Association of Selective Serotonin Reuptake Inhibitor Use and Acute Angle–Closure Glaucoma

Hsin-Yi Chen, MD[a,c]; Cheng-Li Lin, MSc[a,d]; Shih-Wei Lai, MD[a,e]; and Chia-Hung Kao, MD[f,b,*]

ABSTRACT

Objective: Selective serotonin reuptake inhibitors (SSRIs) are the most widely used antidepressant medications for treating patients with depression; however, ocular complication has been noted occasionally. This study investigated the relationship between recent SSRI use and the risk of acute angle–closure glaucoma (AACG) in the ethnic Chinese population in Taiwan.

Methods: In this case-control study that involved using data from the Taiwan National Health Insurance database for the period 2000–2011, we recruited 1,465 patients with newly diagnosed AACG as case participants and 5,712 persons without glaucoma who were matched according to sex, age, and index year as controls. *Immediate SSRI users* were defined as patients who received at least 1 prescription for SSRIs within 7 days before the date of AACG diagnosis. Patients who received no SSRI prescriptions were defined as *nonusers*. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the risk of AACG associated with SSRI use.

Results: After adjustment for confounding factors including non-SSRI antidepressant use and all comorbidities, the multivariable logistic regression model revealed that the adjusted OR of AACG was 5.80 for immediate SSRI users (95% CI, 1.89–17.9) when compared with nonusers. Further analysis, with nonusers as reference, resulted in an adjusted OR of 8.53 (95% CI, 1.65–44.0) for participants with a mean daily SSRI dose exceeding 20 mg.

Conclusions: Patients immediately using SSRIs have a 5.80-fold increased risk of AACG. Before prescribing SSRIs, clinicians should be aware of the potential AACG risks among elderly patients with depression.

J Clin Psychiatry 2016;77(6):e692–e696
dx.doi.org/10.4088/JCP.15m10038

[a]School of Medicine and [b]Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan
[c]Department of Ophthalmology, [d]Management Office for Health Data, [e]Department of Family Medicine, and [f]Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan
**Corresponding author:* Chia-Hung Kao, MD, Graduate Institute of Clinical Medical Science, China Medical University, No. 2, Yuh-Der Rd, Taichung 404, Taiwan (d10040@mail.cmuh.org.tw).

The currently available selective serotonin reuptake inhibitors (SSRIs) are the most widely used medications for treating patients with depression.[1] Although SSRIs primarily have a favorable safety spectrum, unexpected pathological events have been noted occasionally.[1] Acute angle–closure glaucoma (AACG) is the most severe SSRI-related ocular complication.[1,2] Several instances of AACG associated with use of SSRIs such as paroxetine,[3–7] fluvoxamine,[8] citalopram,[9,10] escitalopram,[11] and sertraline[12] have been reported.[2] Acute angle–closure glaucoma is a potentially blinding ocular emergency common in Asian populations, particularly in ethnic Chinese populations.[13–16] To more comprehensively understand the association between recent SSRI use and the risk of AACG in the ethnic Chinese population in Taiwan, we conducted this study by using a population-based dataset from the Taiwan National Health Insurance (NHI) program. To the best of our knowledge, this study is one of the few that address this critical topic on the basis of a large claims database.

METHODS

Data Source

All analytic data were retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000), which is maintained and released by the Taiwan National Health Research Institute (NHRI) for research purposes. The Bureau of National Health Insurance established the NHI program on March 1, 1995, and more than 99% of the 23.74 million residents in Taiwan are enrolled in the program (http://www.nhi.gov.tw/english/index.aspx). The LHID2000 contains data for 1 million insurants randomly selected from the NHI program who represent 5% of all enrollees in Taiwan in 2000. The distribution of age and sex does not differ between the LHID2000 and the NHI beneficiaries (http://nhird.nhri.org.tw/en/Data_Subsets.html#S3). All beneficiary data are confidential and have been anonymized by the NHRI. In the LHID2000, disease identification was based on the *International Classification of Diseases*, Ninth Revision, Clinical Modification (*ICD-9-CM*) codes. The Institutional Review Board of China Medical University Hospital (CMUH104-REC2-115) approved this study.

Participant Selection

Figure 1 shows a flowchart of the study design, participant selections, and SSRI use definition. In this retrospective case-control study, the AACG case group comprised patients aged 20–84 years, newly diagnosed with AACG (*ICD-9-CM* code: 365.22) between 2000 and 2011, who were selected from the LHID2000. The date of initial AACG diagnosis was set as the index date. The non-AACG control group was randomly selected from the LHID2000; the control participants had no history of AACG and were frequency-matched with the AACG case group participants according to age (every 5-year span), sex, and the year of index date. The index date in the non-AACG control group was randomly assigned as the date of AACG diagnosis in the case group. Patients treated with SSRIs for more than 30 days before the index date and with incomplete age or sex information were excluded from the study.

Clinical Points

- Acute angle–closure glaucoma (AACG) is the most severe SSRI-related ocular complication.
- Older immediate SSRI users with depression have an increased risk of AACG.
- Clinicians should be aware of the potential risk of AACG among older patients with depression before prescribing SSRIs.

Definition of Recent Exposure to SSRIs

Patients who used SSRIs within 7 days of the index date were defined as *immediate users*. *Nonimmediate SSRI users* were defined as patients who received no prescriptions within 7 days of the index date but received at least 1 SSRI prescription 8–30 days before the index date. Patients who received no SSRI prescriptions within 1 month but received at least 1 SSRI prescription at least 1 month before the index date were excluded from the study. Patients who had never used SSRIs were defined as *nonusers*. We further analyzed the dose-response effect among immediate SSRI users. The mean daily SSRI dose was calculated as the total prescribed dose divided by the total number of days that the medication was prescribed for. We classified SSRI users into 2 subgroups according to dosage: a high-dose group (mean daily SSRI dose > 20 mg) and a low-dose group (mean daily SSRI dose ≤ 20 mg).

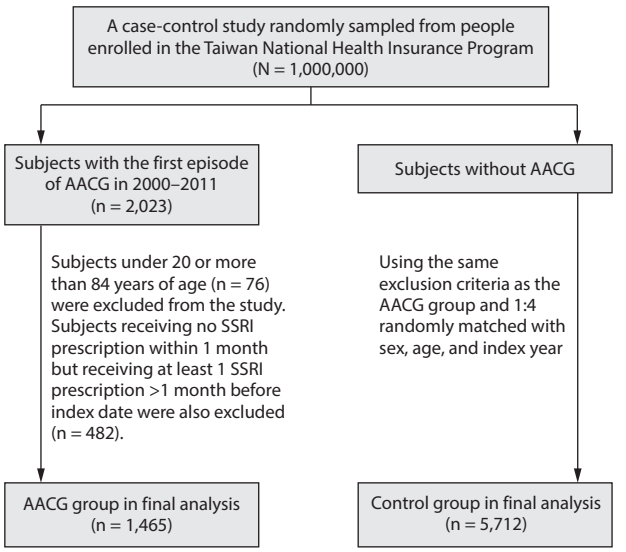
Potential Comorbidities and Medications Associated With AACG

The baseline comorbidity history for each patient was determined and included 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 depression (*ICD-9-CM* codes: 296.2, 296.3, 300.4, 311). A medication history of non-SSRI antidepressant use was also included.

Statistical Analysis

We first compared AACG cases with non-AACG controls according to the proportional distributions of sex, age, SSRI medications and non-SSRI antidepressants, and comorbidities by using the χ^2 test. A *t* test was used to assess the difference between the mean ages of the 2 groups. Univariable and multivariable unconditional logistic regression models were used to estimate the effect of SSRI use, non-SSRI antidepressant use, and comorbidities on the risk of AACG as indicated by the odds ratios (ORs) with 95% confidence intervals (CIs). The multivariable analysis was conducted to simultaneously adjust for potential confounders including non-SSRI antidepressant use, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, anxiety, and depression. All analyses were executed using SAS software Version 9.3 (SAS Institute, Inc, Cary, North Carolina), and the significance level was set at .05 for 2-tailed tests.

Figure 1. Study Flowchart



Abbreviation: AACG = acute angle–closure glaucoma.

Table 1. Characteristics of Cases With AACG and Controls in Taiwan From 2000 Through 2011

Variable	Controls (n = 5,712)	AACG Cases (n = 1,465)	*P* Value[a]
Sex, n (%)			.98
Female	3,316 (58.1)	851 (58.1)	
Male	2,396 (42.0)	614 (41.9)	
Age group, n (%)			.68
20–39 y	532 (9.31)	133 (9.08)	
40–64 y	2,380 (41.7)	595 (40.6)	
65–84 y	2,800 (49.0)	737 (50.3)	
Age, mean (SD), y[b]	61.7 (13.8)	62.4 (14.2)	.07
SSRIs (nonuser, reference), n (%)	5,684 (99.5)	1,449 (98.9)	< .001
Immediate use (0–7 d)	5 (0.09)	10 (0.68)	
Nonimmediate use (7–30 d)	23 (0.40)	6 (0.41)	
Non-SSRI antidepressants, n (%)			< .001
Never use	5,591 (97.9)	1,404 (95.8)	
Ever use	121 (2.12)	61 (4.16)	
Comorbidity, n (%)			
Diabetes mellitus	640 (11.2)	205 (14.0)	.003
Hypertension	2,470 (43.2)	752 (51.3)	< .001
Hyperlipidemia	1,385 (24.3)	402 (27.4)	.01
Coronary artery disease	1,098 (19.2)	342 (23.3)	< .001
Anxiety	293 (5.13)	110 (7.51)	< .001
Depression	100 (1.75)	39 (2.66)	.02

[a] χ^2 Test.
[b] *t* Test comparing subjects with and without AACG.
Abbreviations: AACG = acute angle–closure glaucoma, SSRI = selective serotonin reuptake inhibitor.

RESULTS

A total of 1,465 patients with AACG and 5,712 participants without AACG were included in the case and control groups, respectively. No significant differences in the sex and age distributions were observed between the 2 groups (Table 1). In the AACG group, 58.1% of the participants were women and 50.3% were aged 65–84 years. The AACG group had higher proportions of immediate SSRI users (0.68% vs 0.09%) and non-SSRI antidepressant users (4.16% vs 2.12%) than did the non-AACG group. Compared with

Table 2. Crude and Adjusted Odds Ratio and 95% Confidence Interval for AACG Associated With Antidepressant Use and Comorbidities in Taiwan From 2000 Through 2011

	Crude		Adjusted[a]	
Variable	OR	(95% CI)	OR	(95% CI)
Sex (male vs female)	1.00	(0.99–1.12)	…[b]	…[b]
Age (per 1 year)	1.00	(1.00–1.01)	…[b]	…[b]
SSRIs (nonuser, reference)				
Immediate use (0–7 d)	7.85	(2.68–23.0)***	5.80	(1.89–17.9)**
Nonimmediate use (7–30 d)	1.02	(0.42–2.52)	0.67	(0.25–1.75)
Non-SSRI antidepressants				
Never use	1	(Reference)	1	(Reference)
Ever use	2.01	(1.47–2.75)***	1.73	(1.23–2.44)**
Comorbidity (yes vs no)				
Diabetes mellitus	1.29	(1.09–1.53)**	1.15	(0.96–1.38)
Hypertension	1.38	(1.23–1.55)***	1.29	(1.13–1.47)**
Hyperlipidemia	1.18	(1.04–1.35)*	0.99	(0.86–1.14)
Coronary artery disease	1.28	(1.12–1.47)***	1.07	(0.92–1.25)
Anxiety	1.50	(1.20–1.89)***	1.30	(1.03–1.65)*
Depression	1.54	(1.06–2.23)*	0.99	(0.64–1.55)

[a]Adjusted for non-SSRI antidepressants and comorbidities of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, anxiety, and depression.
[b]Only confounding variables that were found to be significant in the univariable model were further included in the multivariable model. We did not include sex and age in the multivariable model.
*$P < .05$.
**$P < .01$.
***$P < .001$.
Abbreviations: AACG = acute angle–closure glaucoma, SSRI = selective serotonin reuptake inhibitor.

Table 3. AACG Associated With Average Daily Dose of Immediate Use of SSRI in Taiwan From 2000 Through 2011

Variable	Case No./ Control No.	Crude Odds Ratio	(95% CI)	Adjusted Odds Ratio[a]	(95% CI)
SSRI nonusers (reference)	1,449/5,684	1.00	(reference)	1.00	(reference)
Mean daily dose					
≤ 20 mg	4/3	5.23	(1.17–23.4)*	4.17	(0.89–19.5)
> 20 mg	6/2	11.8	(2.37–58.4)**	8.53	(1.65–44.0)*
P for trend		.02		.03	

[a]Adjusting for antidepressants of non-SSRIs and comorbidities of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, anxiety, and depression.
*$P < .05$.
**$P < .01$.
Abbreviations: AACG = acute angle–closure glaucoma, SSRI = selective serotonin reuptake inhibitor.

Table 4. Summary of AACG Cases With SSRI Use

SSRI Administered	Patient's Age, y	Patient's Sex	Interval From the Administration
Immediate use			
Fluoxetine	73	Male	4 days
Fluoxetine	68	Female	Same day
Fluoxetine	72	Female	2 days
Fluoxetine	67	Female	3 days
Citalopram	68	Female	1 day
Sertraline	68	Female	Same day
Sertraline	79	Male	4 days
Sertraline	61	Female	Same day
Escitalopram	67	Female	3 days
Escitalopram	61	Female	6 days
Nonimmediate use			
Fluoxetine	55	Male	14 days
Fluoxetine	71	Female	9 days
Fluoxetine	63	Male	14 days
Sertraline	52	Male	13 days
Sertraline	67	Female	26 days
Escitalopram	70	Male	12 days

Abbreviations: AACG = acute angle–closure glaucoma, SSRI = selective serotonin reuptake inhibitor.

the non-AACG group, the AACG group had a significantly higher proportion of the comorbidities of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, anxiety, and depression ($P < .05$).

Table 2 shows the crude and adjusted ORs for the model fitted to examine the association between potential factors and the risk of AACG. After adjustment for potential confounding factors, the adjusted OR of AACG was 5.80 among the immediate SSRI users (95% CI, 1.89–17.9) compared with SSRI nonusers. The adjusted OR of AACG was 1.73-fold (95% CI, 1.23–2.44) for non-SSRI antidepressant users and the comorbidities of hypertension (adjusted OR = 1.29; 95% CI, 1.13–1.47) and anxiety (adjusted OR = 1.30; 95% CI, 1.03–1.65).

Table 3 shows the relationship between AACG and immediate SSRI use by a dose–response effect. Compared with SSRI nonusers, the AACG risk was higher in patients who were administered a > 20 mg mean daily dose of SSRIs (adjusted OR = 8.53; 95% CI, 1.65–44.0).

Table 4 shows a summary of the AACG case series with immediate/nonimmediate SSRI use. Ten case patients with immediate SSRI use were aged from 61 to 79 years; 4 patients used fluoxetine, 3 used sertraline, 2 used escitalopram, and 1 patient used citalopram. Among 6 case patients with nonimmediate SSRI use, 2 patients used fluoxetine, 2 used sertraline, and 1 patient used citalopram.

DISCUSSION

Acute angle–closure glaucoma is an ocular emergency that may be induced by certain types of medications,[2] such as SSRI antidepressants.[2] Our study supports evidence that in the ethnic Chinese population in Taiwan, immediate SSRI users have a 5.8-fold increased risk of AACG compared with that of nonusers. Furthermore, in the AACG group, 58.1% of the patients were women and 50.3% were aged 65–84 years. The 10 AACG case participants with immediate SSRI use were aged from 61 to 79 years. These crucial findings confirm the presumption that SSRIs increase the risk of AACG in older adults, particularly in older women.[17] Seitz et al[17] reported a similar result; they determined that recent exposure to antidepressant drugs is associated with an increased risk of AACG among older adults according to data from population administrative databases in Canada. Possible mechanisms for AACG induced by SSRIs are purportedly the weak anticholinergic activity and the

mydriatic effect of increased serotonin levels.[2,17] Moreover, among SSRIs, fluoxetine (4 AACG cases) was noted to be the most associated with AACG in our population. Fluoxetine was first reported to induce AACG in a 35-year-old man.[18] Costagliola and colleagues[19] also reported that oral administration of fluoxetine might increase intraocular pressure. According to our results, sertraline was the second most common SSRI drug that might induce AACG. In a previous study, sertraline-induced AACG risk was the highest among immediate users.[17] Pupil dilatation mediated by 5-HT (5-hydroxytryptamine, serotonin) receptors and norepinephrine receptors are proposed mechanisms underlying AACG induced by SSRIs.[12,20] Another 2 AACG case participants (aged 61 and 67 years) used escitalopram, and 1 AACG case participant (aged 68 years) used citalopram. In contrast to the previous case reports, our AACG case participants using escitalopram and citalopram were much older in age. A 41-year-old woman was reported to have bilateral AACG after escitalopram use,[11] and 2 young women presented with AACG after citalopram administration.[9,10] The mechanism of citalopram-induced AACG remains unclear.[1] Another noteworthy finding of the current study was that no single AACG case involving paroxetine use was noted. Among SSRIs, paroxetine has been the most widely reported medication to be strongly associated with AACG.[3–7] For younger AACG patients with normal lenses, hyperopia has been posited to be a risk factor,[4,6,7] whereas among older patients, cataracts, a shorter axial length, and paroxetine-induced mydriasis cause AACG.[3] Although we observed no AACG case involving paroxetine use in the current study, the possibility that paroxetine induces AACG in predisposed patients should still be considered.

We also analyzed the dose effect of SSRI on AACG, determining that AACG risk was higher in patients who were administered > 20 mg of SSRIs on average daily (adjusted OR = 8.53; 95% CI, 1.65–44.0) compared with the risk in SSRI nonusers. The presence of serotonin and its metabolites in aqueous humor and their availability on 5-HT receptors in the iris-ciliary body complex both are involved in regulating aqueous humor dynamics.[1,21] Whether increasing the daily dose of SSRIs increases serotonin levels in the aqueous humor as well as the availability of serotonin on the receptors is not clearly understood. Additional prospective studies are required to ascertain the actual dose effect of SSRIs on the angle structure.

Our study has the following strengths. First, the database was large and had optimal sample randomization. Second, the dataset captures data on a broad range of people with different sociodemographic profiles, unlike the datasets used in smaller studies, in which patients were recruited from specific regions that might be unrepresentative of the entire population. Third, to avoid potential confounding factors, we also considered non-SSRI antidepressant use, medical comorbidities, and psychiatric disorders (anxiety and depression) during analysis. However, the current study also has limitations. First, we defined glaucoma by relying entirely on claims data (*ICD-9-CM* coding from clinicians), a method that may be less accurate than determining diagnoses individually through a standardized procedure. Second, a selection bias existed in this study. Because the NHI database includes only patients who receive treatment, people who receive no treatment for depression might have been recruited in the comparison cohort. Third, according to the limitations of a claims database, predisposing factors for AACG, such as shallow angle depth, family history of angle closure, hyperopia, shorter axial length, and thicker lenses, are unavailable. Fourth, because of the lack of laboratory and imaging data from individual chart records, the NHIRD is primarily used for insurance requests and has not been entirely validated for research; thus, uncontrolled confounding factors and potential biases may have affected this retrospective case-control study. 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.[22] However, our study has major findings and value. Although only a few cases of AACG induced by SSRI administration are reported in MEDLINE, the World Health Organization Adverse Drug Reactions database indicates that certain undefined glaucoma cases were associated with various types of SSRIs.[1] Thus, asymptomatic side effects are underestimated.[1] Therefore, in addition to the risk of AACG, glaucoma risk factors such as female sex, race, glaucoma family history, hyperopia, cataracts, and advanced age should be considered during ophthalmologic consultation before patients begin SSRI antidepressant treatment. In conclusion, clinicians should be aware of the potential risk of AACG among older patients with depression before prescribing SSRIs.

Submitted: April 8, 2015; accepted June 25, 2015.
Online first: April 26, 2016.
Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).
Author contributions: All authors have contributed considerably and agreed upon the manuscript content: conception/design: Drs Chen, Lai, and Kao; provision of study materials: Dr Kao; collection and/or assembly of data: all authors; data analysis and interpretation: all authors; manuscript writing: all authors; and final approval of manuscript: all authors.
Potential conflicts of interest: The authors have no proprietary or commercial interest in any of the materials discussed in this article.
Funding/support: This study was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019); China Medical University Hospital; Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037); NRPB Stroke Clinical Trial Consortium (MOST 104-2325-B-039 -005); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.
Role of the sponsor: The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Additional information: The LHID2000 database used in this study can be accessed at http://nhird.nhri.org.tw/en/Data_Subsets.html#S3.

REFERENCES

1. Costagliola C, Parmeggiani F, Semeraro F, et al. Selective serotonin reuptake inhibitors: a review of its effects on intraocular pressure. *Curr Neuropharmacol*. 2008;6(4):293–310.
2. Lachkar Y, Bouassida W. Drug-induced acute

angle closure glaucoma. *Curr Opin Ophthalmol*. 2007;18(2):129–133.
3. Eke T, Bates AK. Acute angle closure glaucoma associated with paroxetine. *BMJ*. 1997;314(7091):1387.
4. Levy J, Tessler Z, Klemperer I, et al. Late bilateral acute angle-closure glaucoma after administration of paroxetine in a patient with plateau iris configuration. *Can J Ophthalmol*. 2004;39(7):780–781.
5. Kirwan JF, Subak-Sharpe I, Teimory M. Bilateral acute angle closure glaucoma after administration of paroxetine. *Br J Ophthalmol*. 1997;81(3):252–254.
6. Bennett HG, Wyllie AM. Paroxetine and acute angle-closure glaucoma. *Eye (Lond)*. 1999;13(pt 5):691–692.
7. Browning AC, Reck AC, Chisholm IH, et al. Acute angle closure glaucoma presenting in a young patient after administration of paroxetine. *Eye (Lond)*. 2000;14(pt 3A):406–408.
8. Jiménez-Jiménez FJ, Ortí-Pareja M, Zurdo JM. Aggravation of glaucoma with fluvoxamine. *Ann Pharmacother*. 2001;35(12):1565–1566.
9. Croos R, Thirumalai S, Hassan S, et al. Citalopram associated with acute angle-closure glaucoma: case report. *BMC Ophthalmol*. 2005;5(1):23.
10. Massaoutis P, Goh D, Foster PJ. Bilateral symptomatic angle closure associated with a regular dose of citalopram, an SSRI antidepressant. *Br J Ophthalmol*. 2007;91(8):1086–1087.
11. Zelefsky JR, Fine HF, Rubinstein VJ, et al. Escitalopram-induced uveal effusions and bilateral angle closure glaucoma. *Am J Ophthalmol*. 2006;141(6):1144–1147.
12. Ho HY, Kam KW, Young AL, et al. Acute angle closure glaucoma after sertraline. *Gen Hosp Psychiatry*. 2013;35(5):575.e1–575.e2.
13. Chen HY, Huang ML, Tsai YY, et al. Comparing glaucomatous optic neuropathy in primary open angle and primary angle closure glaucoma eyes by scanning laser polarimetry-variable corneal compensation. *J Glaucoma*. 2008;17(2):105–110.
14. Hu CC, Lin HC, Chen CS. A 7-year population study of primary angle closure glaucoma admissions and climate in Taiwan. *Ophthalmic Epidemiol*. 2008;15(1):66–72.
15. Lavanya R, Baskaran M, Kumar RS, et al. Risk of acute angle closure and changes in intraocular pressure after pupillary dilation in Asian subjects with narrow angles. *Ophthalmology*. 2012;119(3):474–480.
16. Lam DS, Leung DY, Tham CC, et al. Randomized trial of early phacoemulsification versus peripheral iridotomy to prevent intraocular pressure rise after acute primary angle closure. *Ophthalmology*. 2008;115(7):1134–1140.
17. Seitz DP, Campbell RJ, Bell CM, et al. Short-term exposure to antidepressant drugs and risk of acute angle-closure glaucoma among older adults. *J Clin Psychopharmacol*. 2012;32(3):403–407.
18. Ahmad S. Fluoxetine and glaucoma. *DICP*. 1991;25(4):436.
19. Costagliola C, Mastropasqua L, Steardo L, et al. Fluoxetine oral administration increases intraocular pressure. *Br J Ophthalmol*. 1996;80(7):678.
20. Costagliola C, Parmeggiani F, Sebastiani A. SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms. *CNS Drugs*. 2004;18(8):475–484.
21. Tobin AB, Unger W, Osborne NN. Evidence for the presence of serotonergic nerves and receptors in the iris-ciliary body complex of the rabbit. *J Neurosci*. 1988;8(10):3713–3721.
22. Woldu H, Porta G, Goldstein T, et al. Pharmacokinetically and clinician-determined adherence to an antidepressant regimen and clinical outcome in the TORDIA trial. *J Am Acad Child Adolesc Psychiatry*. 2011;50(5):490–498.