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Long-Term Use of Selective Serotonin Reuptake Inhibitors and Risk of Glaucoma in Depression Patients

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Abstract: This study investigated whether the long-term use of selective serotonin reuptake inhibitors (SSRIs) influences the risk of primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) in the Chinese ethnic population in Taiwan.

The authors retrieved the data under analysis from the National Health Insurance Research Database in Taiwan and identified 26,186 newly diagnosed depression patients without preexisting glaucoma. The study cohort included 13,093 patients with over 1 year of SSRI use, and a comparison cohort of 13,093 patients who had never used SSRIs. The main outcome was a diagnosis of POAG or PACG during follow-up. The authors used univariable and multivariable Cox proportional hazards regression models to assess the effects of SSRIs on the risk of POAG and PACG.

The cumulative incidences of POAG and PACG between the SSRI and comparison cohorts exhibited nonsignificant differences (log-rank test $P = .52$ for POAG, $P = .32$ for PACG). The overall incidence of POAG in the SSRI cohort was nonsignificantly higher than that in the comparison cohort (1.51 versus 1.39 per 1000 person-years), with an adjusted hazard ratio of 1.07 (95% confidence interval = 0.82–1.40). The overall incidence of PACG in the SSRI cohort was nonsignificantly lower than that in the comparison cohort (0.95 versus 1.11 per 1000 person-years), with an adjusted hazard ratio of 0.85 (95% confidence interval = 0.62–1.18).

The long-term use of SSRIs does not influence the risk of POAG or PACG in depression patients.

(*Medicine* 94(45):e2041)

Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID2000 = Longitudinal Health Insurance Database 2000, PACG = primary angle closure glaucoma, POAG = primary open angle glaucoma, SSRIs = selective serotonin reuptake inhibitors.

INTRODUCTION

Depression is a highly prevalent mood disorder that can lead to serious disabilities and functional impairment.[1,2] One study indicated that from 1997 to 2005, the prevalence of antidepressant usage among elderly people increased substantially in Taiwan.[3] Currently, available selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed type of medication for depression patients.[4] Short-term SSRI exposure induces acute angle-closure glaucoma (AACG),[4,5] which is a potentially blinding ocular emergency, and is relatively common in Asians, especially those of Chinese ethnicity.[6–8] We recently reported that patients with short-term SSRI use are at a 5.8-folds increased risk of AACG.[9] It, however, remains unclear whether long-term SSRI use influences intraocular pressure (IOP) or increases the risk of glaucoma.[4,10] Glaucoma comprises a set of ocular disorders that lead to optic nerve damage that is often associated with increased IOP.[11] It is also the leading cause of irreversible blindness worldwide.[12] Primary glaucoma can be divided into 2 major types, primary open-angle glaucoma (POAG), and primary angle-closure glaucoma (PACG), which are the 2 most common types in the Chinese ethnic population of Taiwan.[6,7,13] Furthermore, previous studies have reported a strong association between glaucoma and depression.[14–16] Therefore, to evaluate whether long-term SSRI use influences the risk of POAG and POAG in patients diagnosed with depression, we conducted this study by using a population-based dataset from the National Health Insurance (NHI) program of Taiwan. According to a review of relevant literature, this study is the first to address this crucial problem by using a large claims database.

METHOD

Data Source

The data for analysis in this retrospective cohort study were retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000), an electronic claims database of the NHI program. The NHI program, which started on March 1, 1995, provides comprehensive medical coverage for people residing in Taiwan.[17] The LHID2000 was established by the National Health Research Institutes and contains all the original claims data of 1000,000 patients (approximately 5% of the Taiwan population), who were randomly sampled from the

Editor: Turkcu Fatih.
Received: July 8, 2015; revised: August 17, 2015; accepted: September 7, 2015.
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Final approval of manuscript: all authors.
This study is supported in part by the Research Center of Excellence for Clinical Trials, Ministry of Health and Welfare, Taiwan (MOHW104-TDU-B-212–113002); China Medical University (CMU) Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092); NRPB Stroke Clinical Trial Consortium (MOST 103–2325-B-039 -006); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002041

2000 Registry of Beneficiaries of the National Health Insurance Research Database. The diagnostic codes in the LHID2000 are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was exempted from informed consent by the Institutional Review Board of China Medical University (CMU-REC-101–012).

Sample Selection

This study included patients aged >20 years who were diagnosed with depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), had complete information regarding age and sex, and had no history of glaucoma (ICD-9-CM code 365) from 2000 to 2010. The depression patients were divided into 2 cohorts on the basis of their SSRI use: the SSRI cohort included patients who had undergone SSRIs therapy for at least 1 year (365 days), whereas the comparison cohort included patients who had not received SSRI therapy. The index date for the SSRI cohort as well as the comparison cohort was day 365. Patients in the SSRI and comparison cohorts were selected through 1:1 matching based on a propensity score.[18] The propensity score was calculated using logistic regression to estimate the probability of treatment assignment on the basis of baseline variables, namely the year of SSRI treatment, age, sex, the comorbidities of diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (ICD-9-CM codes 410–414), anxiety (ICD-9-CM code 300.00), and non-SSRI medication for treating depression. The C-statistic of the logistic regression model was 0.53.

Outcome Measurement

The main outcome was a diagnosis of POAG (ICD-9-CM code 365.1) or PACG (ICD-9-CM code 365.2) during follow-up. All patients were followed from the index date until a new diagnosis of POAG or PACG, censorship because of death, withdrawal from the insurance system, loss to follow-up, or the end of follow-up on December 31, 2011.

Statistical Analysis

The distributions of demographic variables, namely age, sex, non-SSRI use, and comorbidities, were compared between the 2 cohorts. The baseline characteristics of the SSRI cohort and comparison cohort were compared using standardized mean differences, calculated as the difference in the mean or proportion of a variable divided by a pooled estimate of the standard deviation of the variable. A value of the standardized mean differences equal to 0.1 or less indicates a negligible difference in the mean between the 2 cohorts. The cumulative incidence of POAG and PACG between the SSRI and comparison cohorts was assessed using the Kaplan–Meier method and the differences between the curves were evaluated by conducting a log-rank test. The incidence density rates of POAG and PACG were calculated according to age, sex, non-SSRI antidepressant use, and comorbidity. Univariable and multivariable Cox proportional hazards regression models were used to assess the effects of SSRIs on the risk of POAG and PACG. In addition, hazard ratios and 95% confidence intervals (CIs) were estimated in the Cox models. In the multivariable Cox model, only diabetes mellitus and hyperlipidemia were found to be significant. Further data analysis was performed to determine the interaction effect between SSRIs, diabetes mellitus, and hyperlipidemia. SAS version 9.4 for Windows (SAS Institute, Cary, NC) was used to conduct all statistical analyses, and all statistical testing was performed at a 2-tailed significance level of 0.05.

RESULTS

Eligible study patients comprised 13,093 patients who had used SSRIs for more than 1 year, and 13,093 patients who had never undergone SSRI therapy, matched according to the propensity score (Table 1). The mean ages in the SSRI cohort and the comparison cohort were 49.3 years (SD = 16.2) and 49.4 years (SD = 16.5), respectively. Certain patients in the SSRI cohort did not have a medicinal history for non-SSRI

TABLE 1. Demographic Characteristics of Study Subjects Among Medicine in the Propensity Score Matched Sample

	Selective Serotonin Reuptake Inhibitors				
	No (n = 13,093)		Yes (n = 13,093)		Standardized Differences
	n	%	n	%	
Age, mean (SD)[†]	49.4	16.5	49.3	16.2	0.007
Stratify Age					
20–49	4163	31.8	4206	32.1	0.007
50–64	6354	48.5	6279	48.0	0.011
65+	2576	19.7	2608	19.9	0.006
Sex					
Women	8470	64.7	8513	65.0	0.007
Men	4623	35.3	4580	35.0	0.007
Nonselective Serotonin Reuptake Inhibitors					
Never use	5702	43.6	6062	46.3	0.06
Ever use	7391	56.5	7031	53.7	0.06
Comorbidity					
Diabetes mellitus	1290	9.85	1298	9.91	0.002
Hypertension	4726	36.1	4705	35.9	0.003
Hyperlipidemia	3501	26.7	3494	26.7	0.001
Coronary artery disease	3050	23.3	2966	22.7	0.015
Anxiety	4670	35.7	4852	37.1	0.029

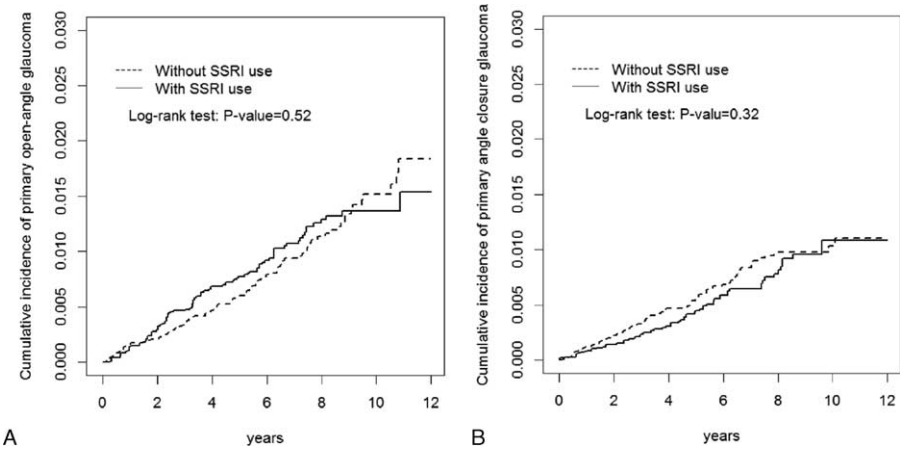

FIGURE 1. Cumulative incidence of primary open-angle glaucoma and primary angle-closure glaucoma in a comparison between the selective serotonin reuptake inhibitor and comparison cohorts.

antidepressant use (53.7%), diabetes mellitus (9.91%), hypertension (35.9%), hyperlipidemia (26.7%), coronary artery disease (22.7%), and anxiety (37.1%). The Kaplan–Meier graph in Figure 1A-B illustrates that the cumulative incidence of POAG and PACG between the SSRI cohort and the comparison cohort exhibited nonsignificant differences (log-rank test $P = 0.52$ in Figure 1A, and log-rank test $P = 0.32$ in Figure 1B).

During the mean follow-up periods of 5.55 years (SD = 2.97) and 5.71 years (SD = 3.11) for the SSRI cohort and the comparison cohort, respectively, the overall POAG incidence was nonsignificantly higher in the SSRI cohort than in the comparison cohort (1.51 versus 1.39, respectively, per 1000 person-years), with an adjusted hazard ratio (aHR) of 1.07 (95% CI = 0.82–1.40; Table 2). In both cohorts, the POAG incidence increased with the presence of comorbidity. The relative risk of POAG between the SSRI and comparison cohorts, however, was higher among patients without comorbidity (aHR = 1.76, 95% CI = 1.03–3.02).

The overall incidence of PACG in the SSRI cohort was nonsignificantly lower than that in the comparison cohort (0.95 versus 1.11, respectively, per 1000 person-years), with an aHR of 0.85 (95% CI = 0.62–1.18). Furthermore, the risk of PACG in the SSRI cohort varied nonsignificantly relative to that in the comparison group for age subdivisions.

Table 3 lists the joint effects of SSRI use and comorbidity on the risk of POAG or PACG. Compared with patients with SSRI use and nondiabetes mellitus, patients who used an SSRI and had diabetes mellitus were 3.16-folds more likely to develop POAG (95% CI = 2.05–4.87), followed by patients without SSRI use and with diabetes mellitus (aHR = 1.87, 95% CI = 1.11–3.16). Compared with patients without SSRI use and hyperlipidemia, those without SSRI use but with hyperlipidemia were 2.66-folds more likely to develop POAG (95% CI = 1.79–3.97), followed by patients who used an SSRI and had hyperlipidemia (aHR = 1.85, 95% CI = 1.20–2.86). We observed a significantly higher risk of PACG in patients without SSRI use and with hyperlipidemia (aHR = 2.43, 95% CI = 1.55–3.80) and in patients who used SSRIs and had hyperlipidemia (aHR = 1.80, 95% CI = 1.11–2.90) compared with patients without SSRI use and hyperlipidemia.

DISCUSSION

A literature review revealed a relatively high prevalence of anxiety and depression among glaucoma patients.[19] The level of depression was found to be significantly higher in PACG patients than in POAG patients and controls.[14] Depression is more common in patients with increasing glaucoma severity.[20] Currently, available SSRIs are the most widely used medications for treating depression patients.[4,5] Acute angle-closure glaucoma is the most severe SSRI-related ocular complication.[4,5] Several instances of AACG associated with the use of SSRIs, such as paroxetine,[21–25] fluvoxamine,[26] citalopram,[27,28] escitalopram,[29] and sertraline[30] have been reported.[5] We also recently reported that patients using SSRIs immediately are at a 5.8-folds increased risk of AACG.[9] Acute angle-closure glaucoma is a subtype of PACG, which is an ocular emergency characterized by a sudden spike in IOP. By contrast, chronic angle-closure glaucoma consists of slow and progressive angle closure with an elevated IOP,[6,7,9,13] and is a more common occurrence than AACG in PACG. By comparison, POAG is painless, tends to advance slowly over time, and often exhibits no symptoms until the disease has progressed substantially. Pupil dilatation mediated by 5-hydroxytryptamine, serotonin receptors and noradrenaline receptors has been proposed as the mechanism underlying SSRI-induced AACG.[10,30] The presence of serotonin and its metabolites in the aqueous humor, in addition to its availability on 5-hydroxytryptamine receptors in the iris–ciliary body complex, are involved in regulating aqueous humor dynamics.[4] Although SSRIs might influence IOP in humans,[31] the literature presents conflicting data on whether the activation of serotonin receptors induces changes in IOP. One study group expressed the concern that long-term SSRI use might raise the risk of POAG.[31] In the premarketing and subsequent clinical trials for fluoxetine, 585 adult patients were assessed by an ophthalmologist.[31] In these trials, 63 cases of glaucoma were reported as a suspected adverse effect of fluoxetine from an estimated patient population of 21 million (Dista Products Limited, personal communication).[31] The manufacturers of paroxetine are aware of 4 cases of AACG, 6 cases of glaucoma (unspecified), and a single case of increased IOP in a UK patient population of more than one million people (SmithKline Beecham Pharmaceuticals, personal communication).[31] Moreover, no long-term study regarding the influence of SSRIs on IOP has been reported. All of these data indicate that the understanding of long-term SSRI effects on IOP remains relatively limited, although the manufacturers' own data suggest that less than 1% of patients exhibited any IOP changes after SSRI treatment.

TABLE 2. Comparison of Incidence and Hazard Ratio of Primary Open-Angle Glaucoma and Primary Angle-Closure Glaucoma Stratified by Sex, Age, and Comorbidity According to Medication Status

	SSRIs							
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]	Crude HR[&] (95 % CI)	Adjusted HR[†] (95% CI)
POAG								
All	104	74,775	1.39	110	72,662	1.51	1.09 (0.84.1.43)	1.07 (0.82, 1.40)
Age								
20–49	13	26,056	0.50	24	25,280	0.95	1.96 (0.99, 3.85)	1.95 (0.98, 3.87)
50–64	58	36,134	1.60	66	34,645	1.91	1.20 (0.84, 1.71)	1.17 (0.82, 1.66)
65 +	33	12,406	2.66	20	12,738	1.57	0.59 (0.34, 1.03)	0.60 (0.34, 1.04)
Sex								
Female	68	49,294	1.38	53	47,061	1.13	0.83 (0.58, 1.18)	0.83 (0.58, 1.19)
Male	36	25,481	1.41	57	25,601	2.23	1.57 (1.04, 2.39)*	1.52 (1.00, 2.31)
Non-SSRIs								
No	46	38,962	1.18	52	37,228	1.40	1.20 (0.81, 1.79)	1.19 (0.80, 1.78)
Yes	58	35,814	1.62	58	35,433	1.64	1.01 (0.70, 1.45)	1.01 (0.70, 1.46)
Comorbidity								
No	22	32,905	0.67	34	28,972	1.17	1.78 (1.04, 3.05)*	1.76 (1.03, 3.02)*
Yes	82	41,870	1.96	76	43,690	1.74	0.89 (0.65, 1.22)	0.90 (0.66, 1.23)
PACG								
All	83	74,811	1.11	69	72,807	0.95	0.85 (0.62, 1.17)	0.85 (0.62, 1.18)
Age								
20–49	4	26,091	0.15	10	25,334	0.39	2.52 (0.79, 8.04)	2.44 (0.76, 7.84)
50–64	47	36,354	1.29	31	34,784	0.89	0.69 (0.44, 1.08)	0.71 (0.45, 1.11)
65 +	32	12,366	2.59	28	12,689	2.21	0.85 (0.51, 1.42)	0.83 (0.50, 1.38)
Sex								
Female	65	49,251	1.32	46	47,105	0.98	0.73 (0.50, 1.07)	0.74 (0.50, 1.07)
Male	18	25,561	0.70	23	25,701	0.89	1.27 (0.69, 2.35)	1.26 (0.68, 2.34)
Non-SSRIs								
No	31	39,018	0.79	33	37,301	0.88	1.10 (0.68, 1.80)	1.05 (0.64, 1.71)
Yes	52	35,794	1.45	36	35,505	1.01	0.70 (0.45, 1.06)	0.73 (0.48, 1.12)
Comorbidity								
No	8	32,934	0.24	7	29,056	0.24	0.96 (0.35, 2.65)	0.96 (0.35, 2.66)
Yes	75	41,878	1.79	62	43,750	1.42	0.79 (0.57, 1.11)	0.83 (0.59, 1.16)

HR = hazard ratio, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, PY = person-years, SSRI = serotonin reuptake inhibitors, HR = hazard ratio.

*$P < 0.05$

Rate[†], incidence rate, per 1000 person-years.

Adjusted HR[†]: multivariable analysis including age, sex, non-SSRIs, and comorbidity of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, and anxiety.

Crude HR[&], relative hazard ratio.

In the current study, the cumulative incidence of POAG and PACG exhibited nonsignificant differences between the SSRI and comparison cohorts. Furthermore, the overall incidences of POAG and PACG in the SSRI cohort were found to be nonsignificantly higher than those in the comparison cohort after using a nationally representative dataset. This result offers new insight supporting the belief that long-term SSRI use does not influence the risk of POAG and PACG in the Taiwan population. Although we cannot understand the real effect of SSRIs on IOP on the basis of the claims database, we believe that this result provides indirect support to the notion that depression patients who use SSRIs are not at a risk of glaucoma.

According to recent epidemiologic studies conducted in Taiwan, patients with open-angle glaucoma are significantly more likely to have comorbidities.[16,32] Therefore, we considered the interaction effect of comorbidities and SSRI usage on the risk of glaucoma. The results revealed that diabetes mellitus and hyperlipidemia are 2 strong risk factors for POAG in patients with SSRI use as well as in those without. This finding confirms the previously held notion that POAG patients are significantly more likely to have comorbidities.[16] Another observation was that hyperlipidemia raised the risk of PACG in patients without SSRI use (aHR = 2.43, 95% CI = 1.55–3.80) as well as in patients with SSRI use (aHR = 1.80, 95% CI = 1.11–2.90) compared with patients without SSRI use and without hyperlipidemia. In the literature, few studies have evaluated the medical comorbid condition in PACG patients. This study is the first to report that hyperlipidemia is a critical risk factor for PACG in patients with depression. Plausible reasons for this finding remain unclear, and further observation is warranted to address this finding.

TABLE 3. Cox Proportional Hazard Regression Analysis for the Risk of Primary Open-Angle Glaucoma and Primary Angle-Closure Glaucoma—Interaction Effect of Selective Serotonin Reuptake Inhibitors Usage and Diabetes Mellitus and Hyperlipidemia

Variables		N	n	PY	Rate†	Adjusted HR† (95% CI)	*P* Value§
POAG							
SSRIs	Diabetes Mellitus						0.07
−	−	11,803	86	68,557	1.25	1.06 (0.78, 1.43)	
−	+	1290	18	6218	2.89	1.87 (1.11, 3.16)*	
+	−	11,795	79	66,447	1.19	1 (Reference)	
+	+	1298	31	6215	4.99	3.16 (2.05, 4.87)***	
SSRIs	Hyperlipidemia						0.01
−	−	9592	50	56,694	0.88	1 (reference)	
−	+	3501	54	18,081	2.99	2.66 (1.79, 3.97)***	
+	−	9599	72	54,444	1.32	1.50 (1.05, 2.15)*	
+	+	3494	38	18,217	2.09	1.85 (1.20, 2.86)**	
PACG							
SSRIs	Diabetes Mellitus						0.98
−	−	11,803	69	68,564	1.01	1.17 (0.82, 1.66)	
−	+	1290	14	6247	2.24	1.44 (0.79, 2.60)	
+	−	11,795	57	66,522	0.86	1 (reference)	
+	+	1298	12	6284	1.91	1.18 (0.63, 2.22)	
SSRIs	Hyperlipidemia						0.30
−	−	9592	36	56,684	0.64	1 (reference)	
−	+	3501	47	18,128	2.59	2.43 (1.55, 3.80)***	
+	−	9599	35	54,593	0.64	1.00 (0.63, 1.60)	
+	+	3494	34	18,213	1.87	1.80 (1.11, 2.90)*	

HR = hazard ratio, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, PY = person-years, SSRI = serotonin reuptake inhibitors, N = sample size; n = events of POAG and PACG.

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$.

† Rate, incidence rate, per 1000 person-years.

§ *P*-value for interaction. Adjusted HR†: multivariable analysis including age, sex, non-SSRIs, and comorbidity of hypertension, coronary artery disease, and anxiety.

Despite obtaining promising results, our study had the following limitations. First, we defined glaucoma by relying entirely on claims data (ICD-9-CM coding from clinicians), an approach that may be less accurate than determining diagnoses individually through a standardized procedure. In this type of claims database study, clinical information, such as that on IOP, central corneal thickness, visual field findings, and optic nerve evaluations is unavailable. Second, this study had a selection bias. Because the NHI database is composed only of data from patients who underwent treatment, patients who had not received treatment for depression might have been recruited in the comparison cohort. Third, because of the lack of laboratory and imaging data in individual chart records, the National Health Insurance Research Database is used primarily for insurance purposes and has not been validated entirely for research; thus, uncontrolled confounding factors, such as visual field severity, IOP reading, and potential biases may have affected our retrospective case-control study. Fourth, despite the large sample, the study cohort consisted of Taiwanese patients, and thus these findings are not easily generalizable to other population groups. Finally, the SSRI use reported in the LHID2000 does not necessarily correspond to actual SSRI use. This is because of the possibility of poor medication compliance and the ease with which such medication use can be initiated and ceased.[33]

Our study had the following strengths. First, the strength of the database is excellent because of the large sample randomization, and we could follow patient cases over time to assess the relationship between SSRI exposure and the subsequent onset of POAG or PACG. Second, the database includes data on a broad range of people with different sociodemographic profiles, unlike those used in smaller studies, in which patients are recruited from specific regions that might not be representative of the entire population. Third, our study is the first to evaluate the relationship between long-term SSRI use and glaucoma risk in a purely Asian depression population by using a large claims database. Our findings can provide a strong foundation for further longitudinal research.

In conclusion, long-term SSRI use does not influence the risk of POAG or PACG in depression patients. Clinicians, however, should still consider the potential risk of glaucoma in certain high-risk groups.

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