BMJ Open

Second-generation antipsychotic medications and risk of chronic kidney disease in schizophrenia

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019868
Article Type:	Research
Date Submitted by the Author:	06-Oct-2017
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	second-generation antipsychotics, chronic kidney disease, schizophrenia

Second-generation antipsychotic medications and risk of chronic kidney disease in schizophrenia

Running title: Antipsychotics and kidney disease

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Key words: second-generation antipsychotics; chronic kidney disease; schizophrenia

ABSTRACT

Objectives: The study aims to compare the risk of chronic renal diseases (CKD between schizophrenic patients 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 hospitalized for psychiatric disorders between 2000 and 2013 (n = 267807). 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 hospitalization or three outpatient visits. The diagnosis of CKD follows the criteria of 'Kidney Disease: Improving Global Outcomes (KDIGO)' in Taiwan. CKD is defined as kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, for 3 months or more.

Results: We found that the risks for CKD for those who used second generation antipsychotics longer cumulatively were higher than those who did not use second generation antipsychotics. Using nonusers as reference group, the risks for CKD comparing those using second generation antipsychotics for 90 to 180 days with nonusers and those using second generation antipsychotics 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 second-generation antipsychotics and risk of CKD.

Article summary:

Strengths: We tracked subjects for period longer than 1000 days after the index day.

Limitations: Using existing dataset without personal identification, we cannot investigate all risk factors in the study.

Bullet points: The risk of CKD of inpatients of schizophrenia deserves furthers investigation. Besides, the study of risk of CKD for schizophrenic patients might need longer tracking duration.

1. Introduction

Schizophrenia is a chronic mental illness with lifetime prevalence rate around 1% (Chien et al., 2009; Hovatta et al., 1997). Patients with schizophrenia have been shown to have an excess mortality, being 2 or 3 times as high as that in the general population (Brown, 1997; Brown et al., 2010; Osby et al., 2000). Cardiovascular diseases have an increased prevalence among patients with schizophrenia (Capasso et al., 2008). Metabolic syndrome (MetS), 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 (Grundy et al., 2005), also seems to be a vital health problem to schizophrenia patients (Correll et al., 2015; Manu et al., 2015). Furthermore, patients with schizophrenia are liable to develop diabetes mellitus (DM) (Chien et al., 2009; Saddichha et al., 2008) and chronic kidney diseases (CKD) (Tzeng et al., 2015).

The introduction of second-generation antipsychotics in the early 1990s was initially associated with better quality of life, lower rate of relapse, and better tolerability than first-generation antipsychotics.(Awad and Voruganti, 2004; Leucht et al., 2003a; Leucht et al., 2003b). However, the superiority of second-generation antipsychotics has been criticized by subsequent studies (Jones et al., 2006; Lieberman et al., 2005). For example, the association between weight gain and use of second-generation antipsychotics, clozapine in particular, has been reported (Bai et al., 2011).

More recent studies confirmed the above finding regarding to the concern of using second-generation antipsychotic medications. A study using the National Health Insurance Research Database in Taiwan (Kuo et al., 2013) found that use of clozapine, quetiapine, olanzapine, zotepine, and risperidone was associated with increased risk of pneumonia. A nationwide German/Austrian Diabetes Survey, which recruiting 60,162 teenagers with type 1 diabetes, demonstrated that subjects treated with second-generation antipsychotics, risperidone in particular, showed higher BMI (Galler et al., 2015). A national study (Rubin et al., 2015) conducted in the US compared 107,551 youths using second-generation antipsychotics with 1,221,434 youths not using second-generation antipsychotics. The risk for incident diabetes mellitus was increased in youths taking second-generation antipsychotics. The risk was higher among those using ziprasidone and aripiprazole. However, the risk for incident type 2 diabetes mellitus was not associated with newer second-generation antipsychotics, quetiapine and olanzapine.

In order to provide a more comprehensive evaluation comparing the side effects of second- and first-generation antipsychotics, we consider CKD to be included as an outcome variable, too. DM was one of risk factors to develop CKD (Hwang et al.,

2010). In addition, schizophrenia has been shown to be associated with an increased risk of CKD in a nationwide study in Taiwan (Tzeng et al., 2015).

2. Methods

2.1. Study subjects

Taiwan started a single-payer National Health Insurance program on March 1, 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 hospitalized for psychiatric disorders between 2000 and 2013 (n = 267807). 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 (Gau et al., 2010). 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 (Gau et al., 2008).
We enrolled patients with at least one psychiatric admission between 2000 and 2013 but no psychiatric admissions between 1996 and 1999 (n = 13644). 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.

2.2. Case and control definition

Using the patients with CKD (ICD-9 code 582, 583, 585, 586, 588) requiring hospitalization or three outpatient visits as cases (n = 3411), we conducted a nested case-control study derived from the cohort. The date of hospitalization 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 (KDIGO)' in Taiwan. CKD is defined as kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, for 3 months or more. For each case, 3 matched control subjects were randomly selected from the same schizophrenia cohort. Control subjects were matched to the patients for

age, gender, and the index date. Each control was assigned the index date of the corresponding case.

2.3. Measurement of exposure

The data of antipsychotic drug use was derived from the prescription files. The duration of treatment was calculated using the dispensed number of units and the dosing regimen for each patient. Second-generation antipsychotic drugs used in our study included clozapine, olanzapine, quetiapine, zotepine, risperidone, amisulpride, ziprasidone, aripiprazole, and paliperidone. First-generation antipsychotic 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 second-generation antipsychotic drug and the risk of CKD, all first-generation antipsychotic drugs were grouped together in the data analysis.

2.4. Covariates

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

2.5. 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 multivariate conditional logistic regressions were used to estimate the associations between the exposure to antipsychotic use and risk of CKD. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value .05 was considered significant.

3. Results

We identified 3411 cases of CKD. The age and gender distributions of the cases and control subjects were well matched. The cases were more likely than controls to have comorbid conditions (Table 1).

Table 2 showed that 1364 cases (40.0%) and 3559 controls (34.8%) were nonusers of antipsychotics. Using nonusers as reference group, the adjusted odds ratios for those who used first generation antipsychotics alone and those who used both first and second generation antipsychotics were 0.76 and 0.64, respectively.

Table 3 showed that 303 cases and 1304 controls did not use any second

generation antipsychotics. Using nonusers as reference group, the risks for CKD comparing those using second generation antipsychotics for 90 to 180 days with nonusers and those using second generation antipsychotics for more than 1000 days were 1.42 and 1.30, respectively (table 3). Considering varied second generation antipsychotics individually, using nonusers as reference group, the risks for CKD varied from 1.14 to 1.48.

4. Discussion

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

Also using the dataset of Taiwan National Health Insurance, Tzeng et al. (Tzeng et al., 2015) found that neither first nor second generation antipsychotics increased the risk of CKD. However, the study design of Tzeng et al. and ours varied a lot. Firstly, we focused on in patients while Tzeng et al. recruited patients with a first-time diagnosis of schizophrenia. Secondly, subjects of Tzeng et al. were tracked for 3 years or the end of 2010 from the index date until 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 of second-generation antipsychotics in the early 1990s was initially shown better quality of life, lower rate of relapse, and better tolerability than first-generation antipsychotics for patients of schizophrenia.(Awad and Voruganti, 2004; Leucht et al., 2003a; Leucht et al., 2003b) but has been criticized by other studies (Jones et al., 2006; Lieberman et al., 2005). The risk of pneumonia in inpatients with schizophrenia was examined using the National Health Insurance Research Database in Taiwan from 2000 to 2008 (Kuo et al., 2013). They found that current used of clozapine, one kind of second-generation antipsychotics, was associated with a dose-dependent increase in the risk of pneumonia for inpatients with schizophrenia. In addition, other kinds of second-generation antipsychotics, including quetiapine, olanzapine, zotepine, and risperidone, were associated with increased risk of pneumonia while no clear dose-dependent relationship was found. They suggested that patients with schizophrenia who used these antipsychotics to be monitored for pneumonia. Our study further suggests that inpatients with schizophrenia being monitored for CKD since we found that the risks for CKD for those who used second generation antipsychotics longer cumulatively were higher than those who did not use second generation antipsychotics. Similar to the findings of kuo et al., we did not see

dose-dependent relationship second generation antipsychotics and risk of CKD.

The increasing prevalence of end-stage renal disease (ESRD) has been a global challenge. In the US, chronic renal diseases are the nation's ninth leading cause of death (Arias et al., 2003). In Taiwan, chronic renal diseases have been the eighth leading cause of death since 1997, and was still the tenth leading cause of death recently (Department of Health, 2017). Meanwhile, the high prevalence of CKD might contribute to the high prevalence of ESRD in Taiwan (Hsu et al., 2006). Our finding that inpatients with schizophrenia who used second generation antipsychotics longer have higher risks for CKD than those who did not use second generation antipsychotics 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 take. Second, we can not include variables not captured in claim database, such as patients' lifestyle and family history. However, the current study suggests a hypothesis regarding the relationship between using second-generation antipsychotics and risk of CKD which warrants further study.

Declaration of interest

All authors declare that they have no conflicts of interest.

Contributors

Hui-Chun Tsuang and Hsien-Yi Wang initiated the study. Hui-Chun Tsuang, Hsien-Yi Wang and Charles Lung-Cheng Huang designed the study. I Jung Feng analyzed the data. Hui-Chun Tsuang wrote the manuscript and Hsien-Yi Wang, Charles Lung-Cheng Huang and I Jung Feng approved the final manuscript.

Acknowledgements

The authors thank the Bureau of National Health Insurance and National Health Institutes for making available the databases for this study.

DATA SHARING STTEMENT

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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Table 1 Basic characteristics of the study population

Characteristic	Cases (n = 3411) n (%)	Controls (n = 10,233) n (%)	p
Age (mean ± SD years)	41.05 ± 10.23	41.05 ± 10.240	0.999
Male	1871 (54.9)	5613 (54.9)	> 0.999
Follow-up duration (mean ± SD years)	7.71 ± 4.71	7.71 ± 4.71	0.971
Comorbidities			
Diabetes mellitus	1299 (38.1)	1006 (9.8)	< 0.0001
Congestive heart failure	207 (6.1)	86 (0.8)	< 0.0001
Myocardial infarction	41 (1.2)	23 (0.2)	< 0.0001
Stroke	220 (6.5)	195 (1.9)	< 0.0001
Hyperlipidemia	502 (14.7)	433 (4.2)	< 0.0001
Hypercholesterolemia	111 (3.3)	90 (0.9)	< 0.0001
Hypertriglyceridemia	86 (2.5)	62 (0.6)	< 0.0001
Hypertension	1232 (36.1)	1147 (11.2)	< 0.0001
Obesity	49 (1.4)	37 (0.4)	< 0.0001

SD: standard deviation.

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

Drug used	CKD cases (n = 3411)	Controls (n = 10,233)	OR (95% CI)	AOR[a] (95% CI)
Nonusers	1364	3559	1	1
FGA alone	930	2890	0.84 (0.76-0.93)*	0.76 (0.68-0.84)*
SGA alone	178	470	0.99 (0.82-1.19)	0.85 (0.69-1.04)
Combination	939	3314	0.74 (0.67-0.81)*	0.64 (0.57-0.71)*

OR: odds ratio; C I: confidence interval; AOR: adjusted odds ratio; FGA: first generation antipsychotic; SGA: second generation antipsychotic.

[a]Adjusted for age, gender, diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity.

Table 3 Overall cumulative period of using second generation antipsychotics

Period of SGA use	CKD cases (n = 3411)	Controls (n = 10,233)	OR (95% CI)	AOR[a] (95% CI)
Cumulative SGA use				
nonusers	303	1304	1	1
0 < period ≤ 90	177	552	1.38 (1.12-1.71)*	1.20 (0.95-1.51)
90 < period ≤ 180	92	241	1.65 (1.26-2.16)*	1.42 (1.06-1.91)*
180 < period ≤ 1000	409	1271	1.39 (1.17-1.64)*	1.19 (0.99-1.43)
1000 > period	2430	6865	1.53 (1.34-1.75)*	1.30 (1.13-1.51)*
Cumulative clozapine use (days)				
nonusers	2318	7215	1	1
0 < period ≤ 90	183	351	1.63 (1.35-1.96)*	1.48 (1.20-1.81)*
90 < period ≤ 180	49	140	1.09 (0.79-1.52)	0.91 (0.63-1.32)
180 < period ≤ 1000	178	549	1.01 (0.85-1.20)	0.94 (0.77-1.14)
1000 > period	683	1978	1.08 (0.98-1.19)	1.14 (1.02-1.27)*
Cumulative olanzapine use (days)				
nonusers	2046	6465	1	1
0 < period ≤ 90	396	1018	1.23 (1.09-1.40)	1.18 (1.02-1.35)
90 < period ≤ 180	156	344	1.44 (1.18-1.75)*	1.37 (1.11-1.70)*
180 < period ≤ 1000	401	1038	1.22 (1.08-1.39)*	1.15 (1.00-1.32)*
1000 > period	412	1368	0.95 (0.85-1.08)	1.05 (0.92-1.19)
Cumulative quetiapine use (days)				
nonusers	1669	6198	1	1

Period of SGA use	CKD cases (n = 3411)	Controls (n = 10,233)	OR (95% CI)	AOR[a] (95% CI)
0 < period ≤ 90	399	967	1.54 (1.35-1.75)*	1.36 (1.19-1.57)*
90 < period ≤ 180	147	356	1.54 (1.26-1.88)	1.27 (1.02-1.58)*
180 < period ≤ 1000	534	1180	1.69 (1.50-1.89)*	1.48 (1.30-1.68)*
1000 > period	662	1532	1.61 (1.45-1.79)*	1.44 (1.28-1.62)*
Cumulative zotepine use (days)				
nonusers	2292	7375	1	1
0 < period ≤ 90	319	743	1.38 (1.20-1.59)*	1.26 (1.08-1.47)*
90 < period ≤ 180	120	265	1.46 (1.17-1.82)*	1.27 (0.99-1.63)
180 < period ≤ 1000	310	770	1.30 (1.13-1.49)*	1.16 (1.00-1.36)*
1000 > period	370	1080	1.11 (0.97-1.26)	1.00 (0.87-1.15)
Cumulative risperidone use (days)				
nonusers	896	3056	1	1
0 < period ≤ 90	396	1078	1.26 (1.09-1.44)*	1.14 (0.98-1.33)
90 < period ≤ 180	207	511	1.39 (1.16-1.66)*	1.26 (1.03-1.53)*
180 < period ≤ 1000	733	2028	1.24 (1.10-1.38)*	1.12 (0.99-1.26)
1000 < period	1179	3560	1.13 (1.03-1.25)*	1.10 (0.99-1.23)

OR: odds ratio; C I: confidence interval; AOR: adjusted odds ratio; SGA: second generation antipsychotic.

[a]Adjusted for age, gender, diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019868.R1
Article Type:	Research
Date Submitted by the Author:	24-Nov-2017
Complete List of Authors:	Wang, Hsien-Yi ; Chi Mei Medical Center, Nephrology Huang, Charles Lung-Cheng ; Chi Mei Medical Center, Psychiatry Feng, I Jung ; Chi Mei Medical Center, Chi Mei Hospital, Department of Medical Research Tsuang, Hui-Chun
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	second-generation antipsychotics, chronic kidney disease, schizophrenia

Second-generation antipsychotic medications and risk of chronic kidney disease in schizophrenia: A case-control study in Taiwan

Running title: Antipsychotics and kidney disease

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ABSTRACT

Objectives: The study aims to compare the risk of chronic renal diseases (CKD between schizophrenic patients 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 hospitalized for psychiatric disorders between 2000 and 2013 (n = 267807). 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 hospitalization or three outpatient visits. The diagnosis of CKD follows the criteria of 'Kidney Disease: Improving Global Outcomes (KDIGO)' in Taiwan. CKD is defined as kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, for 3 months or more.

Results: We found that the risks for CKD for those who used second generation antipsychotics longer cumulatively were higher than those who did not use second generation antipsychotics. Using nonusers, patients didn't have any second generation antipsychotics records, as reference group, the risks for CKD comparing those using second generation antipsychotics for 90 to 180 days with nonusers and those using second generation antipsychotics 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 second-generation antipsychotics and risk of CKD.

Article summary:

Strengths:

(1) We tracked subjects for period longer than 1000 days after the initial schizophrenia diagnosis day.

(2) This is the first study investing the relationship between antipsychotics and risk of CKD in inpatients with schizophrenia.

Limitations:

(1) The measurement of exposure, use of antipsychotic drugs, can only be estimated

by the existing dataset we used.

(2) Using existing dataset without personal identification, we cannot investigate all risk factors in the study.

Bullet points: The risk of CKD of inpatients of schizophrenia deserves furthers investigation. Besides, the study of risk of CKD for schizophrenic patients might need longer tracking duration.

1. 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 2 or 3 times as high as that in the general population[3-5]. Cardiovascular diseases have an increased prevalence among patients with schizophrenia[6]. Metabolic syndrome (MetS), 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 schizophrenia patients[8-9]. Furthermore, patients with schizophrenia are liable to develop diabetes mellitus (DM)[1, 10] and chronic kidney diseases (CKD)[11].

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

More recent studies confirmed the above finding regarding to the concern of using second-generation antipsychotic 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 increased risk of pneumonia. A nationwide German/Austrian Diabetes Survey, which recruiting 60,162 teenagers with type 1 diabetes, demonstrated that subjects treated with second-generation antipsychotics, risperidone in particular, showed higher BMI[19]. A national study[20] conducted in the US compared 107,551 youths using second-generation antipsychotics with 1,221,434 youths not using second-generation antipsychotics. The risk for incident diabetes mellitus was increased in youths taking second-generation antipsychotics. The risk was higher among those using ziprasidone and aripiprazole. However, the risk for incident type 2 diabetes mellitus was not associated with newer second-generation antipsychotics, quetiapine and olanzapine.

DM was one of risk factors to develop CKD[21]. In addition, schizophrenia has been shown to be associated with an increased risk of CKD in a nationwide study in Taiwan[11]. In order to provide a more comprehensive evaluation comparing the side effects of second- and first-generation antipsychotics, 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.

2. Methods

2.1. Study subjects

Taiwan started a single-payer National Health Insurance program on March 1, 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 hospitalized for psychiatric disorders between 2000 and 2013 (n = 267807). 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 = 13644). 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.

2.2. Case and control definition

Using the patients with CKD (ICD-9 code 582, 583, 585, 586, 588) requiring hospitalization or three outpatient visits as cases (n = 3411), we conducted a nested case-control study derived from the cohort. The date of hospitalization 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 (KDIGO)' in Taiwan. CKD is defined as kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, for 3 months or more. For each case, 3 matched control subjects were randomly selected from the same schizophrenia cohort. 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. Patients diagnosed with CKD before the schizophrenia diagnosis date were excluded.

2.3. Measurement of exposure

The data of antipsychotic drug use was derived from the prescription files. The duration of treatment was calculated using the dispensed number of units and the dosing regimen for each patient. Second-generation antipsychotic drugs used in our study included clozapine, olanzapine, quetiapine, zotepine, risperidone, amisulpride, ziprasidone, aripiprazole, and paliperidone. First-generation antipsychotic 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 second-generation antipsychotic drug and the risk of CKD, all first-generation antipsychotic drugs were grouped together in the data analysis. The date of diagnosed CKD is defined as index date in this study. The follow up period is from the schizophrenia diagnosis date to the index date.

2.4. Covariates

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

2.5. 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. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value .05 was considered significant.

3. Results

We identified 3411 cases of CKD. The age and gender distributions of the cases and control subjects were well matched. The cases were more likely than controls to have comorbid conditions (Table 1).

Table 2 showed that 1364 cases (40.0%) and 3559 controls (34.8%) were nonusers of antipsychotics. Using nonusers as reference group, the adjusted odds ratios for those who used first generation antipsychotics alone and those who used both first and second generation antipsychotics were 0.76 and 0.64, respectively.

Table 3 showed that 303 cases and 1304 controls did not use any second

generation antipsychotics. Using nonusers as reference group, the risks for CKD comparing those using second generation antipsychotics for 90 to 180 days with nonusers and those using second generation antipsychotics for more than 1000 days were 1.42 and 1.30, respectively (table 3). Considering varied second generation antipsychotics individually, using nonusers as reference group, the risks for CKD varied from 1.14 to 1.48.

4. Discussion

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

Also using the dataset of Taiwan National Health Insurance, Tzeng et al.[11] found that neither first nor second generation antipsychotics increased the risk of CKD. However, the study design of Tzeng et al. and ours varied a lot. Firstly, we focused on in patients while Tzeng et al. recruited patients with a first-time diagnosis of schizophrenia. Secondly, subjects of Tzeng et al. were tracked for 3 years or the end of 2010 from the initial diagnosis date until 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 of second-generation antipsychotics in the early 1990s was initially shown better quality of life, lower rate of relapse, and better tolerability than first-generation antipsychotics for patients of schizophrenia[13-14, 24] but has been criticized 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 current used of clozapine, one kind of second-generation antipsychotics, was associated with a dose-dependent increase in the risk of pneumonia for inpatients with schizophrenia. In addition, other kinds of second-generation antipsychotics, including quetiapine, olanzapine, zotepine, and risperidone, were associated with increased risk of pneumonia while no clear dose-dependent relationship was found. They suggested that patients with schizophrenia who used these antipsychotics to be monitored for pneumonia. Our study further suggests that inpatients with schizophrenia being monitored for CKD since we found that the risks for CKD for those who used second generation antipsychotics longer cumulatively were higher than those who did not use second generation antipsychotics. Similar to the findings of kuo et al., we did not see dose-dependent relationship second generation antipsychotics and risk of CKD.

The increasing prevalence of end-stage renal disease (ESRD) has been a global challenge. In the US, chronic renal diseases are the nation's ninth leading cause of death[24]. In Taiwan, chronic renal diseases have been the eighth leading cause of death since 1997, and was still the tenth 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 second generation antipsychotics longer have higher risks for CKD than those who did not use second generation antipsychotics 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 take. Second, we can not include variables not captured in claim database, such as patients' lifestyle and family history. However, the current study suggests a hypothesis regarding the relationship between using second-generation antipsychotics and risk of CKD which warrants further study.

Declaration of interest

All authors declare that they have no conflicts of interest.

Contributors

Hui-Chun Tsuang and Hsien-Yi Wang initiated the study. Hui-Chun Tsuang, Hsien-Yi Wang and Charles Lung-Cheng Huang designed the study. I Jung Feng analyzed the data. Hui-Chun Tsuang wrote the manuscript and Hsien-Yi Wang, Charles Lung-Cheng Huang and I Jung Feng approved the final manuscript.

Acknowledgements

The authors thank the Bureau of National Health Insurance and National Health Institutes for making available the databases for this study.

DATA SHARING STTEMENT

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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Table 1 Basic characteristics of the study population

Characteristic	Cases (n = 3411) n (%)	Controls (n = 10,233) n (%)	p
Age (mean ± SD years)	41.1 ± 10.2	41.1 ± 10.2	0.999
Male	1871 (54.9)	5613 (54.9)	> 0.999
Follow-up duration (mean ± SD years)	7.71 ± 4.71	7.71 ± 4.71	0.971
Comorbidities			
Diabetes mellitus	1299 (38.1)	1006 (9.8)	< 0.0001
Congestive heart failure	207 (6.1)	86 (0.8)	< 0.0001
Myocardial infarction	41 (1.2)	23 (0.2)	< 0.0001
Stroke	220 (6.5)	195 (1.9)	< 0.0001
Hyperlipidemia	502 (14.7)	433 (4.2)	< 0.0001
Hypercholesterolemia	111 (3.3)	90 (0.9)	< 0.0001
Hypertriglyceridemia	86 (2.5)	62 (0.6)	< 0.0001
Hypertension	1232 (36.1)	1147 (11.2)	< 0.0001
Obesity	49 (1.4)	37 (0.4)	< 0.0001

SD: standard deviation.

Table 2 Comparison of crude and adjusted odds ratio 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[a] (95% CI)	p-value
Nonusers	3	17	0.76 (0.22-2.59)	0.6570	0.53 (0.13-2.21)	0.3857
FGA alone	300	1278	1		1	-
SGA alone	26	102	1.10 (0.70-1.72)	0.6920	1.06 (0.65-1.74)	0.8068
Combination	3082	8827	1.50 (1.32-1.71)	<.0001	1.28 (1.11-1.47)	.0009

OR: odds ratio; C I: confidence interval; AOR: adjusted odds ratio; FGA: first generation antipsychotic; SGA: second generation antipsychotic.

[a]Adjusted for age, gender, diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity.

Table 3 Overall cumulative period of using second generation antipsychotics

Period of SGA use	CKD cases (n = 3411)	Controls (n = 10,233)	OR (95% CI)	p-value	AOR[a] (95% CI)	p-value
Cumulative SGA use						
nonusers	303	1304	1		1	
0 < period ≤ 90	177	552	1.38 (1.12-1.71)	0.0026	1.20 (0.95-1.51)	0.1247
90 < period ≤ 180	92	241	1.65 (1.26-2.16)	0.0003	1.42 (1.06-1.91)	0.0208
180 < period ≤ 1000	409	1271	1.39 (1.17-1.64)	0.0001	1.19 (0.99-1.43)	0.0654
1000 > period	2430	6865	1.53 (1.34-1.75)	<.0001	1.30 (1.13-1.51)	0.0004
Cumulative clozapine use (days)						
nonusers	2318	7215	1		1	
0 < period ≤ 90	183	351	1.63 (1.35-1.96)	<.0001	1.48 (1.20-1.81)	0.0002
90 < period ≤ 180	49	140	1.09 (0.79-1.52)	0.6057	0.91 (0.63-1.32)	0.6281
180 < period ≤ 1000	178	549	1.01 (0.85-1.20)	0.9091	0.94 (0.77-1.14)	0.5099
1000 > period	683	1978	1.08 (0.98-1.19)	0.1456	1.14 (1.02-1.27)	0.0181
Cumulative olanzapine use (days)						
nonusers	2046	6465	1		1	
0 < period ≤ 90	396	1018	1.23 (1.09-1.40)	0.0012	1.18 (1.02-1.35)	0.0225
90 < period ≤ 180	156	344	1.44 (1.18-1.75)	0.0003	1.37 (1.11-1.70)	0.0039
180 < period ≤ 1000	401	1038	1.22 (1.08-1.39)	0.0017	1.15 (1.00-1.32)	0.0561
1000 > period	412	1368	0.95 (0.85-1.08)	0.4401	1.05 (0.92-1.19)	0.4954

Period of SGA use	CKD cases (n = 3411)	Controls (n = 10,233)	OR (95% CI)	p-value	AOR[a] (95% CI)	p-value
Cumulative quetiapine use (days)						
nonusers	1669	6198	1		1	
0 < period ≤ 90	399	967	1.54 (1.35-1.75)	<.0001	1.36 (1.19-1.57)	<.0001
90 < period ≤ 180	147	356	1.54 (1.26-1.88)	<.0001	1.27 (1.02-1.58)	0.0358
180 < period ≤ 1000	534	1180	1.69 (1.50-1.89)	<.0001	1.48 (1.30-1.68)	<.0001
1000 > period	662	1532	1.61 (1.45-1.79)	<.0001	1.44 (1.28-1.62)	<.0001
Cumulative zotepine use (days)						
nonusers	2292	7375	1		1	
0 < period ≤ 90	319	743	1.38 (1.20-1.59)	<.0001	1.26 (1.08-1.47)	0.0038
90 < period ≤ 180	120	265	1.46 (1.17-1.82)	0.0008	1.27 (0.99-1.63)	0.0592
180 < period ≤ 1000	310	770	1.30 (1.13-1.49)	0.0003	1.16 (1.00-1.36)	0.0572
1000 > period	370	1080	1.11 (0.97-1.26)	0.1240	1.00 (0.87-1.15)	0.9854
Cumulative risperidone use (days)						
nonusers	896	3056	1		1	
0 < period ≤ 90	396	1078	1.26 (1.09-1.44)	0.0012	1.14 (0.98-1.33)	0.0927
90 < period ≤ 180	207	511	1.39 (1.16-1.66)	0.0003	1.26 (1.03-1.53)	0.0220
180 < period ≤ 1000	733	2028	1.24 (1.10-1.38)	0.0002	1.12 (0.99-1.26)	0.0845
1000 < period	1179	3560	1.13 (1.03-1.25)	0.0148	1.10 (0.99-1.23)	0.0756

OR: odds ratio; C I: confidence interval; AOR: adjusted odds ratio; SGA: second generation antipsychotic.

[a]Adjusted for age, gender, diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

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Other information		
Funding	22	CMFHR 10537; Source of funding: Chi-Mei Medical Center. The role of the funder: Three of the authors work in Chi-Mei Medical Center.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019868.R2
Article Type:	Research
Date Submitted by the Author:	10-Jan-2018
Complete List of Authors:	Wang, Hsien-Yi ; Chi Mei Medical Center, Nephrology Huang, Charles Lung-Cheng ; Chi Mei Medical Center, Psychiatry Feng, I Jung ; Chi Mei Medical Center, Chi Mei Hospital, Department of Medical Research Tsuang, Hui-Chun
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	second-generation antipsychotics, chronic kidney disease, schizophrenia

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

Running title: Antipsychotics and kidney disease

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Key words: second-generation antipsychotics; chronic kidney disease; schizophrenia

ABSTRACT

Objectives: The study aims to compare the risk of chronic renal diseases (CKD between schizophrenic patients 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 hospitalized for psychiatric disorders between 2000 and 2013 (n = 267807). 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 hospitalization or three outpatient visits. The diagnosis of CKD follows the criteria of 'Kidney Disease: Improving Global Outcomes (KDIGO)' in Taiwan. CKD is defined as kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, or glomerular filtration rate (GFR) <60 mL/min/1.73 m2, for 3 months or more.

Results: We found that the risks for CKD for those who used second generation antipsychotics longer cumulatively were higher than those who did not use second generation antipsychotics. Using nonusers, patients didn't have any second generation antipsychotics records, as reference group, the risks for CKD comparing those using second generation antipsychotics for 90 to 180 days with nonusers and those using second generation antipsychotics 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 second-generation antipsychotics and risk of CKD.

Article summary:

Strengths:

(1) We tracked subjects for period longer than 1000 days after the initial schizophrenia diagnosis day.

(2) This is the first study investing the relationship between antipsychotics and risk of CKD in inpatients with schizophrenia.

Limitations:

(1) The measurement of exposure, use of antipsychotic drugs, can only be estimated by the existing dataset we used.

(2) Using existing dataset without personal identification, we cannot investigate all risk factors in the study.

Bullet points: The risk of CKD of inpatients of schizophrenia deserves furthers investigation. Besides, the study of risk of CKD for schizophrenic patients might need longer tracking duration.

1. 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 2 or 3 times as high as that in the general population[3-5]. Cardiovascular diseases have an increased prevalence among patients with schizophrenia[6]. Metabolic syndrome (MetS), 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 schizophrenia patients[8-9]. Furthermore, patients with schizophrenia are liable to develop diabetes mellitus (DM)[1, 10] and chronic kidney diseases (CKD)[11].

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

More recent studies confirmed the above finding regarding to the concern of using second-generation antipsychotic 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 increased risk of pneumonia. A nationwide German/Austrian Diabetes Survey, which recruiting 60,162 teenagers with type 1 diabetes, demonstrated that subjects treated with second-generation antipsychotics, risperidone in particular, showed higher BMI[19]. A national study[20] conducted in the US compared 107,551 youths using second-generation antipsychotics with 1,221,434 youths not using second-generation antipsychotics. The risk for incident diabetes mellitus was increased in youths taking second-generation antipsychotics. The risk was higher among those using ziprasidone and aripiprazole. However, the risk for incident type 2 diabetes mellitus was not associated with newer second-generation antipsychotics, 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 and second generation antipsychotics, people who use only second generation antipsychotics with those who used only first generation

drugs in our study.

2. Methods

2.1. Study subjects

Taiwan started a single-payer National Health Insurance program on March 1, 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 hospitalized for psychiatric disorders between 2000 and 2013 (n = 267807). 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 = 13644). 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.

2.2. Case and control definition

In this study we conducted a nested case-control study derived from the cohort. Patients with CKD (ICD-9 code 582, 583, 585, 586, 588) requiring hospitalization or three outpatient visits were selected as cases (n = 3411). The date of first hospitalization 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 (KDIGO)' in Taiwan. CKD is defined as kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, for 3 months or more. For each case, 3 matched control subjects were randomly selected from the same schizophrenia patients who have not been diagnosed with CKD before 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. Patients diagnosed with CKD before the schizophrenia diagnosis date were excluded.

2.3. Measurement of exposure

The data of antipsychotic drug use was derived from the prescription files. The duration of treatment was calculated using the dispensed number of units and the dosing regimen for each patient. Second-generation antipsychotic drugs used in our study included clozapine, olanzapine, quetiapine, zotepine, risperidone, amisulpride, ziprasidone, aripiprazole, and paliperidone. First-generation antipsychotic 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 second-generation antipsychotic drug and the risk of CKD, all first-generation antipsychotic drugs were grouped together in the data analysis. The follow up period is from the schizophrenia diagnosis date to the index date.

2.4. Covariates

Age, gender and the duration of schizophrenia were Comorbidity factors, such as diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity, were entered into adjusted model controlled by the matching process of the study design.

2.5. 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 diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity, were entered into adjusted model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value .05 was considered significant.

3. Results

A total of 3411 patients with CKD and 10233 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 Table1.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 (Table2). 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 (Table2). Patients used both FGA and SGA have significant greater risk than patients used FGA only (p=0.0009) (Table2).

With the adjustment of comorbidity factors, the analysis results showed that greater risks of CKD for patients who received SGA than patients didn't 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 to reference group (adjusted OR[95%CI]=1.42[1.06-1.91], 1.30 [1.13-1.51]) (Table3). The adjusted ORs for patients exposed for 0 - 90 days and 180 -1000 days were close to the margin of statistical significance, p-value=0.1236 and 0.0646 separately (Table3). Patients used olanzapine, quetiapine, zotepine or risperidone all displayed greater odds of developing CKD than reference group. Patients with quetiapine exposure have statistically significant higher risk than the reference group.

4. Discussion

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

Also using the dataset of Taiwan National Health Insurance, Tzeng et al.[11] found that neither first nor second generation antipsychotics increased the risk of CKD. However, the study design of Tzeng et al. and ours varied a lot. Firstly, we focused on in patients while Tzeng et al. recruited patients with a first-time diagnosis of schizophrenia. Secondly, subjects of Tzeng et al. were tracked for 3 years or the end of 2010 from the initial diagnosis date until 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 of second-generation antipsychotics in the early 1990s was initially shown better quality of life, lower rate of relapse, and better tolerability than first-generation antipsychotics for patients of schizophrenia[13-14, 24] but has been criticized 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 current used of clozapine, one kind of second-generation antipsychotics, was associated with a dose-dependent increase in the risk of pneumonia for inpatients with schizophrenia. In addition, other kinds of second-generation antipsychotics, including quetiapine, olanzapine, zotepine, and risperidone, were associated with increased risk of pneumonia while no clear dose-dependent relationship was found. They suggested that patients with schizophrenia who used these antipsychotics to be monitored for pneumonia. Our study further suggests that inpatients with schizophrenia being monitored for CKD since we found that the risks for CKD for those who used second generation antipsychotics longer cumulatively were higher than those who did not use second generation antipsychotics. Similar to the findings of kuo et al., we did not see dose-dependent relationship second generation antipsychotics and risk of CKD.

The increasing prevalence of end-stage renal disease (ESRD) has been a global challenge. In the US, chronic renal diseases are the nation's ninth leading cause of death[24]. In Taiwan, chronic renal diseases have been the eighth leading cause of death since 1997, and was still the tenth 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 second generation antipsychotics longer have higher risks for CKD than those who did not use second generation antipsychotics 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 take. Second, we can not include variables not captured in claim database, such as patients' lifestyle and family history. However, the current study suggests a hypothesis regarding the relationship between using second-generation antipsychotics and risk of CKD which warrants further study.

Declaration of interest

All authors declare that they have no conflicts of interest.

Contributors

Hui-Chun Tsuang and Hsien-Yi Wang initiated the study. Hui-Chun Tsuang, Hsien-Yi Wang and Charles Lung-Cheng Huang designed the study. I Jung Feng analyzed the data. Hui-Chun Tsuang wrote the manuscript and Hsien-Yi Wang, Charles Lung-Cheng Huang and I Jung Feng approved the final manuscript.

Funding

The study was supported by Chi-Mei Medical Center (CMFHR 10537)

Acknowledgements

The authors thank the Bureau of National Health Insurance and National Health Institutes for making available the databases for this study.

DATA SHARING STTEMENT

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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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)
Hyperlipidemia***	502 (14.7)	433 (4.2)
Hypercholesterolemia***	111 (3.3)	90 (0.9)
Hypertriglyceridemia***	86 (2.5)	62 (0.6)
Hypertension***	1232 (36.1)	1147 (11.2)
Obesity***	49 (1.4)	37 (0.4)

SD: standard deviation.

*** < 0.0001

Table 2 Comparison of crude and adjusted odds ratio 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[a] (95% CI)	p-value
no FGA, no SGA	3	17	0.76 (0.22-2.59)	0.6570	0.53 (0.13-2.21)	0.3857
FGA alone	300	1278	1		1	-
SGA alone	26	102	1.10 (0.70-1.72)	0.6920	1.06 (0.65-1.74)	0.8068
Combination	3082	8827	1.50 (1.32-1.71)	<.0001	1.28 (1.11-1.47)	.0009

OR: odds ratio; C I: confidence interval; AOR: adjusted odds ratio; FGA: first generation antipsychotic; SGA: second generation antipsychotic.

[a]Adjusted for diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity.

Table 3 Overall cumulative period of using second generation antipsychotics

Period of SGA use	CKD cases (n = 3411)	Controls (n = 10,233)	OR (95% CI)	p-value	AOR[a] (95% CI)	p-value
Cumulative SGA use						
nonusers	303	1304	1		1	
0 < period ≤ 90	177	552	1.38 (1.12-1.71)	0.0026	1.20 (0.95-1.51)	0.1247
90 < period ≤ 180	92	241	1.65 (1.26-2.16)	0.0003	1.42 (1.06-1.91)	0.0208
180 < period ≤ 1000	409	1271	1.39 (1.17-1.64)	0.0001	1.19 (0.99-1.43)	0.0654
1000 > period	2430	6865	1.53 (1.34-1.75)	<.0001	1.30 (1.13-1.51)	0.0004
Cumulative clozapine use (days)						
nonusers	2318	7215	1		1	
0 < period ≤ 90	183	351	1.63 (1.35-1.96)	<.0001	1.48 (1.20-1.81)	0.0002
90 < period ≤ 180	49	140	1.09 (0.79-1.52)	0.6057	0.91 (0.63-1.32)	0.6281
180 < period ≤ 1000	178	549	1.01 (0.85-1.20)	0.9091	0.94 (0.77-1.14)	0.5099
1000 > period	683	1978	1.08 (0.98-1.19)	0.1456	1.14 (1.02-1.27)	0.0181
Cumulative olanzapine use (days)						
nonusers	2046	6465	1		1	
0 < period ≤ 90	396	1018	1.23 (1.09-1.40)	0.0012	1.18 (1.02-1.35)	0.0225
90 < period ≤ 180	156	344	1.44 (1.18-1.75)	0.0003	1.37 (1.11-1.70)	0.0039
180 < period ≤ 1000	401	1038	1.22 (1.08-1.39)	0.0017	1.15 (1.00-1.32)	0.0561
1000 > period	412	1368	0.95 (0.85-1.08)	0.4401	1.05 (0.92-1.19)	0.4954

Period of SGA use	CKD cases (n = 3411)	Controls (n = 10,233)	OR (95% CI)	p-value	AOR[a] (95% CI)	p-value
Cumulative quetiapine use (days)						
nonusers	1669	6198	1		1	
0 < period ≤ 90	399	967	1.54 (1.35-1.75)	<.0001	1.36 (1.19-1.57)	<.0001
90 < period ≤ 180	147	356	1.54 (1.26-1.88)	<.0001	1.27 (1.02-1.58)	0.0358
180 < period ≤ 1000	534	1180	1.69 (1.50-1.89)	<.0001	1.48 (1.30-1.68)	<.0001
1000 > period	662	1532	1.61 (1.45-1.79)	<.0001	1.44 (1.28-1.62)	<.0001
Cumulative zotepine use (days)						
nonusers	2292	7375	1		1	
0 < period ≤ 90	319	743	1.38 (1.20-1.59)	<.0001	1.26 (1.08-1.47)	0.0038
90 < period ≤ 180	120	265	1.46 (1.17-1.82)	0.0008	1.27 (0.99-1.63)	0.0592
180 < period ≤ 1000	310	770	1.30 (1.13-1.49)	0.0003	1.16 (1.00-1.36)	0.0572
1000 > period	370	1080	1.11 (0.97-1.26)	0.1240	1.00 (0.87-1.15)	0.9854
Cumulative risperidone use (days)						
nonusers	896	3056	1		1	
0 < period ≤ 90	396	1078	1.26 (1.09-1.44)	0.0012	1.14 (0.98-1.33)	0.0927
90 < period ≤ 180	207	511	1.39 (1.16-1.66)	0.0003	1.26 (1.03-1.53)	0.0220
180 < period ≤ 1000	733	2028	1.24 (1.10-1.38)	0.0002	1.12 (0.99-1.26)	0.0845
1000 < period	1179	3560	1.13 (1.03-1.25)	0.0148	1.10 (0.99-1.23)	0.0756

OR: odds ratio; C I: confidence interval; AOR: adjusted odds ratio; SGA: second generation antipsychotic.

[a]Adjusted for diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

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Other information		
Funding	22	CMFHR 10537; Source of funding: Chi-Mei Medical Center. The role of the funder: Three of the authors work in Chi-Mei Medical Center.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019868.R3
Article Type:	Research
Date Submitted by the Author:	23-Feb-2018
Complete List of Authors:	Wang, Hsien-Yi ; Chi Mei Medical Center, Nephrology; Chia-Nan University of Pharmacy and Science Huang, Charles Lung-Cheng ; Chi Mei Medical Center, Psychiatry Feng, I Jung ; Chi Mei Medical Center, Chi Mei Hospital, Department of Medical Research Tsuang, Hui-Chun; Chang Jung Christian University, Center of General Education
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	second-generation antipsychotics, chronic kidney disease, schizophrenia

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

Running title: Antipsychotics and kidney disease

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Key words: second-generation antipsychotics; chronic kidney disease; schizophrenia

ABSTRACT

Objectives: The study aims to compare the risk of chronic renal diseases (CKD between schizophrenic patients 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 hospitalized for psychiatric disorders between 2000 and 2013 (n = 267807). 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 hospitalization or three outpatient visits. The diagnosis of CKD follows the criteria of 'Kidney Disease: Improving Global Outcomes (KDIGO)' in Taiwan. CKD is defined as kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, or glomerular filtration rate (GFR) <60 mL/min/1.73 m2, for 3 months or more.

Results: We found that the risks for CKD for those who used second generation antipsychotics longer cumulatively were higher than those who did not use second generation antipsychotics. Using nonusers, patients didn't have any second generation antipsychotics records, as reference group, the risks for CKD comparing those using second generation antipsychotics for 90 to 180 days with nonusers and those using second generation antipsychotics 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 second-generation antipsychotics and risk of CKD.

Article summary:

Strengths:

(1) We tracked subjects for period longer than 1000 days after the initial schizophrenia diagnosis day.

(2) This is the first study investing the relationship between antipsychotics and risk of CKD in inpatients with schizophrenia.

Limitations:

(1) The measurement of exposure, use of antipsychotic drugs, can only be estimated by the existing dataset we used.

(2) Using existing dataset without personal identification, we cannot investigate all risk factors in the study.

Bullet points: The risk of CKD of inpatients of schizophrenia deserves furthers investigation. Besides, the study of risk of CKD for schizophrenic patients might need longer tracking duration.

1. 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 2 or 3 times as high as that in the general population[3-5]. Cardiovascular diseases have an increased prevalence among patients with schizophrenia[6]. Metabolic syndrome (MetS), 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 schizophrenia patients[8-9]. Furthermore, patients with schizophrenia are liable to develop diabetes mellitus (DM)[1, 10] and chronic kidney diseases (CKD)[11].

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

More recent studies confirmed the above finding regarding to the concern of using second-generation antipsychotic 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 increased risk of pneumonia. A nationwide German/Austrian Diabetes Survey, which recruiting 60,162 teenagers with type 1 diabetes, demonstrated that subjects treated with second-generation antipsychotics, risperidone in particular, showed higher BMI[19]. A national study[20] conducted in the US compared 107,551 youths using second-generation antipsychotics with 1,221,434 youths not using second-generation antipsychotics. The risk for incident diabetes mellitus was increased in youths taking second-generation antipsychotics. The risk was higher among those using ziprasidone and aripiprazole. However, the risk for incident type 2 diabetes mellitus was not associated with newer second-generation antipsychotics, 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 and second generation antipsychotics, people who use only second generation antipsychotics with those who used only first generation

drugs in our study.

2. Methods

2.1. Study subjects

Taiwan started a single-payer National Health Insurance program on March 1, 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 hospitalized for psychiatric disorders between 2000 and 2013 (n = 267807). 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 = 13644). 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.

2.2. Case and control definition

In this study we conducted a nested case-control study derived from the cohort. Patients with CKD (ICD-9 code 582, 583, 585, 586, 588) requiring hospitalization or three outpatient visits were selected as cases (n = 3411). The date of first hospitalization 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 (KDIGO)' in Taiwan. CKD is defined as kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, for 3 months or more. For each case, 3 matched control subjects were randomly selected from the same schizophrenia patients who have not been diagnosed with CKD before 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. Patients diagnosed with CKD before the schizophrenia diagnosis date were excluded.

2.3. Measurement of exposure

The data of antipsychotic drug use was derived from the prescription files. The duration of treatment was calculated using the dispensed number of units and the dosing regimen for each patient. Second-generation antipsychotic drugs used in our study included clozapine, olanzapine, quetiapine, zotepine, risperidone, amisulpride, ziprasidone, aripiprazole, and paliperidone. First-generation antipsychotic 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 second-generation antipsychotic drug and the risk of CKD, all first-generation antipsychotic drugs were grouped together in the data analysis. The follow up period is from the schizophrenia diagnosis date to the index date.

2.4. Covariates

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

2.5. 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 diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity, were entered into adjusted model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value .05 was considered significant.

2.6 Patient and public involvement

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

3. Results

A total of 3411 patients with CKD and 10233 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 Table1.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 (Table2). 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 (Table2). Patients used both FGA and SGA have significant greater risk than patients used FGA only (p=0.0009) (Table2).

With the adjustment of comorbidity factors, the analysis results showed that greater risks of CKD for patients who received SGA than patients didn't 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 to reference group (adjusted OR[95%CI]=1.42[1.06-1.91], 1.30 [1.13-1.51]) (Table3). Patients used olanzapine, quetiapine, zotepine or risperidone all displayed greater odds of developing CKD than reference group. Patients with quetiapine exposure have statistically significant higher risk than the reference group.

4. Discussion

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

Also using the dataset of Taiwan National Health Insurance, Tzeng et al.[11] found that neither first nor second generation antipsychotics increased the risk of CKD. However, the study design of Tzeng et al. and ours varied a lot. Firstly, we focused on in patients while Tzeng et al. recruited patients with a first-time diagnosis of schizophrenia. Secondly, subjects of Tzeng et al. were tracked for 3 years or the end of 2010 from the initial diagnosis date until 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 of second-generation antipsychotics in the early 1990s was

initially shown better quality of life, lower rate of relapse, and better tolerability than first-generation antipsychotics for patients of schizophrenia[13-14, 24] but has been criticized 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 current used of clozapine, one kind of second-generation antipsychotics, was associated with a dose-dependent increase in the risk of pneumonia for inpatients with schizophrenia. In addition, other kinds of second-generation antipsychotics, including quetiapine, olanzapine, zotepine, and risperidone, were associated with increased risk of pneumonia while no clear dose-dependent relationship was found. They suggested that patients with schizophrenia who used these antipsychotics to be monitored for pneumonia. Our study further suggests that inpatients with schizophrenia being monitored for CKD since we found that the risks for CKD for those who used second generation antipsychotics longer cumulatively were higher than those who did not use second generation antipsychotics. Similar to the findings of kuo et al., we did not see dose-dependent relationship second generation antipsychotics and risk of CKD.

The increasing prevalence of end-stage renal disease (ESRD) has been a global challenge. In the US, chronic renal diseases are the nation's ninth leading cause of death[24]. In Taiwan, chronic renal diseases have been the eighth leading cause of death since 1997, and was still the tenth 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 second generation antipsychotics longer have higher risks for CKD than those who did not use second generation antipsychotics 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 take. Second, we can not include variables not captured in claim database, such as patients' lifestyle and family history. However, the current study suggests a hypothesis regarding the relationship between using second-generation antipsychotics and risk of CKD which warrants further study.

Declaration of interest

All authors declare that they have no conflicts of interest.

Contributors

Hui-Chun Tsuang and Hsien-Yi Wang initiated the study. Hui-Chun Tsuang, Hsien-Yi Wang and Charles Lung-Cheng Huang designed the study. I Jung Feng

analyzed the data. Hui-Chun Tsuang wrote the manuscript and Hsien-Yi Wang, Charles Lung-Cheng Huang and I Jung Feng approved the final manuscript.

Acknowledgements

The authors thank the Bureau of National Health Insurance and National Health Institutes for making available the databases for this study.

DATA SHARING STTEMENT

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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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)
Hyperlipidemia***	502 (14.7)	433 (4.2)
Hypercholesterolemia***	111 (3.3)	90 (0.9)
Hypertriglyceridemia***	86 (2.5)	62 (0.6)
Hypertension***	1232 (36.1)	1147 (11.2)
Obesity***	49 (1.4)	37 (0.4)

SD: standard deviation.

*** < 0.0001

Table 2 Comparison of crude and adjusted odds ratio 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[a] (95% CI)	p-value
no FGA, no SGA	3	17	0.76 (0.22-2.59)	0.6570	0.53 (0.13-2.21)	0.3857
FGA alone	300	1278	1		1	-
SGA alone	26	102	1.10 (0.70-1.72)	0.6920	1.06 (0.65-1.74)	0.8068
Combination	3082	8827	1.50 (1.32-1.71)	<.0001	1.28 (1.11-1.47)	.0009

OR: odds ratio; C I: confidence interval; AOR: adjusted odds ratio; FGA: first generation antipsychotic; SGA: second generation antipsychotic.

[a]Adjusted for diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity.

Table 3 Overall cumulative period of using second generation antipsychotics

Period of SGA use	CKD cases (n = 3411)	Controls (n = 10,233)	OR (95% CI)	p-value	AOR[a] (95% CI)	p-value
Cumulative SGA use						
nonusers	303	1304	1		1	
0 < period ≤ 90	177	552	1.38 (1.12-1.71)	0.0026	1.20 (0.95-1.51)	0.1247
90 < period ≤ 180	92	241	1.65 (1.26-2.16)	0.0003	1.42 (1.06-1.91)	0.0208
180 < period ≤ 1000	409	1271	1.39 (1.17-1.64)	0.0001	1.19 (0.99-1.43)	0.0654
1000 > period	2430	6865	1.53 (1.34-1.75)	<.0001	1.30 (1.13-1.51)	0.0004
Cumulative clozapine use (days)						
nonusers	2318	7215	1		1	
0 < period ≤ 90	183	351	1.63 (1.35-1.96)	<.0001	1.48 (1.20-1.81)	0.0002
90 < period ≤ 180	49	140	1.09 (0.79-1.52)	0.6057	0.91 (0.63-1.32)	0.6281
180 < period ≤ 1000	178	549	1.01 (0.85-1.20)	0.9091	0.94 (0.77-1.14)	0.5099
1000 > period	683	1978	1.08 (0.98-1.19)	0.1456	1.14 (1.02-1.27)	0.0181
Cumulative olanzapine use (days)						
nonusers	2046	6465	1		1	
0 < period ≤ 90	396	1018	1.23 (1.09-1.40)	0.0012	1.18 (1.02-1.35)	0.0225
90 < period ≤ 180	156	344	1.44 (1.18-1.75)	0.0003	1.37 (1.11-1.70)	0.0039
180 < period ≤ 1000	401	1038	1.22 (1.08-1.39)	0.0017	1.15 (1.00-1.32)	0.0561
1000 > period	412	1368	0.95 (0.85-1.08)	0.4401	1.05 (0.92-1.19)	0.4954

Period of SGA use	CKD cases (n = 3411)	Controls (n = 10,233)	OR (95% CI)	p-value	AOR[a] (95% CI)	p-value
Cumulative quetiapine use (days)						
nonusers	1669	6198	1		1	
0 < period ≤ 90	399	967	1.54 (1.35-1.75)	<.0001	1.36 (1.19-1.57)	<.0001
90 < period ≤ 180	147	356	1.54 (1.26-1.88)	<.0001	1.27 (1.02-1.58)	0.0358
180 < period ≤ 1000	534	1180	1.69 (1.50-1.89)	<.0001	1.48 (1.30-1.68)	<.0001
1000 > period	662	1532	1.61 (1.45-1.79)	<.0001	1.44 (1.28-1.62)	<.0001
Cumulative zotepine use (days)						
nonusers	2292	7375	1		1	
0 < period ≤ 90	319	743	1.38 (1.20-1.59)	<.0001	1.26 (1.08-1.47)	0.0038
90 < period ≤ 180	120	265	1.46 (1.17-1.82)	0.0008	1.27 (0.99-1.63)	0.0592
180 < period ≤ 1000	310	770	1.30 (1.13-1.49)	0.0003	1.16 (1.00-1.36)	0.0572
1000 > period	370	1080	1.11 (0.97-1.26)	0.1240	1.00 (0.87-1.15)	0.9854
Cumulative risperidone use (days)						
nonusers	896	3056	1		1	
0 < period ≤ 90	396	1078	1.26 (1.09-1.44)	0.0012	1.14 (0.98-1.33)	0.0927
90 < period ≤ 180	207	511	1.39 (1.16-1.66)	0.0003	1.26 (1.03-1.53)	0.0220
180 < period ≤ 1000	733	2028	1.24 (1.10-1.38)	0.0002	1.12 (0.99-1.26)	0.0845
1000 < period	1179	3560	1.13 (1.03-1.25)	0.0148	1.10 (0.99-1.23)	0.0756

OR: odds ratio; C I: confidence interval; AOR: adjusted odds ratio; SGA: second generation antipsychotic.

[a]Adjusted for diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

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Funding	22	CMFHR 10537; Source of funding: Chi-Mei Medical Center. The role of the funder: Three of the authors work in Chi-Mei Medical Center.