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Second-generation antipsychotic medications and risk of chronic kidney disease in schizophrenia: population-based nested case–control study

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ABSTRACT

Objectives The study aims to compare the risk of chronic kidney diseases (CKDs) between patients with schizophrenia using first and second-generation antipsychotics.

Setting Datasets of 2000–2013 National Health Insurance in Taiwan were used.

Participants The National Health Insurance reimbursement claims data have been transferred to and managed by the National Health Research Institute in Taiwan since 1996. We used the Psychiatric Inpatient Medical Claims database, a subset of the National Health Insurance Research Database, comprising a cohort of patients hospitalised for psychiatric disorders between 2000 and 2013 (n=2 67 807). The database included patients with at least one psychiatric inpatient record and one discharge diagnosis of mental disorders coded by the International Classification of Diseases, Ninth Revision (ICD-9) codes 290–319. The age of patients at first admission was restricted to 18–65 years.

Primary outcome CKD (ICD-9 code 582, 583, 585, 586, 588) requiring hospitalisation or three outpatient visits. The diagnosis of CKD follows the criteria of 'Kidney Disease: Improving Global Outcomes' in Taiwan. CKD is defined as a kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens or glomerular filtration rate <60 mL/min/1.73 m^2 for 3 months or more.

Results We found that the risks for CKD were higher for those who used second-generation antipsychotics (SGAs) longer cumulatively than those who did not. Using non-users, patients did not have any SGA records, as reference group, the risks for CKD comparing those using SGAs for 90 to 180 days with non-users and those using SGAs for more than 1000 days were 1.42 (1.06–1.91) and 1.30 (1.13–1.51), respectively.

Conclusions The current study suggests the relationship between using SGAs and risk of CKD.

Strengths and limitations of this study

- ► We tracked subjects for a period longer than 1000 days after the initial schizophrenia diagnosis day.
- ► This is the first study investigating the relationship between antipsychotics and risk of chronic kidney disease (CKD) among inpatients with schizophrenia.
- ► The measurement of exposure, use of antipsychotic drugs, can only be estimated by the existing dataset we used.
- ► Using the existing dataset without personal identification, we cannot investigate all risk factors in the study.
- ► The risk of CKD in patients with schizophrenia deserves further investigation. Besides, the study of CKD risk for patients with schizophrenia might need longer tracking duration.

INTRODUCTION

Schizophrenia is a chronic mental illness with lifetime prevalence rate around 1%.[1 2] Patients with schizophrenia have been shown to have an excess mortality, being two or three times as high as that in the general population.[3–5] Cardiovascular diseases have an increased prevalence among patients with schizophrenia.[6] Metabolic syndrome, a collection of visceral adiposity (measured by waist size), high-fasting glucose, increased blood pressure, elevated triglyceride levels and low high-density lipoprotein cholesterol levels,[7] also seems to be a vital health problem to patients with schizophrenia.[8 9] Furthermore, patients with schizophrenia are liable to develop diabetes mellitus (DM)[1 10] and chronic kidney diseases (CKDs).[11]

The introduction of second-generation antipsychotics (SGAs) in the early 1990s was initially associated with better quality of life, lower rate of relapse and better tolerability than first-generation antipsychotics (FGAs).[12–14] However, the superiority of SGAs has been criticised by subsequent studies.[15 16] For example, the association between weight gain and use of SGAs, clozapine in particular, has been reported.[17]

More recent studies confirmed the above finding regarding the concern of using SGA medications. A study using the National Health Insurance Research Database in Taiwan[18] found that use of clozapine,

quetiapine, olanzapine, zotepine and risperidone was associated with the increased risk of pneumonia. A nationwide German/Austrian Diabetes Survey, which recruited 60 162 teenagers with type 1 DM, demonstrated that subjects treated with SGAs, risperidone in particular, showed higher body mass index.[19] A national study[20] conducted in the USA compared 107 551 youths using SGAs with 1 221 434 youths who do not. The risk for incident DM was increased in youths taking SGAs. The risk was higher among those using ziprasidone and aripiprazole. However, the risk for incident type 2 DM was not associated with newer SGAs, quetiapine and olanzapine.

DM was one of risk factors to develop CKD.[21] Besides, schizophrenia has been shown to be associated with an increased risk of CKD in a nationwide study in Taiwan.[11] Therefore, we consider CKD to be included as an outcome variable, too. A population-based, nested case–control study is carried out here by applying the large national psychiatric database, the Psychiatric Inpatient Medical Claims database. Meanwhile, to provide a comprehensive picture of the risk of using antipsychotics, we compare people who used both first-generation antipsychotics (FGAs) and SGAs, people who use only SGAs with those who used only FGA drugs in our study.

METHODS

Study subjects

Taiwan started a single-payer National Health Insurance programme on 1 March 1995. The National Health Insurance reimbursement claims data have been transferred to and managed by the National Health Research Institute in Taiwan since 1996. The database includes medical claim files representative of the entire population in Taiwan. All investigators signed an agreement that guarantees patient confidentiality before using the data. We used the Psychiatric Inpatient Medical Claims database, a subset of the National Health Insurance Research Database, comprising a cohort of patients hospitalised for psychiatric disorders between 2000 and 2013 (n=267 807). The database included patients with at least one psychiatric inpatient record and one discharge diagnosis of mental disorders coded by the International Classification of Diseases, Ninth Revision (ICD-9) codes 290–319. The database includes patients' demographic characteristics, diagnoses, medical expenditures and prescription claims data.[22] Each prescription record contains type of medication, dosage, time of prescription and duration of drug supply. Information which could be used to identify beneficiaries and medical care providers were scrambled by the Bureau of National Health Insurance.[23]

We enrolled patients with at least one psychiatric admission between 2000 and 2013 but no psychiatric admissions between 1996 and 1999 (n=13 644). The inclusion criteria for the study cohort was that one's diagnosis at each discharge fulfilled the principal diagnosis of schizophrenia (ICD-9 code 295.**) if a patient had several psychiatric admissions. The age of patients at first admission was restricted to 18–65 years.

Case and control definition

In this study, we conducted a nested case–control study derived from the cohort. Patients with CKD (ICD-9 codes 582, 583, 585, 586, 588) requiring hospitalisation or three outpatient visits were selected as cases (n=3411). The date of first hospitalisation for CKD or the third outpatient visit was defined as the index date. The diagnosis of CKD follows the criteria of 'Kidney Disease: Improving Global Outcomes' in Taiwan. CKD is defined as a kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens or glomerular filtration rate <60 mL/min/1.73 m^2 for 3 months or more. For each case, three matched control subjects were randomly selected from the same patients with schizophrenia who have not been diagnosed with CKD before the index date. Control subjects were matched to the patients for age diagnosed with schizophrenia, gender and the year diagnosed with schizophrenia. Each control was assigned the index date of the corresponding case. The patients diagnosed with CKD before the schizophrenia diagnosis date were excluded.

Measurement of exposure

The data of antipsychotic drug use were derived from the prescription files. The duration of treatment was calculated using the dispensed number of units and the dosing regimen for each patient. SGA drugs used in our study included clozapine, olanzapine, quetiapine, zotepine, risperidone, amisulpride, ziprasidone, aripiprazole and paliperidone. FGA drugs used in our study included chlorpromazine, levomepromazine, fluphenazine, perphenazine, trifluoperazine, thioridazine, pipotiazine, haloperidol, moperone, flupentixol, clopenthixol, chlorprothixene, pimozide, loxapine, sulpiride, clotiapine and penfluridol. Because this study focused on the associations between the individual SGA drug and the risk of CKD, all FGA drugs were grouped together in the data analysis. The follow-up period is from the schizophrenia diagnosis date to the index date.

Covariates

Age, gender and the duration of schizophrenia were controlled by the matching process of the study design.

Statistical analysis

For the comparisons of demographic between cases and controls, t test was used for continuous variables and χ^2 tests for discrete variables. Univariate and multivariable conditional logistic regressions were used to estimate the associations between the exposure to antipsychotic use and risk of CKD. Comorbidity factors, such as DM, congestive heart failure, myocardial infarction, stroke, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, hypertension and obesity were entered into adjusted model. ORs with 95% CIs were calculated. A p value of 0.05 was considered significant.

Table 1 Basic characteristics of the study population

Characteristic	Cases (n=3411) n (%)	Controls (n=10 233) n (%)
Age (mean±SD years)	41.1±10.2	41.1±10.2
Male	1871 (54.9)	5613 (54.9)
Follow-up duration (mean±SD years)	7.71±4.71	7.71±4.71
Comorbidities		
Diabetes mellitus*	1299 (38.1)	1006 (9.8)
Congestive heart failure*	207 (6.1)	86 (0.8)
Myocardial infarction*	41 (1.2)	23 (0.2)
Stroke*	220 (6.5)	195 (1.9)
Hyperlipidaemia*	502 (14.7)	433 (4.2)
Hypercholesterolaemia*	111 (3.3)	90 (0.9)
Hypertriglyceridaemia*	86 (2.5)	62 (0.6)
Hypertension*	1232 (36.1)	1147 (11.2)
Obesity*	49 (1.4)	37 (0.4)

*P<0.0001.

Patient and public involvement

We used the National Health Insurance reimbursement claims data in Taiwan.

RESULTS

A total of 3411 patients with CKD and 10 233 matched controls were enrolled in this study. Age, gender and the duration of schizophrenia of the cases and control subjects were well matched. The characteristics of patients with CKD and matched controls were compared and showed in table 1.The cases were more likely to have comorbid conditions than controls (table 1).

More than 85% subjects were received both FGA and SGA medications. Case and control groups separately include 3082 (90.4%) and 8827 (86.3%) subjects (table 2). Taking patients using FGA only as reference group, the adjusted ORs (95% CI) for those who used no FGA and no SGA, SGA alone, both FGA and SGA were 0.53 (0.13–2.21), 1.06 (0.65–1.74), 1.28 (1.11–1.47), respectively (table 2). Patients used both FGA and SGA have significant greater risk than patients used FGA only (p=0.0009) (table 2).

With the adjustment of comorbidity factors, the analysis results showed that greater risks of CKD for patients who received SGA than patients who did not receive as the reference group. Especially, patients cumulatively used SGA 90–180 days and more than 1000 days have 42% and 30% significantly higher odds of developing CKD compared with the reference group (adjusted OR (95% CI)=1.42 (1.06 to 1.91), 1.30 (1.13 to 1.51)) (table 3). Patients who used olanzapine, quetiapine, zotepine or risperidone all displayed greater odds of developing CKD than the reference group. Patients with quetiapine exposure have statistically significant higher risk than the reference group.

DISCUSSION

We found that the risks for CKD for those who used SGAs longer cumulatively were higher than those who did not. In addition, those who used only FGAs and those who used both SGAs and FGAs seemed to have lower risk for CKD.

Also using the dataset of Taiwan National Health Insurance, Tzeng *et al*[11] found that neither FGAs nor SGAs increased the risk of CKD. However, the study design of Tzeng *et al* and ours varied a lot. First, we focused on in patients while Tzeng *et al* recruited patients with a first-time diagnosis of schizophrenia. Second, subjects of Tzeng *et al* were tracked for 3 years or the end of 2010 from the initial diagnosis date until the date of CKD diagnosis. We tracked subjects for longer period with one group tracked for 180–1000 days and another for period longer than 1000 days.

The introduction ofSGAs in the early 1990s was initially shown better quality of life, lower rate of relapse and better tolerability than FGAs for patients of schizophrenia[13 14 24] but has been criticised by other studies.[15 16] The risk of pneumonia in inpatients with schizophrenia was examined using the National Health Insurance Research Database in Taiwan from 2000 to 2008.[18] They found that the current use of clozapine, one kind of SGAs, was associated with a dose-dependent increase in the risk of pneumonia for inpatients with schizophrenia. In addition, other kinds of SGAs, including quetiapine, olanzapine, zotepine and risperidone were associated with increased risk of pneumonia while no clear dose-dependent

Table 2 Comparison of crude and adjusted OR for CKD among types of antipsychotics by conditional logistic regression

Drug used	CKD cases (n=3411)	Controls (n=10 233)	OR (95% CI)	P value	AOR* (95% CI)	P value
No FGA, no SGA	3	17	0.76 (0.22 to 2.59)	0.6570	0.53 (0.13 to 2.21)	0.3857
FGA alone	300	1278	1		1	—
SGA alone	26	102	1.10 (0.70 to 1.72)	0.6920	1.06 (0.65 to 1.74)	0.8068
Combination	3082	8827	1.50 (1.32 to 1.71)	<0.0001	1.28 (1.11 to 1.47)	0.0009

*Adjusted for diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, hypertension and obesity.
AOR, adjusted OR; CKD, chronic kidney disease; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

Table 3 Overall cumulative period of using SGAs

Period of SGA use	CKD cases (n=3411)	Controls (n=10 233)	OR (95% CI)	P value	AOR* (95% CI)	P value
Cumulative SGA use						
Non-users	303	1304	1		1	
0<period≤ 90	177	552	1.38 (1.12 to 1.71)	0.0026	1.20 (0.95 to 1.51)	0.1247
90<period≤ 180	92	241	1.65 (1.26 to 2.16)	0.0003	1.42 (1.06 to 1.91)	0.0208
180<period≤ 1000	409	1271	1.39 (1.17 to 1.64)	0.0001	1.19 (0.99 to 1.43)	0.0654
1000>period	2430	6865	1.53 (1.34 to 1.75)	<0.0001	1.30 (1.13 to 1.51)	0.0004
Cumulative clozapine use (days)						
Non-users	2318	7215	1		1	
0<period≤ 90	183	351	1.63 (1.35 to 1.96)	<0.0001	1.48 (1.20 to 1.81)	0.0002
90<period≤180	49	140	1.09 (0.79 to 1.52)	0.6057	0.91 (0.63 to 1.32)	0.6281
180<period≤1000	178	549	1.01 (0.85 to 1.20)	0.9091	0.94 (0.77 to 1.14)	0.5099
1000>period	683	1978	1.08 (0.98 to 1.19)	0.1456	1.14 (1.02 to 1.27)	0.0181
Cumulative olanzapine use (days)						
Non-users	2046	6465	1		1	
0<period≤90	396	1018	1.23 (1.09 to 1.40)	0.0012	1.18 (1.02 to 1.35)	0.0225
90<period≤180	156	344	1.44 (1.18 to 1.75)	0.0003	1.37 (1.11 to 1.70)	0.0039
180<period≤1000	401	1038	1.22 (1.08 to 1.39)	0.0017	1.15 (1.00 to 1.32)	0.0561
1000>period	412	1368	0.95 (0.85 to 1.08)	0.4401	1.05 (0.92 to 1.19)	0.4954
Cumulative quetiapine use (days)						
Non-users	1669	6198	1		1	
0<period≤90	399	967	1.54 (1.35 to 1.75)	<0.0001	1.36 (1.19 to 1.57)	<0.0001
90<period≤180	147	356	1.54 (1.26 to 1.88)	<0.0001	1.27 (1.02 to 1.58)	0.0358
180<period≤1000	534	1180	1.69 (1.50 to 1.89)	<0.0001	1.48 (1.30 to 1.68)	<0.0001
1000>period	662	1532	1.61 (1.45 to 1.79)	<0.0001	1.44 (1.28 to 1.62)	<0.0001
Cumulative zotepine use (days)						
Non-users	2292	7375	1		1	
0<period≤90	319	743	1.38 (1.20 to 1.59)	<0.0001	1.26 (1.08 to 1.47)	0.0038
90<period≤180	120	265	1.46 (1.17 to 1.82)	0.0008	1.27 (0.99 to 1.63)	0.0592
180<period≤1000	310	770	1.30 (1.13 to 1.49)	0.0003	1.16 (1.00 to 1.36)	0.0572
1000>period	370	1080	1.11 (0.97 to 1.26)	0.1240	1.00 (0.87 to 1.15)	0.9854
Cumulative risperidone use (days)						
Non-users	896	3056	1		1	
0<period≤90	396	1078	1.26 (1.09 to 1.44)	0.0012	1.14 (0.98 to 1.33)	0.0927
90<period≤180	207	511	1.39 (1.16 to 1.66)	0.0003	1.26 (1.03 to 1.53)	0.0220
180<period≤1000	733	2028	1.24 (1.10 to 1.38)	0.0002	1.12 (0.99 to 1.26)	0.0845
1000<period	1179	3560	1.13 (1.03 to 1.25)	0.0148	1.10 (0.99 to 1.23)	0.0756

*Adjusted for diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, hypertension and obesity.
AOR, adjusted OR; CKD chronic kidney disease; SGA, second-generation antipsychotic.

relationship was found. They suggested that patients with schizophrenia who used these antipsychotics were to be monitored for pneumonia. Our study further suggests that inpatients with schizophrenia were being monitored for CKD, since we found that the risks for CKD were higher for those who used SGAs longer cumulatively than those who did not. Similar to the findings of Kuo *et al*, we did not see dose-dependent relationship SGAs and risk of CKD.

The increasing prevalence of end-stage renal disease (ESRD) has been a global challenge. In the USA, CKDs are the nation's ninth leading cause of death.[24] In Taiwan, CKDs have been the eighth leading cause of death since 1997 and was still the 10th leading cause of death

recently.[25] Meanwhile, the high prevalence of CKD might contribute to the high prevalence of ESRD in Taiwan.[26] Our finding that inpatients with schizophrenia who used SGAs longer have higher risks for CKD than those who did not reminds this population being monitored for CKD.

Some limitations need to be considered in the current study. First, because our data source is from a claim data set, it is hard to know how much medication each patient really took. Second, we cannot include variables not captured in the claimed database, such as patients' lifestyle and family history. However, the current study suggests a further study on the relationship between using SGAs and risk of CKD.

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Contributors H-CT and H-YW initiated the study. H-CT, H-YW and CL-CH designed the study. IJF analysed the data. H-CT wrote the manuscript and H-YW, CL-CH and IJF approved the final manuscript.

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Competing interests None declared.

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Data sharing statement Datasets of National Health Insurance in Taiwan were used. All investigators should sign an agreement that guarantees patient confidentiality before using the data.

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