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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;■:1–10 © 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.[1] The condition affects approximately 73.6 million people worldwide and 2.2 million people in the United States.[2] 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.[3–5]

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

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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)1ii 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) 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) 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.[6–8] 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, available at www.aaojournal.org) 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) 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) 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, available at www.aaojournal.org) 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, available at www.aaojournal.org), or use of glaucoma medication (Table S2, available at www.aaojournal.org) 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