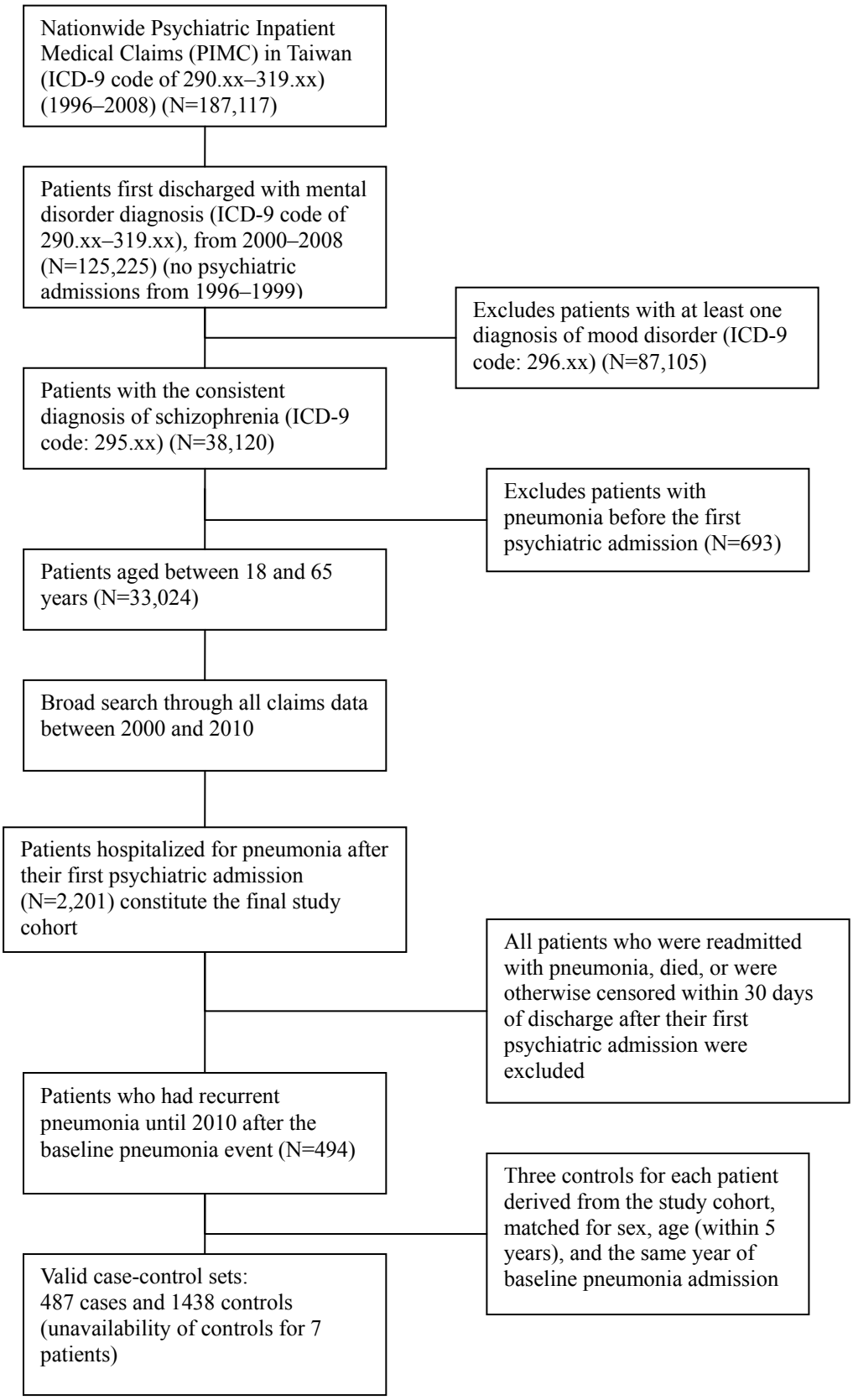
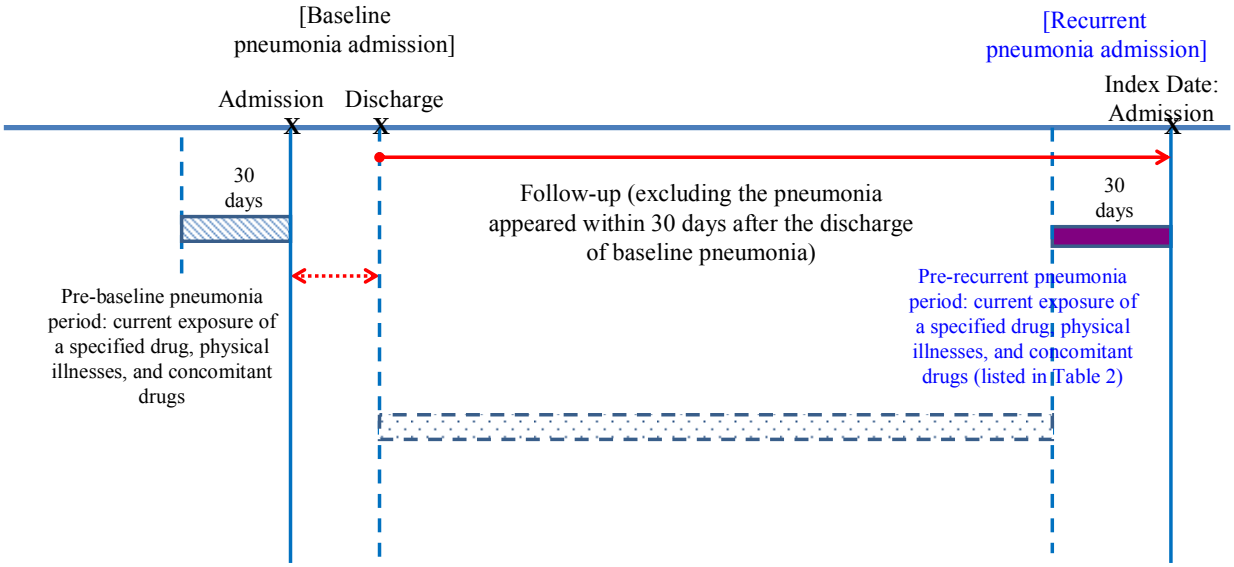
Supplementary Material

e-Figure 1. Study flow diagram



e-Figure 2. Overview of study design



e-Table 1. Demographic and Clinical Characteristics of Recurrent Pneumonia Cases and Non-recurrent-pneumonia Controls Derived from a Nationwide Schizophrenia Cohort with Pneumonia Requiring Hospitalization

Characteristic	Cases (n=487)	Controls (n=1438)	Unadjusted risk ratio[a]	95% CI
At baseline pneumonia admission	*N (%)*	*N (%)*		
Men	316 (65.0)	937 (65.2)	-	-
Mean age (SD), years	49.7 (12.1)	49.6 (11.8)	-	-
Charlson comorbidity index				
0–1	374 (76.8)	1150 (80.0)	Reference	
2	84 (17.3)	200 (13.9)	1.31	0.0613
≥3	29 (6.0)	88 (6.1)	1.02	0.9338
Duration between the discharge date of baseline pneumonia and the index date, days			-	-
≤180 days (6 months)	161 (33.1)	-	-	-
>180, ≤365 days (1 year)	93 (19.1)	-	-	-
>365 days	233 (47.8)	-	-	-
	Mean (SD)	*Mean (SD)*		
Number of psychiatric hospital admissions within 180 days before the baseline pneumonia	0.5 (0.8)	0.6 (0.8)	0.89	0.0884

[a]Estimated using univariate conditional logistic regression.

Appendix: list of first- and second-generation antipsychotics included in this study

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