



# Systemic Medication Associations with Presumed Advanced or Uncontrolled Primary Open-Angle Glaucoma

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**Purpose:** To identify associations between systemic medications and primary open-angle glaucoma (POAG) requiring a procedure using United States insurance claims data in a hypothesis-generating study.

**Design:** Database study.

**Participants:** In total, 6130 POAG cases (defined as patients with POAG undergoing a glaucoma procedure) were matched to 30 650 controls (defined as patients undergoing cataract surgery but without a coded glaucoma diagnosis, procedure, or medication) by age, gender, and region of residence.

**Methods:** Participant prescription drug use was calculated for the 5-year period before the glaucoma procedure or cataract surgery. Separately for individual generic drugs and drug classes, logistic regression was used to assess the association with POAG status. This was done across all generic drugs and drug classes that were prescribed in at least 1% of cases and controls. Analyses were adjusted for age, sex, region of residence, employment status, insurance plan type, and the total number of drugs prescribed.

**Main Outcome Measures:** Odds ratio (OR) and 95% confidence intervals (CIs) for the association between each drug or drug class and POAG.

**Results:** The median age of participants was 72 years, and 52% were women. We tested for associations of POAG with 423 drug classes and 1763 generic drugs, resulting in a total of 2186 statistical tests and a Bonferroni-adjusted significance threshold of  $P < 2.3 \times 10^{-5}$ . Selective serotonin reuptake inhibitors (SSRIs) were strongly associated with a reduced risk of POAG (OR, 0.70; 95% CI, 0.64–0.76;  $P = 1.0 \times 10^{-15}$ ); the most significant drug in this class was citalopram (OR, 0.66; 95% CI, 0.57–0.77;  $P = 1.2 \times 10^{-7}$ ). Calcium channel blockers were strongly associated with an increased risk of POAG (OR, 1.26; 95% CI, 1.18–1.35;  $P = 1.8 \times 10^{-11}$ ); the most significant drug in this class was amlodipine (OR, 1.27; 95% CI, 1.18–1.37;  $P = 5.9 \times 10^{-10}$ ).

**Conclusions:** We present data documenting potential associations of SSRIs and calcium channel blockers with POAG requiring a procedure. Further research may be indicated to better evaluate any associates of serotonin metabolism or calcium channels in glaucoma, or establish whether the associations are due to variations in the patterns for prescribing these drugs. *Ophthalmology* 2018;125:984–993 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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Primary open-angle glaucoma (POAG) is one of the most common causes of irreversible visual impairment globally.<sup>1</sup> The condition affects approximately 73.6 million people worldwide and 2.2 million people in the United States.<sup>2</sup> All current proven medical and surgical therapies for POAG aim to reduce intraocular pressure (IOP), although many patients still progress to blindness despite maximal treatment. Therefore, there is a need for novel treatments for POAG.

Examining the association between a disease and systemic medications used for unrelated conditions may help provide knowledge that can lead to new treatments. If a systemic medication is found to be associated with POAG, this may lead to drug repositioning for the treatment of POAG or to the development of drugs that modify a related biological pathway. The knowledge would also be helpful for clinicians who regularly manage patients with glaucoma with systemic

comorbidity. At the least, a novel drug association with POAG may help point toward new biological pathways underlying the disease that can prompt new streams of research. The findings can be compared with population-based explorations of associations between systemic medications and IOP in healthy participants previously reported.<sup>3–5</sup>

The aim of our study was to examine associations of prescription drug use with POAG in a hypothesis-independent study of US insurance claims data.

## Methods

### Data Source

We used patient-level data from Truven Health MarketScan Commercial and Medicare Supplemental Insurance Databases (Truven

Health Analytics, Ann Arbor, MI). The databases contain medical claims from more than 170 million unique patients since 1995 for healthcare services performed in both inpatient and outpatient settings, and for outpatient prescription drug claims. Person-level enrollment data were available through unique enrollee identifiers. We examined data from January 1, 2007, to December 31, 2014; this included a 2-year period for identification of cases and controls from January 1, 2012, to December 31, 2013, a 5-year look-back period for examination of prescription drug use, and a 1-year look-forward period to exclude delayed glaucoma diagnosis in controls. We used a combination of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and Current Procedural Terminology, 4th Edition (CPT-4) codes to define case or control status, as described next. All MarketScan database records are de-identified and fully compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The databases have been evaluated and certified by an independent third party to be in compliance with the HIPAA statistical de-identification standard. The databases were certified to satisfy the conditions set forth in Sections 164.514 (a)-(b)iii of the HIPAA privacy rule regarding the determination and documentation of statistically de-identified data. Because the proposed approach does not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board approval to conduct this study is not required.

### Case Definition

To minimize the risk of misclassification bias (i.e., patients being coded with a POAG diagnosis or treatment for POAG but without true progressive disease), we required cases to have undergone a glaucoma procedure. Case inclusion criteria were at least 1 glaucoma procedure code (Table S1, available at [www.aaojournal.org](http://www.aaojournal.org)) during the identification period January 1, 2012, to December 31, 2013 (the first encounter date of such codes was defined as the index date); aged 45 years or older on the index date; at least 1 ICD-9-CM code for POAG (365.11 or 365.12) on the index date; and continuous enrollment in medical and pharmacy benefit plans during the entire study period (from 5 years before the index date to 1 year after the index date). The glaucoma procedure codes considered were CPT-4-66160-fistulization of sclera for glaucoma sclerectomy with punch or scissors, with iridectomy; CPT-4-66170-fistulization of sclera for glaucoma trabeculectomy ab externo in absence of previous surgery; CPT-4-66172-fistulization of sclera for glaucoma trabeculectomy ab externo with scarring from previous ocular surgery or trauma (includes injection of antifibrotic agents); CPT-4-66174-transluminal dilation of aqueous outflow canal without retention of device or stent; CPT-4-66175-transluminal dilation of aqueous outflow canal with retention of device or stent; CPT-4-66180-aqueous shunt to extraocular reservoir (e.g., Molteno, Schocket, Denver-Krupin); CPT-4-66183-insertion of anterior segment aqueous drainage device, without extraocular reservoir, external approach; CPT-4-66185-revision of aqueous shunt to extraocular reservoir; CPT-4-66710-ciliary body destruction cyclophotocoagulation, transscleral; CPT-4-66711-ciliary body destruction cyclophotocoagulation, endoscopic; CPT-4-0191T-insertion of anterior segment aqueous drainage device, without extraocular reservoir; CPT-4-65855-trabeculoplasty by laser surgery, 1 or more sessions (defined treatment series); ICD-9-CM Procedure-1261-trephination of sclera with iridectomy; ICD-9-CM Procedure-1264-trabeculectomy ab externo; ICD-9-CM Procedure-1265-other scleral fistulization with iridectomy; ICD-9-CM Procedure-1267-insertion of aqueous drainage device; ICD-9-CM Procedure-1273-cyclophotocoagulation. Case exclusion criteria were diagnosis codes for glaucoma other than POAG (e.g., angle-closure glaucoma or secondary glaucoma) (Table S1,

available at [www.aaojournal.org](http://www.aaojournal.org)) during the entire study period or a glaucoma procedure code in the 5 years before the index date.

### Control Definition

Epidemiological studies of glaucoma prevalence in developed countries suggest that approximately 50% of patients with glaucoma remain undiagnosed.<sup>6-8</sup> To minimize the risk of misclassification bias (i.e., patients with undiagnosed POAG being classified as controls), we required all controls to have had a reasonable opportunity to be diagnosed with glaucoma if affected. Our primary control population was patients who underwent cataract surgery, the assumption being that the preoperative and postoperative ophthalmic assessments would detect glaucoma if present. To increase the power of our study and because patients with cataract are plentiful, we included 5 times as many controls as glaucoma cases in a matched design. Inclusion criteria for controls were at least 1 ICD-9-CM diagnostic code for cataract and at least 1 procedure code for cataract surgery (Table S1) on the same day during the identification period January 1, 2012, to December 31, 2013 (if both eyes of 1 patient underwent cataract surgery, the date of surgery for the first eye was considered the index date); aged at least 45 years on the index date; and continuous enrollment in medical and pharmacy benefit plans in the entire study period from 5 years before index date to 1 year after index date. Exclusion criteria for controls were nonroutine cataract surgery (Table S1, available at [www.aaojournal.org](http://www.aaojournal.org)) in the entire study period; a diagnosis code for any type of glaucoma; a procedure code for a glaucoma procedure during the entire study period; and use of glaucoma medication (Table S2, available at [www.aaojournal.org](http://www.aaojournal.org)) anytime during the entire study period. In addition, we matched controls to the case population at a ratio of 1:5 by 5-year age group, gender, and geographic region of the United States where the patients resided. Complete matching on all parameters was achieved for more than 99% of controls; for the remaining controls required to achieve a 1:5 ratio with cases, the matching requirements were relaxed by sex or age group. As expected, cases and controls were similar for age, sex, and residential location (Table 1).

To evaluate the possibility that our primary findings were due to associations with cataract risk rather than POAG, we further defined an alternative, more general control population; these controls were required to have had any general office visit to an ophthalmologist. We included 7 times as many alternative controls as cases using a matched design. Inclusion criteria for the alternative control population were at least 1 diagnostic code (excluding codes for “ruling out” a disease) or procedure code for ophthalmic-related conditions (ICD-9-CM: 360-379.9; CPT-4: 65091-68899, 92002-92499) (Table S1) during the identification period from January 1, 2012, to December 31, 2013 (the first encounter date was defined as the index date); continuous enrollment in medical and pharmacy benefit plans in the entire study period (from 5 years before index date to 1 year after index date); and aged at least 45 years on the index date. Exclusion criteria for the alternative control population were no recorded visit to an eye care practitioner in the 5-year look-back period and any glaucoma diagnosis code, glaucoma procedure code (Table S1), or use of glaucoma medication (Table S2) in the entire study period. We also matched the alternative control population to cases at a 7:1 ratio by 5-year age group, gender, and geographic region of residence in the United States.

### Definition of Drug Exposure

We used the information from outpatient prescription pharmacy claims in the preidentification period (from 5 years to 30 days before the index date) to calculate participant-level total days of

Table 1. Participant Demographics

	Cases (N = 6130)	Controls (N = 30650)	Standardized Difference
Age, mean (SD)	71.8 (11.3)	71.7 (10.7)	0.010
Age, median (IQR)	72 (18)	72 (17)	
Sex			0.036
Men	2964 (48%)	14 883 (48%)	
Women	3166 (52%)		
Region			0.000
Northeast region	850 (14%)	4250 (14%)	
North central region	2482 (40%)	12 410 (40%)	
South region	1951 (32%)	9755 (32%)	
West region	841 (14%)	4205 (14%)	
Unknown region	6 (0%)	30 (0%)	
Plan type			0.112
Fee for service	5596 (91%)	28 024 (91%)	
Unknown	32 (1%)	484 (2%)	
HMO and POS capita	502 (8%)	2142 (7%)	
Employment status			0.334
Active full time	1104 (18%)	5762 (19%)	
Active part time or seasonal	31 (1%)	129 (0%)	
Early retiree	555 (9%)	3000 (10%)	
Medicare eligible retiree	3437 (56%)	16 894 (55%)	
Retiree (status unknown)	258 (4%)	2554 (8%)	
COBRA continuee	5 (0%)	42 (0%)	
Long-term disability	6 (0%)	53 (0%)	
Surviving spouse/depend	368 (6%)	1974 (6%)	
Other/unknown	366 (6%)	242 (1%)	

COBRA = Consolidated Omnibus Budget Reconciliation Act; HMO = Health Maintenance Organization; IQR = interquartile range; POS = point-of-service; SD = standard deviation.

Counts and percentages are presented unless otherwise stated.

supply for each prescription drug at the National Drug Code (NDC) level.<sup>9</sup> We calculated days of supply for every drug for each individual. For a given patient and NDC drug code, when a pharmacy claim provided days of supply sufficient to cover past the date of the next claim, the carryover days were not counted. The drug coding was further summarized by generic drug name and the Uniform System of Classification (USC) levels.<sup>10</sup> Drugs for ophthalmic indications (Table S2) were excluded from the analysis. Individuals with more than 90 days of supply of a particular drug anytime during the preidentification period were classified as exposed to that drug; individuals with 0 days of supply were classified as nonexposed; and individuals with 1 to 90 days of supply were classified as having uncertain exposure and were excluded from analyses for that drug.

## Statistical Analysis

We summarized the baseline characteristics of sociodemographic status, Elixhauser comorbidities,<sup>11</sup> and drug use in case and control populations using descriptive statistics. Standardized difference scores were calculated to compare the differences between cases and controls; these scores measure the effect size between 2 groups, but unlike a *t* test or Wilcoxon rank-sum test, they are independent of sample size.<sup>12</sup> A standardized difference score of 0.5 and 0.8 can be used to represent medium and large effect sizes, respectively.

To assess the association between drug use and POAG, our primary analyses were logistic regressions carried out separately for each individual generic drug or USC-level drug class, using case/control status (1 = case; 0 = control) as the response variable and generic drug or drug class exposure as the key predictor (1 = exposed; 0 = nonexposed). We adjusted for

sociodemographic variables (age, sex, geographic region of residence, employment status, and insurance plan type), and the total number of drugs each individual patient submitted claims for during the preidentification period. To avoid the risk of over-adjustment, we did not initially adjust for comorbidities in the primary analyses. On the basis of the significant results, pertinent comorbidities were adjusted for in subsequent analyses. We only considered medications that were prescribed in at least 1% of cases and controls.

For drug classes significantly associated with POAG in primary analyses, we also tested for a dose-response relationship. For each drug class, we divided participants into tertiles of days of supply. By using logistic regression, we examined for a dose-response trend across tertiles with reference to nonusers and among users only with reference to the lowest tertile of days of supply. These analyses were adjusted for the same covariables as in the primary regression models. To distinguish effects from certain drug classes that are commonly coprescribed, we also fitted multidrug variable models with multiple drug exposure variables in the same model.

Software packages used for statistical analysis in this study were SAS version 9.3 (SAS Institute, Inc, Cary, NC) for cohort extraction, R version 3.3.2 (R development core team, Vienna, Austria) for modeling, and Stata version 12.1 (StataCorp LP, College Station, TX) for model diagnostics.

## Results

### Participant Selection and Demographics

A total of 6272 cases met the study inclusion and exclusion criteria out of 46 954 patients with POAG undergoing surgery in the

Table 2. Drug Classes and Individual Drugs Significantly Associated with Primary Open-Angle Glaucoma

	Odds Ratio (95% CI)	P Value
USC drug class		
SSRI	0.70 (0.64–0.76)	$1.04 \times 10^{-15}$
Beta-blockers	0.77 (0.72–0.83)	$2.71 \times 10^{-14}$
Calcium channel blockers	1.26 (1.18–1.35)	$1.78 \times 10^{-11}$
Sexual function disorder medications	1.39 (1.22–1.58)	$4.93 \times 10^{-7}$
SNRI	0.71 (0.61–0.82)	$2.31 \times 10^{-6}$
Fibric acid derivatives	0.74 (0.65–0.84)	$2.55 \times 10^{-6}$
Angiotensin II antagonists	1.19 (1.10–1.28)	$1.78 \times 10^{-5}$
Generic drug name		
Amlodipine	1.27 (1.18–1.37)	$5.92 \times 10^{-10}$
Citalopram	0.66 (0.57–0.77)	$1.18 \times 10^{-7}$
Esomeprazole	0.81 (0.73–0.89)	$1.59 \times 10^{-5}$
Tamsulosin	1.29 (1.15–1.44)	$1.93 \times 10^{-5}$

CI = confidence interval; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; USC = Uniform System of Classification.

All associations presented are significant at the Bonferroni-corrected threshold of  $2.3 \times 10^{-5}$ .

identification period. A total of 75 189 cataract controls met the study inclusion and exclusion criteria out of 453 678 patients undergoing cataract surgery in the identification period; of these, 30 650 were matched to 6130 cases at a 5:1 ratio by age, gender, and the geographic region in which they lived. Table S3 (available at [www.aojournal.org](http://www.aojournal.org)) provides details of the participant flow and selection.

Demographic characteristics of the participants are presented in Table 1. Cases and controls had similar distributions of age, gender, and geographic region of residence, as expected given the matched study design. The median age in both populations was 72 years, with an interquartile range of 17 to 18 years; 52% of both populations were women. Approximately 40% of patients resided in the north central United States, and 32% resided in the southern United States. In total, 91% of patients were covered by fee-for-service insurance plans, whereas 55% to 56% of patients were Medicare-eligible retirees, and 18% to 19% of patients were active full-time employees. On average, each participant submitted 115 to 121 pharmacy claims covering 30 unique NDC codes, 18 unique generic names, and 16 USC drug classes (Table S4, available at [www.aojournal.org](http://www.aojournal.org)). Case and control populations were exposed to approximately the same total number of generic drug types. Cases and controls did not have an apparent imbalance in any drug use measures, as demonstrated by the small standardized difference scores (Table S4, available at [www.aojournal.org](http://www.aojournal.org)).

To characterize disease comorbidity status in the study population, we summarized counts and frequencies of 31 major Elixhauser comorbidities from 5 years to 30 days before each participant's specific index date. The major comorbidities were diseases known to be highly prevalent: approximately 70% of patients had uncomplicated hypertension, 30% of patients had uncomplicated diabetes, and 30% of patients had chronic pulmonary disease. A participant on average carried diagnoses for 4 Elixhauser disease groups in the time period 5 years to 30 days before their index date (Table S4, available at [www.aojournal.org](http://www.aojournal.org)). Case and control populations did not have any large imbalance in any disease group or in the overall

number of diseases per patient, although there was a trend for a higher prevalence of hypertension in cases compared with controls.

## Drug Use in the Study Population

In total, the study population was exposed to drugs from 21 753 unique NDC codes, 1763 unique generic names, and 423 unique USC classes. Only 292 generic names and 168 USC classes were used by more than 1% of cases and controls. The 2 most widely used USC classes were codeine and combinations non-injectable, which were used by 60% of cases and 62% of controls with approximately 100 days of supply on average, and HMG-CoA reductase inhibitors, which were used by 55% of cases and 56% of controls with approximately 1000 days of supply on average. The 2 most widely used generic drugs were hydrocodone bitartrate/acetaminophen, which was used by 50% of cases and 52% of controls with approximately 100 days of supply on average, and azithromycin, which was used by 43% of cases and 44% of controls with 13 days of supply on average. Use of all prescription medications in cases and controls appear online in the drug utilization summary (Appendices 1 and 2; available at [www.aojournal.org](http://www.aojournal.org)).

## Drug Associations with Incident Glaucoma Procedure for Primary Open-Angle Glaucoma

We tested for associations of incident POAG requiring a procedure with 423 USC drug classes and 1763 generic drug names, resulting in a total of 2186 statistical tests. By applying a Bonferroni correction, we derived a *P* value threshold of  $2.3 \times 10^{-5}$  (0.05/2186) for statistical significance at the 5% level. We identified 8

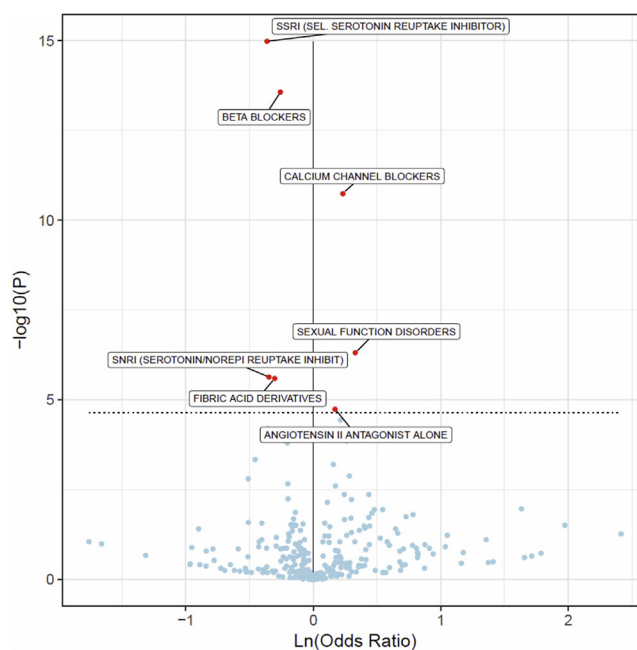
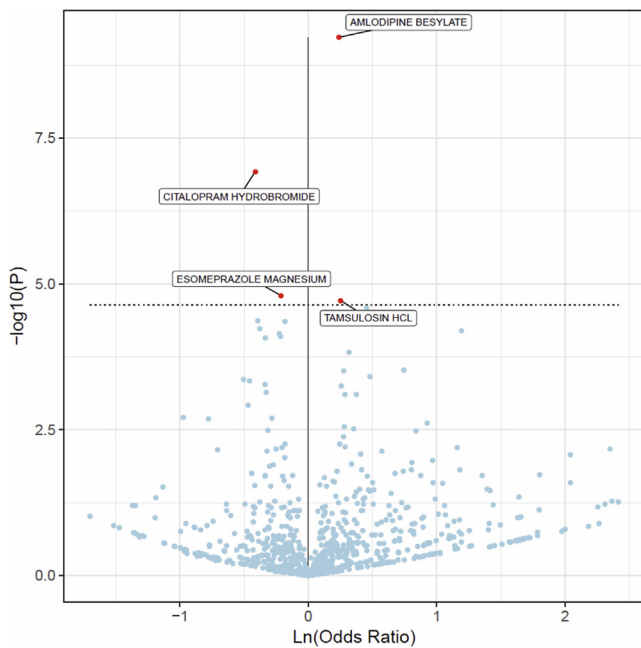


Figure 1. Volcano plot displaying results for the associations between all Uniform System of Classification (USC) drug classes and primary open-angle glaucoma (POAG). Each dot represents a different USC drug class. The x-axis represents the natural log of odds ratio (OR), and the y-axis displays the *P* values for the associations on a logarithmic scale ( $-\log_{10}P$ ). The black vertical line indicates an OR = 1 (i.e., no association). The black horizontal line indicates the Bonferroni-corrected *P* value threshold of  $2.3 \times 10^{-5}$ .



**Figure 2.** Volcano plot displaying results for the associations between all individual generic drugs and primary open-angle glaucoma (POAG). Each dot represents a different generic drug. The x-axis represents the natural log of the odds ratio (OR), and the y-axis displays the  $P$  values for the associations on a logarithmic scale ( $-\log_{10}P$ ). The black vertical line indicates an OR = 1 (i.e., no association). The black horizontal line indicates the Bonferroni-corrected  $P$  value threshold of  $2.3 \times 10^{-5}$ .

USC classes and 4 generic drugs that were significantly associated with POAG requiring a procedure (Table 2; Figs 1 and 2). Full results for all drugs tested are presented in Tables S5 and S6 (available at [www.aaojournal.org](http://www.aaojournal.org)).

The USC drug class selective serotonin reuptake inhibitors (SSRIs) showed the most significant protective association (odds ratio [OR], 0.70; 95% confidence interval [CI], 0.64–0.76;  $P = 1.0 \times 10^{-15}$ ), and a related drug class serotonin-norepinephrine reuptake inhibitors (SNRIs) showed a weaker but still significant protective association (OR, 0.71; 95% CI, 0.61–0.82;  $P = 2.3 \times 10^{-6}$ ). In accord with the association observed with the class of SSRI drugs, an individual SSRI drug citalopram also showed a significant protective association (OR, 0.66; 95% CI, 0.57–0.77;  $P = 1.2 \times 10^{-7}$ ). To further delineate the contributing associations of SSRIs, SNRIs, and the influence of depression overall, we fitted a multivariable logistic regression model with these 3 key predictors (using depression defined by the Elixhauser comorbidity group “Depression”) and adjusted for the same demographic variables as in the primary model (age, sex, geographic region of residence, employment status, and insurance plan type). The multivariable model showed significant associations for SSRIs ( $P = 2.4 \times 10^{-14}$ ) and SNRIs ( $P = 2.0 \times 10^{-6}$ ) but no significant association for a diagnosis of depression ( $P = 0.22$ ).

The drug class beta-blockers showed the second most significant protective association (OR, 0.77; 95% CI, 0.72–0.83;  $P = 2.7 \times 10^{-14}$ ). Because ophthalmic beta-blockers given as eye drops were excluded from the analysis, this signal was purely derived from systemically administered beta-blockers. Individual generic beta-blockers also showed protective associations, the most significant being metoprolol succinate (OR, 0.84; 95% CI, 0.77–0.91;  $P = 4.4 \times 10^{-5}$ ) followed by atenolol (OR, 0.81; 95% CI, 0.72–0.90;  $P = 8.0 \times 10^{-5}$ ), although the level of significance

did not pass the Bonferroni-corrected  $P$  value threshold for either drug. Fibric acid derivatives also demonstrated a protective association with POAG requiring a procedure (OR, 0.74; 95% CI, 0.65–0.84;  $P = 2.6 \times 10^{-6}$ ).

Calcium channel blockers were the most significant drug class associated with an increased risk of POAG (OR, 1.26; 95% CI, 1.18–1.35;  $P = 1.8 \times 10^{-11}$ ), mainly driven by amlodipine (OR, 1.27; 95% CI, 1.18–1.37;  $P = 5.9 \times 10^{-10}$ ). Angiotensin II antagonists, another class of antihypertensive medication, were also significantly associated with increased risk of POAG (OR, 1.19; 95% CI, 1.10–1.28;  $P = 1.8 \times 10^{-5}$ ), although the effect size was less strong than for calcium channel blockers.

Given that multiple antihypertensive medications and lipid-lowering medications are frequently coprescribed, we tested for independent effects of beta-blockers, calcium channel blockers, angiotensin II antagonists, fibric acid derivatives, and hypertension as a comorbidity (defined as falling into Elixhauser comorbidity group “hypertension without complications” or “hypertension with complications”) by fitting a multivariable logistic regression model with all these predictors together and adjusted for the same demographic variables as the primary model. We did not adjust for statin use because statins were not significantly associated with POAG in our study (OR, 0.96; 95% CI, 0.90–1.02;  $P = 0.18$ ). Calcium channel blockers and beta-blockers both remained highly significantly associated with POAG, whereas angiotensin II antagonists and fibric acid derivatives were no longer significant at the Bonferroni-adjusted threshold (Table S7, available at [www.aaojournal.org](http://www.aaojournal.org)). Hypertension as a comorbidity was associated with an increased risk of POAG (OR, 1.21; 95% CI, 1.12–1.31;  $P = 3.8 \times 10^{-7}$ ) in the multivariable model.

Additional findings that were significant at the Bonferroni-adjusted threshold were the USC class of drugs for sexual function disorders, which was significantly associated with an increased risk of POAG, and the individual drugs esomeprazole and tamsulosin, which were associated with a reduced and increased risk of POAG, respectively (Table 2).

## Sensitivity Analysis

We carried out a sensitivity analysis for our primary findings using an alternative control population (Table S8, available at [www.aaojournal.org](http://www.aaojournal.org)); controls were defined as participants with any general office visits to an ophthalmologist during the identification period (i.e., controls were not required to have undergone cataract surgery). In this analysis, 43 883 controls were matched to 6269 cases at a ratio of 7:1. The number of cases in this sensitivity analysis differs slightly from the number of cases in the primary analysis because of different availability of controls using the matching algorithm. All drug classes significant in our primary analyses were also significant in this sensitivity analysis apart from sexual function disorder medication ( $P = 0.002$ ) and angiotensin II antagonists ( $P = 0.84$ ). The association with POAG became considerably stronger for SSRIs in the sensitivity analysis compared with the primary analysis (OR, 0.64; 95% CI, 0.58–0.69;  $P = 6.2 \times 10^{-24}$ ). All individual medications significant in our primary analysis remained significant in the sensitivity analysis apart from tamsulosin ( $P = 0.23$ ).

## Dose-Response Analysis

We also tested for a dose-response relationship between drug exposure and POAG for the 2 novel medication classes with independent effects in both primary and sensitivity analyses (SSRIs and calcium channel blockers). For SSRIs, there was a clear dose-response relationship with progressively lower odds of POAG with

Table 3. Dose-Response Analyses for the Associations of Primary Open-Angle Glaucoma with Selective Serotonin Reuptake Inhibitors and Calcium Channel Blockers

		SSRIs			
		All Participants		SSRI Users Only	
Days of Supply		OR (95% CI)	P Value	OR (95% CI)	P Value
Nonusers	0	Ref		—	—
Lowest tertile	90–482	0.82 (0.72–0.94)	<b>0.003</b>	Ref	
Middle tertile	483–1240	0.69 (0.60–0.79)	<b>1.84 × 10<sup>-7</sup></b>	0.84 (0.70–1.01)	0.06
Highest tertile	1241–1777	0.60 (0.52–0.69)	<b>6.74 × 10<sup>-12</sup></b>	0.74 (0.61–0.89)	<b>0.002</b>
Test for trend			<b>1.67 × 10<sup>-17</sup></b>		<b>0.002</b>
		Calcium Channel Blockers			
		All Participants		Calcium Channel Blocker Users Only	
Days of Supply		OR (95% CI)	P Value	OR (95% CI)	P Value
Nonusers	0	Ref		—	—
Lowest tertile	90–631	1.31 (1.18–1.45)	<b>1.87 × 10<sup>-7</sup></b>	Ref	
Middle tertile	632–1422	1.35 (1.22–1.49)	<b>5.98 × 10<sup>-9</sup></b>	1.03 (0.90–1.17)	0.674
Highest tertile	1423–1785	1.16 (1.04–1.28)	<b>0.006</b>	0.88 (0.77–1.00)	0.054
Test for trend			<b>8.19 × 10<sup>-8</sup></b>		0.06

CI = confidence interval; OR = odds ratio; SSRI = selective serotonin reuptake inhibitor.

Results are from logistic regression models with POAG status as the outcome variable and categorical comparisons of drug usage across tertiles of days of supply. There are 2 forms of regression model: one using all participants with controls as a reference group and the other using only drug users with the lowest tertile of days of supply as the reference group. P values significant at the 0.01 level are in bold.

more days of supply (Table 3). This dose-response relationship was evident when the control group was the reference and also among SSRI users only with the lowest tertile of days of supply as the reference group. In contrast, there was no evidence of a dose-response effect for calcium channel blockers; the odds of POAG were similar among all levels of calcium channel blocker users (Table 3).

## Discussion

To the best of our knowledge, this is the first study to examine potential systemic medication associations with POAG in a hypothesis-independent manner across all known prescription drugs and classes. We identified highly significant associations of POAG with the use of SSRIs, beta-blockers, and calcium channel blockers using a large insurance claims database.

The protective association we found for beta-blockers on the development of POAG requiring a procedure is not surprising given the known IOP-lowering effect of systemic beta-blockers, both at an individual<sup>13–21</sup> and population level.<sup>3</sup> Identifying this expected association supports the validity of our study design and the potential utility of examining insurance claims data. It remains unclear whether the driver for the association in our study was reduced POAG development or slower POAG progression with systemic beta-blocker use, or whether this was simply lower IOP influencing clinicians' decisions on whether a glaucoma procedure was necessary.

We found a highly significant protective association for SSRIs on development of POAG requiring a procedure. The association between SSRIs and POAG in our study was strong; SSRI users were at 30% less risk of POAG than

nonusers, and this association appeared to be independent of an overall diagnosis of depression. To the best of our knowledge, an association between SSRI use and OAG has not been previously reported. Given how commonly SSRIs are prescribed (22% of controls and 16% of cases in our study were prescribed SSRIs), the potential impact on POAG prevalence is significant if we assume the protective association of SSRIs on POAG is causal. We also found a significant dose-response relationship between SSRIs and POAG with progressively lower odds of disease with greater days of drug supply. This suggests that the association with POAG is driven by cumulative exposure to SSRIs. The SNRI class was also associated with an approximately 30% reduced risk of POAG, although less significantly than SSRIs. It remains unclear if the association between serotonin-modulating drugs and POAG in our study is causal, that is, serotonin-related biological pathways are important in the pathogenesis of POAG, or whether the association is a result of confounding, either due to depression as a disease or due to prescribing patterns. It seems unlikely that it is underlying depression driving the reduced risk of POAG given that depression as a comorbidity was not associated with POAG in our study, and that another class of drugs used for depression, tricyclic antidepressants, were not significantly associated with POAG in our study ( $P = 0.03$ ). We did not find evidence that it was beta-blocker-caused depression that was underlying our observed association between SSRIs and POAG; when SSRI use and beta-blocker use were included together in the same regression model, both drugs remained highly significantly associated with POAG (SSRIs: OR, 0.73; 95% CI, 0.68–0.78;  $P = 1.9 \times 10^{-19}$ ; beta-blockers: OR, 0.69; 95% CI, 0.63–0.75;  $P = 8.0 \times 10^{-16}$ ).

There are sporadic case reports of SSRIs potentially triggering angle-closure glaucoma after short-term or long-term exposure.<sup>22–26</sup> A suggested mechanism is that SSRIs result in a slight pupil dilation, in turn precipitating pupillary block angle-closure.<sup>26</sup> It is possible that the SSRI–POAG association is driven by the avoidance of prescribing SSRI in patients with POAG because of the case reports of SSRIs precipitating angle-closure glaucoma. In other words, clinicians uncertain of the type of glaucoma their patient has might avoid prescribing SSRIs for their patient's depression, resulting in a reduction of SSRI users among patients with glaucoma. Although this is a possibility, it seems unlikely that this prescribing pattern would be sufficient to drive such a strong and highly significant association of SSRIs. Furthermore, we would not expect to see a dose-response relationship because clinicians worried about angle-closure glaucoma would be expected to not prescribe SSRIs at all. Finally, we would expect to see a stronger effect for tricyclic antidepressants, which are more robustly associated with angle-closure glaucoma, and we did not. Ocular serotonin biology has not been studied extensively, and the role for serotonin and serotonin receptors in glaucoma is unknown. However, serotonin receptors are present in the eye in retinal ganglion cells,<sup>27</sup> and there is some evidence that they may directly affect IOP.<sup>28</sup>

The association between SSRI use and open-angle glaucoma (OAG) has been examined in a study using US claims data from a database independent of the one used in this study.<sup>29</sup> Stein et al<sup>29</sup> found no significant association between SSRI use and OAG in a secondary analysis ( $P = 0.39$ ). The primary purpose of their study was to examine the association between OAG and bupropion, a norepinephrine-dopamine reuptake inhibitor that is another class of antidepressant and is prescribed for depression or to aid smoking cessation. The rationale for examining the relationship between bupropion and OAG was that bupropion is thought to also suppress tumor necrosis factor production and that tumor necrosis factor pathways have been linked to glaucoma pathogenesis.<sup>29</sup> In our study, bupropion use was associated with a reduced risk of POAG (OR, 0.78; 95% CI, 0.65–0.93;  $P = 0.007$ ), but this was far from statistically significant after considering the large number of drugs we evaluated. The reason for the discrepancy in findings for SSRIs between our study and the report by Stein et al<sup>29</sup> remains unclear. It is possible our study finding is due to chance, although this is extremely unlikely given how statistically significant the association in our study is and the clear dose-response relationship. Another reason for the discrepancy may be due to differences in study design. Stein et al<sup>29</sup> examined all OAG, whereas we focused on POAG, which may be a more biologically homogeneous group. In addition, our case definition was more stringent requiring that a glaucoma procedure had been carried out; this may have reduced misclassification of ocular hypertensives or glaucoma suspects as true cases.

We found a strong and highly significant association between calcium channel blocker use and POAG. Calcium channel blockers, a common class of antihypertensive, were associated with a 26% increased risk of POAG requiring a glaucoma procedure. Amlodipine, a commonly prescribed

calcium channel blocker, was the single drug most significantly associated with POAG in our study. We did not identify a dose-response relationship between calcium channel blockers and POAG. This suggests that if calcium channel blockers are causally associated with POAG, there is a threshold effect and once the threshold is achieved there is no further additional risk attributed to ongoing use. Angiotensin II antagonists were also associated with an increased risk of POAG, although the  $P$  value was close to the Bonferroni-corrected threshold for significance, and this drug class was no longer significant when considered together with calcium channel blockers and hypertension as a comorbidity in a multivariable model. Regardless, it remains difficult to untangle the individual effects of antihypertensive drugs from each other and the effect of hypertension as an underlying disease using data from our study. We found a diagnosis of hypertension to be associated with a 21% increased risk of POAG. This is in keeping with a meta-analysis of observational studies examining the association between hypertension and POAG that found a pooled OR of 1.16 (95% CI, 1.05–1.28).<sup>30</sup> The mechanism by which hypertension is associated with POAG remains unclear; possibilities include a deleterious effect of high blood pressure (BP), a deleterious effect of overtreatment of hypertension and resultant low BP, or specific antihypertensive medication having a deleterious effect independently of BP. The relationship between POAG and BP as a continuous trait is also unclear, with some studies demonstrating greater risk with higher BP and other studies demonstrating greater risk with lower BP.<sup>30</sup> A study examining the association between BP and optic disc measures in a Greek population found that lower BP was associated with a more cupped disc, but only among participants receiving antihypertensive therapy<sup>31</sup>; this potentially suggests that the relationship between POAG and BP may be mediated by antihypertensive medication. In our study, 2 common classes of antihypertensive were not associated with POAG. Angiotensin-converting-enzyme inhibitors, the most frequently prescribed antihypertensive in our study population (prescribed in 33%), were not associated with POAG (OR, 0.97; 95% CI, 0.91–1.03;  $P = 0.29$ ), and loop diuretics (prescribed in 16%) were also not associated with POAG (OR, 0.93; 95% CI, 0.85–1.03;  $P = 0.15$ ). The lack of association between very common classes of antihypertensive and POAG in our study argues against a general deleterious effect of hypertension overall or treatment of hypertension, and supports a deleterious effect of specific classes of antihypertensive, particularly calcium channel blockers.

Prior studies of the role of calcium channel blockers in glaucoma have provided mixed results. Our study's findings are in agreement with an analysis of systemic antihypertensive medication and incident OAG in the population-based Rotterdam Study.<sup>32</sup> Müskens et al<sup>32</sup> found that individuals taking calcium channel blockers had a 1.8-fold (95% CI, 1.04–3.20) increased likelihood of developing OAG during the average follow-up of 6.5 years. No other class of antihypertensive drug showed an association with glaucoma; although beta-blockers reduced the likelihood for developing OAG, the result did not achieve statistical significance.<sup>32</sup> It should be noted that the Rotterdam Study glaucoma case

definition was based on incident visual field changes and did not require that a glaucoma procedure had been carried out. Therefore, it is likely that the Rotterdam Study glaucoma cases were earlier disease than the cases in our study, which all had a glaucoma procedure carried out. In contrast to the Rotterdam Study and our study, research in animals and humans has shown that calcium channel blockers might benefit eyes with glaucoma by increasing blood flow to the optic nerve.<sup>33</sup> A 3-year trial of the calcium channel blocker nilvadipine randomized 33 patients with normal-tension glaucoma.<sup>34</sup> Of the 13 patients in each of the treatment and placebo groups who completed the study, there was no difference in IOP or BP, and only a minimal reduction in the progressive loss of visual field that was of borderline significance.<sup>34</sup> The results of this small trial have not been replicated to the best of our knowledge. However, on the basis of this evidence, it is possible that clinicians have prescribed calcium channel blockers for POAG (or to hypertensive patients who happen to also have POAG), and this may be what is driving the association found in our study. This seems unlikely given the strength and significance of the association we found, and calcium channel blockers do not form part of the preferred practice patterns for POAG in the United States<sup>35</sup> or other established guidelines for the management of glaucoma.<sup>36</sup>

A registry database study from Denmark recently reported a positive association between antihypertensive medication and glaucoma overall, but a protective association of antihypertensive medication on the development of newly diagnosed glaucoma.<sup>37</sup> This study defined glaucoma by the use of any glaucoma medication, and therefore it is unclear whether the associations reported were driven by POAG, ocular hypertension, or other forms of glaucoma, such as angle-closure glaucoma or some of the secondary glaucomas. For example, it may be that antihypertensive treatment reduces the incidence of retinal vein occlusion and diabetic retinopathy, thereby reducing the risk of neovascular glaucoma.

Visually inspecting the volcano plots of our results (Figs 1 and 2) identifies 2 clusters of “hits” (statistically significant results at the Bonferroni-corrected threshold). The hits for SSRI and calcium channel blocker classes and individual medications (specifically amlodipine and citalopram) were some distance above the Bonferroni-corrected threshold in the plots, suggesting highly significant associations and a very small probability that the associations are spurious. The other cluster of hits is much closer to the Bonferroni-corrected threshold. We need to consider the possibility these hits are false-positives. Among these borderline hits were angiotensin II antagonists, fibric acid derivatives (both no longer significant when considered together with calcium channel blockers and beta-blockers), and sexual dysfunction medications. The association between sexual dysfunction drugs and POAG in our primary analyses was mainly driven by tadalafil (OR, 1.57; 95% CI, 1.27–1.95;  $P = 2.58 \times 10^{-5}$ ) and sildenafil (OR, 1.37; 95% CI, 1.17–1.62;  $P = 1.47 \times 10^{-4}$ ). However, the association between sexual dysfunction drugs and POAG was far less significant in our sensitivity analyses using general ophthalmic controls, also potentially signifying a false-positive. If the association in our study is real, a potential

explanation may be related to the reported association between sexual dysfunction medications and anterior ischemic optic neuropathy,<sup>38</sup> and the occasional misclassification of anterior ischemic optic neuropathy as POAG.

For individual medications, tamsulosin and esomeprazole were in the borderline cluster. The association between tamsulosin and POAG was only evident in our primary analysis and a complete null ( $P = 0.23$ ) in our sensitivity analysis using general ophthalmic controls. This suggests that the tamsulosin–POAG association in our primary analysis may be due to the requirement of controls to have undergone cataract surgery. It has been reported that patients undergoing cataract surgery are more likely to have a postoperative spike in IOP if they use tamsulosin.<sup>39</sup> This effect may have driven a greater chance of patients undergoing a glaucoma procedure if they were using tamsulosin and underwent cataract surgery. The borderline protective association of esomeprazole, a proton-pump inhibitor, on POAG is novel. As previously stated, the borderline significance of our result for esomeprazole suggests that this may be a chance finding. Alternatively, it is possible that the use of esomeprazole reduces *Helicobacter pylori* infection rates, and in turn this reduces the risk of POAG.<sup>40</sup> A systematic review and meta-analysis reported a significant association between *H. pylori* infection and glaucoma; participants with a history of infection were at a 3-fold increased odds of POAG (95% CI, 1.76–5.34).<sup>41</sup>

## Study Strengths and Limitations

Strengths of our study include the large sample size, which allowed us to examine all generic medications and classes in a hypothesis-generating manner with stringent controls for the numerous tests. Our case and control definitions aimed to reduce misclassification bias. Eye care providers should be aware of both the potential protective and detrimental effects of systemic medications in patients with glaucoma, and our study provides data in a relatively understudied area. However, there are weaknesses that we could not overcome. Despite careful case definition, our participant selection depends on accurate clinical diagnosis and subsequent coding of patients with POAG, and this will not be uniform across clinicians in the way a well-run protocolized prospective study would be. Clinical data such as perimetry or disc imaging, which would better define glaucoma severity, were not available in this study. Given our case selection criteria, our findings may refer to a select group of patients with progressive POAG and may be less applicable to ocular hypertensives or patients with controlled POAG. As with any observational study, it is not possible to determine whether associations are causal or due to confounding. Prescribing patterns for systemic disease are complex, and untangling the differential effects of disease comorbidity or the pharmacologic effects of the treatment is not straightforward (as we have discussed for hypertension and its treatment). It is also possible that comorbidities or treatments are associated with other environmental factors that are also associated with POAG, and it is these unmeasured environmental factors that are driving the observed associations rather than the biological effects of the medication. In addition, our study only



ascertained dispensed prescriptions of medication rather than actual medication use. It is likely that a significant proportion of individuals did not use their medication as prescribed and may have stopped using the medication altogether.<sup>42</sup> This limitation is especially relevant for our dose-response analyses that assume the length of time that drug prescriptions were collected reflects the time of actual drug use. Future studies to corroborate our findings may make use of electronic medication event monitors to better ascertain actual drug exposure.

In summary, we present novel methodology for exploring systemic medication associations with POAG. Our data suggest a strong protective association of SSRIs for POAG and a strong harmful association of calcium channel blockers for POAG. Given the exploratory nature of the study, our findings should be viewed as hypothesis generating and should be evaluated and confirmed in additional studies of independent groups of patients or using orthogonal methods. If confirmed, the signals are so striking that they may deserve evaluation in clinical trials. At the least, they may serve as the starting point for the investigation of new biochemical pathways that may have a role in glaucoma.

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## Footnotes and Financial Disclosures

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Abbreviations and Acronyms:

**BP** = blood pressure; **CI** = confidence interval; **CPT-4** = Current Procedural Terminology, 4th Edition; **HIPAA** = Health Insurance Portability and Accountability Act; **ICD-9-CM** = International Classification of Diseases, 9th Revision, Clinical Modification; **IOP** = intraocular pressure; **NDC** = National Drug Code; **OR** = odds ratio; **POAG** = primary open-angle glaucoma; **SNRI** = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **USC** = Uniform System of Classification.

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