

A Review of Systemic Medications That May Modulate the Risk of Glaucoma

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ABSTRACT

With increasing longevity, patients are developing more and more chronic diseases that require treatment with medications. Yet it is not fully understood the extent by which these systemic medications affect ocular structures and whether they may increase or decrease the risk of sight-threatening ocular diseases. This review provides a summary of reported associations between different systemic medications and the risk of developing glaucoma or experiencing disease progression. Medication classes covered in this review that are known to or may modulate the risk of open-angle glaucoma include corticosteroids, beta blockers, calcium channel blockers, metformin, statins, selective serotonin reuptake inhibitors, bupropion, postmenopausal hormones, and cannabinoids. Medication classes addressed in this review that may increase the risk of angle closure glaucoma include anticholinergics, adrenergic agonists, certain classes of antidepressants, sulfonamides and topiramate.

INTRODUCTION

Glaucoma is the most common cause of irreversible visual impairment worldwide.¹ It is often a chronic condition characterized by progressive damage to the optic nerve with characteristic visual field loss.² Primary open angle glaucoma (POAG) is the most common type of glaucoma, accounting for more than two-thirds of all glaucoma cases.³ Although less common than POAG, angle-closure glaucoma (ACG) is also a major cause of morbidity, especially for persons residing in Asian countries.⁴ Elevated intraocular pressure (IOP) is the only known modifiable risk factor for glaucoma, yet some patients still experience progressive vision loss despite maintaining low IOPs, suggesting there must be other factors besides IOP that alter the course of this disease. Several classes of systemic medications are known to or suspected to modulate glaucoma risk, either through their direct effects on IOP or via mechanisms independent of IOP (**Table 1**). This review summarizes the literature on associations between common classes of systemic medications, IOP, and risk for POAG or ACG.

SYSTEMIC MEDICATIONS KNOWN TO INCREASE RISK OF OPEN-ANGLE

GLAUCOMA

Corticosteroids

Ocular hypertension secondary to corticosteroid use has been well established and can lead to secondary open-angle glaucoma (OAG) in susceptible individuals.⁵⁻⁸ Studies have demonstrated that exposure to corticosteroids causes increased resistance of aqueous outflow through the trabecular meshwork. This may be attributed to accumulation of undigestible glycosaminoglycans in the human trabecular meshwork^{7,9} as a result of inhibition of matrix

metalloproteinase inhibitors.^{8,10} or through upstream activation of transforming growth factor β (TGF β) signaling.¹¹

Steroid induced ocular hypertension (SIOH) has been linked to a range of drug delivery routes including oral or intravenous, inhaled or intranasal, topical eye drops, topical cutaneous ointments, periocular injection, and intraocular corticosteroids.^{6,12-15} Approximately one quarter to one third of patients develop elevated IOP from corticosteroid use, with 5% classified as “high responders” defined as an IOP increase >15mm Hg and IOP measurements >31mm Hg.¹⁶⁻¹⁹ Patients with a known history of glaucoma or a positive family history of glaucoma have a greater risk of IOP elevation from corticosteroid use.¹⁹ Both acute and chronic IOP elevation can occur with corticosteroid use, and time of onset varies with the dosage and potency of the corticosteroid. For example, studies have reported IOP elevations within 3 to 6 weeks of initiation of topical corticosteroid eye drop therapy.^{17,20}

Fortunately, SIOH usually resolves within 2 to 4 weeks of discontinuing the corticosteroid, although normalization of IOP may take longer with chronic corticosteroid use.²¹ Replacement of corticosteroids with steroid-sparing agents such as non-steroidal anti-inflammatory agents can be very helpful in controlling the underlying inflammatory process for which the corticosteroids had been prescribed while also limiting the risk of glaucoma.²² If discontinuation of corticosteroids is not possible, a lower dose or a lower potency corticosteroid may be used. For cases of persistent IOP elevation from corticosteroids, glaucoma medications may be prescribed. Occasionally surgical interventions are needed to stabilize IOP. Surgical options including laser trabeculoplasty, trabeculotomy, canaloplasty, trabeculectomy, or glaucoma drainage device implantation.²³⁻²⁵ Minimally invasive glaucoma surgery has also been reported to successfully reduce IOP in SIOH; a case report of a pediatric patient with uveitis

requiring intravitreal and subconjunctival corticosteroids who developed SIOH experienced IOP lowering in both eyes following bilateral sequential placement of XEN gel stents.²⁶

Given the wide range of systemic medical conditions for which corticosteroids are prescribed, a considerable number of patients may be unknowingly exposed to the ocular side effects of corticosteroids. The prevalence of corticosteroid use in the general population has been estimated to be as high as 7%.²⁷ Communication between health care providers is key; medical professionals who routinely prescribe corticosteroids should seek consultation with eye care professionals to monitor for IOP elevation especially in cases of anticipated prolonged usage or potent corticosteroid dosing and patients who are known to have glaucoma or a family history of this condition.

MEDICATIONS KNOWN TO DECREASE THE RISK OF OPEN-ANGLE GLAUCOMA

Beta Blockers

Beta blockers are a class of medications commonly used for their antiarrhythmic and antihypertensive properties; selective beta-blockers for the beta-1 receptor are known as cardioselective beta blockers while non-selective beta blockers that target beta-1 and beta-2 receptors are considered to have greater antihypertensive effects. A seminal case series by Phillips and colleagues in 1967 was the first to report IOP reduction from systemic beta blocker use.²⁸ In fact, this study and subsequent others led to the development of topical beta blocker eye drops for use in glaucoma treatment. Many studies have shown that systemic beta blocker use is associated with IOP reduction.²⁹⁻³² Non-selective beta blockers are thought to be more effective in lowering IOP compared to cardioselective agents given increased activity at beta-2 receptors.^{29,33} In a large population-based study conducted in the United Kingdom, patients

receiving oral beta blockers were found to have approximately 1 mm Hg lower IOP compared to those not using these medications after controlling for age, sex, and body mass index.³²

Additional evidence suggests that oral beta blockers may be associated with a decreased risk of incident glaucoma.³⁴

Patients already taking oral beta blockers may not achieve as significant reductions in IOP with the addition of a topical beta blocker. Furthermore, patients taking oral and topical beta blockers concurrently may be at increased risk for the adverse effects from concomitant usage of both of these medications.^{35,36} Alternate classes of topical glaucoma medications should be considered in such cases; brimonidine, an alpha-2 agonist, has been found to be not only free of cardiovascular side effects but also more effective at lowering IOP than timolol, a topical beta blocker, in patients concurrently taking systemic beta blockers.³⁵

MEDICATIONS THAT MAY DECREASE THE RISK OF OPEN-ANGLE GLAUCOMA

Metformin

Metformin, a synthetic biguanide, is one of the most frequently prescribed treatments for type 2 diabetes. Metformin is a caloric-restriction-mimetic drug whose geroprotective effects have been shown to delay or reduce risks for a variety of age-associated systemic diseases; recent studies have demonstrated an association between metformin use and decreased risk of OAG in persons with diabetes mellitus.^{37,38} A large retrospective cohort study by Lin and colleagues found that among patients aged 40 years or older with diabetes mellitus and no preexisting record of OAG, those prescribed the highest quartile of metformin hydrochloride had a 25% reduced OAG risk compared to those who took no metformin. In that study, patients taking a standard dose of 2 grams of metformin per day for 2 years were predicted to have a 21%

reduction in the risk of developing OAG.³⁷ Metformin's protective effects may stem from its beneficial effects on glycemic control and improved vascular health; however, in Lin's study among multiple hypoglycemic medications tested (metformin, sulfonylureas, thiazolidinediones, meglitinides, and insulin), metformin was the only agent that demonstrated a protective effect against OAG, suggesting that the mechanism limiting the risk of OAG may go beyond simply improved glycemic control.³⁷ Furthermore, in their study, OAG risk reduction from metformin persisted even after controlling for glycosylated hemoglobin (HbA1c) levels, again supporting the notion that other mechanisms beside glycemic control such as those involving neurogenesis, inflammatory systems, or longevity pathways may be responsible for the reduction in risk of OAG.^{37,39}

Not all studies have found metformin to be protective against OAG development or disease progression. A retrospective study by Wang and coworkers examining patients with preexisting OAG failed to demonstrate that metformin use could reduce the risk of progression.⁴⁰ Differences in study design may, in part, explain discordances between this study and the study by Lin. Wang's group used receipt of filtration surgery as a proxy for progression of OAG; yet since many patients who experience OAG progression are treated with other interventions such as additional glaucoma medications or laser trabeculoplasty prior to undergoing filtration surgery, it is unclear how omitting those interventions from the analyses affected the results of that study. Additionally, clinical practice varies between glaucoma specialists and the decision to perform filtration surgery may occur at different stages of the disease and for different reasons, not all of which are related to disease progression. In summary, while there is some support that metformin may be beneficial in reducing the risk of OAG, additional studies are warranted before clinicians should begin prescribing this medication as a prevention or treatment of OAG.

Statins

Statins are a class of medications used to treat hyperlipidemia; they function by competitively inhibiting HMG-CoA reductase, the rate-limiting enzyme of the cholesterol biosynthetic pathway. In light of evidence showing a protective effect against cerebrovascular disease, interest in a neuroprotective role for statins in glaucoma has grown in recent years.⁴¹⁻⁴³ Statins have been associated with decreased risk for developing OAG while other cholesterol-lowering agents have not, suggesting properties unique to statins (beyond lowering of cholesterol) may be responsible for such a risk reduction.⁴⁴ One proposed mechanism involves upregulation of endothelial nitric oxide synthase (eNOS); the subsequent increase in nitric oxide causes vasodilation and increased retinal and choroidal blood flow, potentially improving preservation of the optic nerve and retinal nerve fiber layer.⁴⁵ Statins may achieve this through inhibition of Rho and Rho-kinase activity, which consequently leads to upregulation of eNOS expression.^{45,46} Additionally, inhibition of Rho-kinase has been shown to increase outflow facility through the trabecular meshwork, resulting in lowering of IOP, a known risk factor for glaucoma.⁴⁷ Finally, statins may exert a neuroprotective effect by decreasing glutamate-mediated cytotoxicity and protecting against apoptosis within the central nervous system.^{41,48}

There is also mounting evidence in the clinical literature that statins decrease OAG risk and/or mitigate disease progression. Among the population-based studies and retrospective case series in the literature on this topic, 5 have shown decreased OAG risk,^{44,49-52} 2 have shown decreased functional damage from glaucoma as captured on perimetry,^{53,54} and 1 has shown decreased structural damage to the retinal nerve fiber layer with statin use (**Table 2**).⁵⁵ A large retrospective cohort analysis using data on more than 500,000 patients with hyperlipidemia

enrolled in a U.S. managed care network found that the risk of developing OAG decreased 0.3% for every additional month of statin consumption, and patients who took statins continuously for 2 years had an 8% decreased risk of OAG relative to those who received no statin therapy.⁵⁰ The study also found that every additional month of statin exposure decreased the hazard of progressing from a diagnosis of glaucoma suspect to OAG by 0.4%, and decreased the hazard of requiring medications for OAG by 0.4%.⁵⁰ Talwar and colleagues found that among 25,420 commercially-insured patients with hyperlipidemia who were receiving statins, those who filled prescriptions continuously for 2 years had a 21% reduced risk of glaucoma compared with nonusers even after accounting for baseline low-density lipoprotein level, and that there was no significant difference in protective effect between daily dosage of statin (40mg vs. 80mg) or type of statin (atorvastatin, lovastatin, cerivastatin, rosuvastatin, fluvastatin, pravastatin, or simvastatin).⁴⁹ Kang and colleagues showed that among 136,782 adults aged 40 years or older, 5 or more years of statin use was associated with a 21% lower risk of POAG and that 10 or more years of use was associated with a 40% lower risk of POAG compared with patients who never took statins.⁵² A prospective study demonstrated that statin use was correlated with stabilization of visual field findings over 3 years among patients with normal tension glaucoma.⁵⁴ Similarly, statin use has been found to curtail glaucomatous changes to the optic nerve and nerve fiber layer on confocal scanning laser ophthalmoscopy.⁵⁵

By contrast, a study from Taiwan reported high dose statins actually increased the risk of OAG,⁵⁶ and another found a modest association between statin use and IOP elevation,⁵⁷ and 3 others found no significant effect of statins on IOP or use of adjunctive IOP lowering therapies (**Table 2**).^{32,51,58} For example, in a retrospective review of health care claims data from Canada, Iskedjian and colleagues found no significant association between statin use and reduction of

adjunctive IOP-lowering therapies among 8,548 patients taking prostaglandin analogues for OAG.⁵⁸ Additionally, the European Prospective Investigation into Cancer-Norfolk Eye Study (EPIC-Norfolk Eye Study) reported that the observed associations between statin use and IOP reduction were no longer significant after adjustment for concomitant systemic beta-blocker use; the investigators hypothesized that IOP reduction among patients using both medications may have been driven predominantly by beta-blocker use and not use of statins.³²

There is an increasing prevalence of metabolic syndrome, a condition characterized by hyperlipidemia, systemic hypertension, obesity, and elevated fasting blood glucose.⁵⁹ Patients with this condition often require several different systemic medications to address each component of this syndrome. Since several of the underlying components of metabolic syndrome may themselves affect the risk of glaucoma, as may some of the medications used to treat these diseases, it can be challenging for researchers to sufficiently account for confounding, permitting one to isolate the beneficial or detrimental effects of some of these agents on the risk of OAG.⁶⁰ As such, while evidence in the literature supporting the notion that statins may reduce the risk of OAG or disease progression, a large prospective multicenter randomized controlled trial is needed to definitively answer the question regarding whether a causal relationship exists between statin use and reduction of OAG risk.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are used as first line agents in the treatment of depression and other psychiatric conditions, and there is also some suggestion that these medications may reduce the risk of OAG. A large retrospective analysis by Zheng and colleagues found that of all the various systemic drug classes they studied, SSRIs were most

strongly associated with a reduction in the need for laser or incisional glaucoma surgery among patients with underlying OAG.⁶¹ Their study found that SSRI users had a 30% reduced risk of POAG compared with non-users, an association that was independent of the underlying reason for taking these medications. Serotonin and norepinephrine reuptake inhibitors (SNRIs) were also associated with an approximately 30% reduced risk of POAG though less statistically significantly than SSRIs, and the reduction in risk was not seen at all with tricyclic antidepressants.⁶¹ Serotonin receptors are present in retinal ganglion cells, and some evidence suggests that they may directly modulate IOP.⁶² This may explain how these medications may reduce the risk of OAG or disease progression.

Other studies have found no association between SSRIs and OAG.^{40,63} A large retrospective study by Stein and coworkers using health care claims data examined several classes of antidepressants and found no association between SSRI use and OAG.⁶³ Such discrepancies can potentially be explained by differences in study design, given that the former was focused specifically on POAG while the latter considered all forms of OAG; additionally, Zheng's study used receipt of laser or incisional glaucoma surgery to qualify a patient as experiencing disease progression which may have resulted in exclusion of cases of progression that were managed medically. The possibility that the findings from the study by Zheng's group were borne out of chance alone seems unlikely, as Zheng's group also found a significant dose-response relationship between SSRI use and glaucoma risk such that greater use of these medications resulted in greater risk reduction. Furthermore, the argument that prescribers may be avoiding SSRI use among patients with underlying glaucoma due to concern for inducing acute angle closure crisis (AACCC) (from mydriasis-induced pupillary block due to weak anticholinergic effects) would not be consistent with this dose-response finding. In light of these

discordant findings, further work is needed to better understand the relationship between SSRIs and glaucoma.

Bupropion

Bupropion is an antidepressant that functions by selectively inhibiting dopamine and noradrenaline re-uptake. A few studies have connected bupropion use with a reduced risk of OAG. A retrospective review of health care claims data for a large managed care network showed that among patients ≥ 35 years old with newly-diagnosed OAG, each additional month of bupropion use was associated with a 0.6% reduction in risk of developing OAG compared to non-use, and the association did not differ among patients taking the medication for depression or for other purposes like smoking cessation.⁶³ A large cross-sectional study using self-reported survey data found that patients who reported bupropion use for more than 1 year had approximately 90% decreased odds of self-reporting a diagnosis of glaucoma compared with those not using bupropion or using it for less than 1 year duration.⁶⁴ Zheng and colleagues found that bupropion use was associated with a reduced risk of POAG in their retrospective review of claims data, although this fell short of statistical significance after taking into account the large number of prescription drugs they evaluated.⁶¹

Tumor Necrosis Factor (TNF) is a known mediator of retinal ganglion cell death in glaucoma; studies have shown that bupropion lowers the level of TNF- α .⁶⁵ Anti-TNF drugs have been shown to be neuroprotective in animal models; etanercept is a TNF- α antagonist that has been found in rat models to inhibit the inflammatory response mediated by microglial cells, preventing axonal degeneration and subsequent loss of retinal ganglion cells.⁶⁶ Additional basic science and clinical studies would be useful to substantiate whether bupropion or other

medications that inhibit TNF- α may play a role in reducing the risk of OAG or disease progression.

Postmenopausal hormones

There is evidence that sex hormones may play a role in glaucoma pathogenesis. Endogenous estrogen has been found in population-based studies to be protective against OAG; several other studies have found that postmenopausal hormones (PMH), which usually consist of oral preparations containing estrogen, estrogen and progesterone, or estrogen along with an androgen, can decrease IOP or OAG risk (**Tables 3a and 3b**).⁶⁷⁻⁸³ Estrogen receptors are present in RGCs; estrogen activity at these receptors has been found to decrease IOP and provide a protective effect on RGCs in a rat model of retinal ischemia.⁸⁴

Studies have quantified lifetime estrogen exposure (which can be affected by age of menarche, age of menopause, oral contraceptive use, and history of oophorectomy) and assessed whether such exposure affected the risk of OAG. In the Rotterdam Study, a study monitoring more than 3000 women for ocular diseases, those who went through menopause before 45 years of age had a higher OAG risk compared to the reference group who went through menopause at an older age.⁶⁸ The Blue Mountains Eye Study examined 2072 women ages 49-97 years and found significantly increased OAG risk with later (>13 years old) compared with earlier (\leq 12 years old) age of menarche. This study also found an increased risk of OAG associated with increasing parity, though timing of menopause had no significant association with OAG risk.⁶⁷ Data from the Nurses' Health Study spanning 1980 to 2002 found that among the 66417 women prospectively studied, late menopause (entering menopause at age \geq 54 years vs. age 50-54) was associated with reduced risk of POAG, and that use of estrogen with progestin was associated

with a reduced risk of POAG.⁷⁵ Newman-Casey and colleagues conducted a retrospective longitudinal cohort analysis of >150000 enrollees in a U.S. managed-care plan and found that among women aged ≥ 50 years old, each additional month of taking PMH preparations containing estrogen was associated with a 0.4% reduced risk for POAG after adjustment for confounding factors.⁶⁹ Using data from the Women's Health Initiative, a post-hoc analysis found that postmenopausal women aged ≥ 65 years old with a history of hysterectomy who were randomized to receive estrogen-alone treatment had significantly lower IOP than women randomized to receive placebo 5 years after initiation of estrogen treatment, while treatment with estrogen plus progestin had no effect on IOP.⁷³ This study was the first and largest using data from a randomized, double-masked, placebo-controlled trial to find a significant effect of estrogen treatment on IOP, an important risk factor for OAG.

Cannabinoids

Cannabinoids are a class of drugs that act on cannabinoid receptors and alter neurotransmitter release in the central nervous system; cannabinoid type-1 receptors have been found in the ciliary epithelium, trabecular meshwork, and Schlemm's canal.⁸⁵ A number of case reports and in vitro studies have found that cannabinoids can effectively lower IOP.^{86,87} Immunofluorescence studies show that cannabinoids bind to receptors in rat, bovine, and human ciliary epithelial and trabecular meshwork cells, suggesting that cannabinoids may be involved in increasing aqueous humor outflow or by reducing aqueous production.⁸⁸ However, substantial and frequent doses of cannabinoids are required to achieve sustained IOP reduction, and this can predispose patients to cardiovascular and neurologic adverse effects.⁸⁷ Given their short duration of action and multiple psychotropic and cardiovascular adverse effects along with a lack of

evidence supporting an effect on altering the disease course of glaucoma, cannabinoids are generally not recommended for use in glaucoma treatment, and multiple professional societies including the American Academy of Ophthalmology, the American Glaucoma Society, and the Canadian Ophthalmological Society have put forth statements recommending against the use of cannabinoids for management of glaucoma.^{89,90} In an age of increased marijuana legalization, eye care professionals should be cognizant of the limited effectiveness of cannabinoids as a treatment for glaucoma as well as the adverse effects of these agents. More research is needed to try to identify novel ways to administer cannabinoids to attain the beneficial IOP-lowering effects with fewer adverse effects, or to develop novel compounds that effectively lower IOP for lengthier periods of time.

Calcium Channel Blockers

Calcium channel blockers oppose the action of calcium channels located on vascular smooth muscle, myocardium, and adrenal cortex cells, leading to decreased heart rate and decreased systemic blood pressure. Contradictory findings have been reported with respect to calcium channel blocker use, IOP, and risk of OAG. Some studies have suggested that calcium channel blockers can increase optic nerve head and choroidal blood flow, and potentially retard visual field deterioration in patients with OAG.⁹¹⁻⁹⁴ In vitro studies suggest that calcium channel blockade reduces extracellular matrix gene response in lamina cribosa cells induced by mechanical strain.⁹⁵ Others have proposed that venous dilation by calcium channel blockers can increase perfusion to the optic nerve head.^{91,96}

However, other studies have found that calcium channel blocker use is actually associated with increased risk of OAG.^{34,40,61} Zheng and colleagues found that patients who

underwent filtration surgery for POAG were 26% more likely to have had calcium channel blocker exposure within the previous 5 years compared to matched controls with no record of POAG who underwent cataract surgery. These investigators found that this effect was primarily driven by amlodipine, which was the most commonly prescribed calcium channel blocker in their study.⁶¹ The same associations were not found in other classes of antihypertensives; there was no significant association between angiotensin-converting-enzyme (ACE) inhibitors and POAG despite it being the most commonly prescribed antihypertensive drug in the study.⁶¹ In a large prospective population-based cohort study, Muskens and coworkers found a 1.8-fold higher risk of developing OAG among patients exposed to calcium channel blockers, compared with those without exposure to calcium channel blockers.³⁴ In a separate study using two large administrative health care claims databases, Wang and colleagues also found an association between calcium channel blockers and OAG progression, defined as undergoing filtration surgery.⁴⁰ Notably, Wang and coworkers analyzed multiple drugs including angiotensin-II receptor blockers, metformin, SSRIs, fibric-acid derivatives, and calcium channel blockers, with only calcium channel blockers being found to have a significant association with OAG progression.⁴⁰

Calcium channel blockers are generally not first or second line treatments for hypertension. As such, they may be more often used in patients with refractory hypertension,⁹⁷ which is itself a known risk factor for OAG. Unfortunately, retrospective studies such as those cited above, are limited in their ability to control for and quantify duration and severity of comorbidities such as hypertension that may, in and of themselves, affect the risk of OAG. A prospective randomized controlled trial would help better elucidate whether calcium channel blockers adversely affect the risk of developing OAG.

SYSTEMIC MEDICATIONS KNOWN TO INCREASE THE RISK OF ANGLE CLOSURE GLAUCOMA

Sulfonamides

Sulfonamide-induced angle closure glaucoma was first described in 1962; since that time, a variety of sulfa-containing and sulfa-derived drugs including antibiotics (sulfamethoxazole, flucloxacillin), diuretics (hydrochlorothiazide, chlorthalidone, indapamide, furosemide), anti-inflammatory agents (sulfasalazine), and anti-epileptics (topiramate, zonisamide) have been reported to precipitate AACC.⁹⁸⁻¹¹⁶ One proposed mechanism for sulfonamide-induced angle closure is that an osmotic disturbance within the crystalline lens leads to hydration of the lens and subsequent thickening with anterior displacement of the lens-iris diaphragm.¹¹⁷ Another proposed pathophysiological mechanism is that sulfonamides can induce ciliary body edema with subsequent supraciliary effusion, which causes forward rotation of the ciliary body and mechanical angle closure.¹¹⁸

Topiramate is a sulfamate-substituted monosaccharide antiseizure medication that is also used to treat neuropathic pain, depression, and migraine. More than 128 cases of AACC associated with topiramate use have been reported in the literature. Topiramate-induced angle closure glaucoma typically presents bilaterally.¹¹⁹ In one large case-control study, the risk of angle closure from topiramate use was 5 times higher among patients younger than 50 years of age.¹¹⁹ Topiramate is thought to cause angle closure primarily by precipitating supraciliary effusions rather than by inducing increased lens thickness; ultrasound biomicroscopy of eyes with topiramate-induced angle closure show only minimal contribution to anterior chamber

narrowing from increased lens thickness.¹¹⁸ Blurred vision is the most common presenting symptom, and patients typically present with symptoms within the first 2 weeks of initiating use, although a small percentage of patients have been found to develop increased IOP within hours of doubling the dose of topiramate.¹²⁰ Myopia up to 8.75 diopters can be induced, and can take weeks to resolve after discontinuation of the medication.¹²⁰ Supraciliary effusions can be confirmed on ultrasonography; high-frequency ultrasound can be used to evaluate for forward rotation of the ciliary processes and angle closure in ambiguous cases.

Acetazolamide and methazolamide have been implicated in cases of AACC.^{109,110,112,113,121} Both drugs are sulfonamide-derived carbonic anhydrase inhibitors, commonly used as diuretics and in the treatment of intracranial hypertension and to abruptly lower IOP in cases of acute glaucoma. Methazolamide is metabolized by the liver while acetazolamide is renally excreted; the former has a longer half-life and decreased risk of metabolic acidosis. Sulfonamide-induced angle closure has not been reported with use of topical carbonic anhydrase inhibitors.

IOP usually quickly normalizes with discontinuation of the offending agent. Additionally, topical IOP-lowering agents can be used in the acute phase. Although oral acetazolamide is generally used in the acute setting to treat elevated IOP, in the case of sulfonamide-induced angle closure, it should be avoided given potential cross-reactivity and exacerbation of the underlying process. Additionally, topical miotic agents such as pilocarpine can lead to further anteriorization of the lens-iris diaphragm and should be avoided in these cases.¹²⁰ Uveal effusions from sulfonamides are thought to have an underlying inflammatory mechanism; thus, anti-inflammatory treatment with oral or intravenous corticosteroids can be effective. Laser iridotomy is not helpful as the angle closure is not precipitated by pupillary block. In cases refractory to

medical therapy, ciliochoroidal effusion drainage has been reported to successfully restore anterior chamber depth and normalize IOP.¹²² Infrequently, lensectomy, pars plana vitrectomy, or incisional glaucoma surgery may be required.

Anticholinergics

Anticholinergic mydriasis occurs through blockade of parasympathetic muscarinic acetylcholine receptors on the iris sphincter muscle, and can lead to pupillary block in susceptible eyes. Commonly used topical cycloplegics such as tropicamide and scopolamine can directly precipitate angle closure in individuals with narrow angles; these patients may safely undergo cycloplegia after being treated with laser iridotomy.^{123,124} In a large cross-sectional population-based survey, Patel and colleagues identified presence of a shallow anterior chamber on penlight examination, history of glaucoma, and blindness as three screening criteria that if used appropriately, rendered the risk of dilating a potentially occludable angle less than 1 in 333.¹²³

Oral and intravenous anticholinergic therapy have been reported to cause AACC in rare cases. Oxybutynin, an inhibitor of muscarinic receptors on detrusor smooth muscle fibers in the bladder used to treat urinary urge incontinence, has been reported in rare case reports to cause AACC.^{125,126} Over-the-counter herbal remedies may contain substances with anticholinergic properties such as belladonna, which has been reported to cause bilateral angle closure.¹²⁷ Iatrogenic angle closure from commonly used anticholinergic anesthetic or adjunctive anesthetic agents (muscle relaxants, atropine, and scopolamine) has also been reported.¹²⁸⁻¹³⁰

Inhaled anticholinergics used to treat pulmonary disease such as tiotropium and ipratropium have been reported rarely to precipitate AACC.¹³¹⁻¹³³ These cases can result from

both systemic absorption of the medication and inadvertent topical ophthalmic absorption through conjunctival and corneal exposure, which can occur with ill-fitting face masks; such cases can present unilaterally. Knowledge of this potential adverse effect and avoidance of directing nebulizers and inhalers toward the eyes can reduce the risk of AACC from these medications.

Botulinum toxin causes transient muscle paresis by inhibiting the release of acetylcholine at the skeletal muscle neuromuscular junction, and can cause pupillary dilation when injected near the eye. Botulinum toxin has been reported to cause AACC when injected in the periorcular region to treat blepharospasm or for cosmetic purposes.^{134,135} Patients electing to undergo botulinum injections should be counseled to seek care if they develop any of the typical symptoms characteristic of AACC such as nausea, blurred vision, headache, ocular pain, or mydriasis, which may last several weeks following injection.¹³⁵ At-risk patients should be evaluated by gonioscopy and undergo laser iridotomy if indicated for prophylaxis prior to receiving botulinum injections.

Antidepressants and other drugs altering serotonin, dopamine, and norepinephrine metabolism

SSRIs, SNRIs, tricyclic antidepressants, and other drugs involved in serotonin, dopamine, and norepinephrine metabolism have been reported in case reports to rarely trigger AACC after short or long-term exposure, though precise mechanisms are unclear.^{114,136-145} One proposed pathophysiological mechanism is that antidepressant drugs can act as weak cholinergic agents to cause angle closure through mydriasis and pupillary block; additionally, pupil dilatation mediated by 5-HT (5-hydroxytryptamine, serotonin) receptors and norepinephrine receptors can

result from increased levels of serotonin and norepinephrine caused by SSRI or SNRI use.⁶²

Other reports have found uveal effusions to be present in patients presenting with AACC from SSRI and SNRI use, and propose a mechanism similar to that of topiramate.^{138,141,143} Murphy and colleagues reported probable associations between bilateral AACC and multiple drugs involved in serotonin, dopamine, and norepinephrine metabolism, including escitalopram (SSRI), venlafaxine (SNRI), bupropion (norepinephrine and dopamine-reuptake inhibitor), cabergoline (dopamine receptor agonist), and ecstasy (releasing agent of serotonin, norepinephrine, and dopamine).¹¹⁴ Serotonin receptors are present in the ciliary body and choroid; alteration of serotonin metabolism from drug exposure is one proposed mechanism by which these medications may promote uveal effusion and bilateral AACC.^{143,146-148} Dopamine receptors are similarly present in the ciliary body; higher levels of dopamine in aqueous humor may increase binding with adenylyate cyclase-linked dopamine receptors in the ciliary body to alter fluid movement and potentially precipitate ciliochoroidal effusions.¹⁴⁹

Several antidepressants have been implicated in cases of AACC. Documented associations with AACC have been reported for amitriptyline,¹⁵⁰ imipramine,¹⁴⁵ venlafaxine,¹⁴²⁻¹⁴⁴ duloxetine,¹⁵¹ sertraline,¹⁵² paroxetine,¹³⁹⁻¹⁴¹ fluoxetine,¹⁵³ fluoxamine,¹⁵⁴ citalopram,^{136,137} and escitalopram.^{138,145} In a large population-based study using administrative data from an elderly Canadian population, Seitz and colleagues found that recent exposure to antidepressants was associated with increased risk of AACC; among this population there was a 62% increased odds for any antidepressant exposure in a 30-day period immediately preceding AACC.¹⁵⁵ The risk of AACC from SSRI use among a population with narrow iridocorneal angles appears to be even greater; in a large retrospective review of an ethnic Chinese population in Taiwan, Chen and colleagues found that patients taking SSRIs had nearly a 6 fold increase in risk of developing

AACC compared to non-users.¹⁵⁶ Additionally, Chen's group found that this risk of angle closure increased to more than 8 fold greater than nonusers among patients who were administered an average of >20 mg of SSRIs per day, suggesting a dose-dependent response. Given the overall safety profile and widespread use of SSRIs as first-line antidepressant therapy, primary care providers and mental health professionals who routinely prescribe these agents should alert patients about the risk of AACC and the need to seek eye care if AACC symptoms arise after initiating treatment.

Adrenergics

Adrenergic mydriasis occurs from overstimulation of the alpha-1-receptors of the iris dilator muscle, leading to sustained contraction, which can, in turn, lead to pupillary block in individuals with narrow angles. Reports of angle closure with use of oral, inhaled, and intranasal alpha adrenergic medications exist in the literature, including with the use of over-the-counter decongestants and commonly used anesthetic agents.^{130,132,133,157-160} Prone surgical positioning, use of analgesics, and use of anesthetic agents such as ephedrine are potential risk factors for AACC and delayed diagnosis of the condition.¹⁶⁰

Cholinergics

Pilocarpine is a cholinergic parasympathomimetic agent that acts through direct stimulation of muscarinic receptors and smooth muscle such as the iris and secretory glands. Pilocarpine is typically used to treat narrow angles by reducing iris thickness and iris-root pull to counteract forward displacement of the iris-lens diaphragm from ciliary muscle contraction. However, paradoxical acute angle closure following use of pilocarpine has been reported in

patients with spherophakia, zonular weakness from exfoliation syndrome, phacomorphic glaucoma, and as well as in patients without any of these conditions.¹⁶¹

Anticoagulants

Elderly patients taking anticoagulant and/or antiplatelet agents such as coumadin, heparin, and clopidogrel can, in rare cases, develop AACC from spontaneous suprachoroidal hemorrhage.¹⁶²⁻¹⁶⁶ Abrupt forward displacement of the lens-iris diaphragm resulting from a massively detached choroid and retina is the proposed mechanism for causing these cases of AACC.¹⁶⁴ Increased age, systemic hypertension, atherosclerosis, age-related macular degeneration, nanophthalmos, prior vitrectomy, and chronic kidney diseases are risk factors in addition to iatrogenic anticoagulation.^{163,165,166} In patients with age-related macular degeneration, a disciform macular lesion tends to be the source of hemorrhagic retinal or choroidal detachment; however, spontaneous choroidal hemorrhage and AACC has been reported in patients on anticoagulation without a choroidal neovascular membrane as the source of the bleed.¹⁶⁵⁻¹⁶⁸

Topical aqueous suppressants and oral carbonic anhydrase inhibitors may be effective at lowering the IOP in these cases; however, treatment and prevention of recurrence may necessitate discontinuation of the anticoagulant if permitted by the patient's underlying medical condition.^{164,167} Evacuative sclerotomies may facilitate pain relief and IOP reduction, but they have not been found to improve visual and anatomic outcomes.¹⁶⁶

CONCLUSION

Polypharmacy, characterized by multiple medication use, has become increasingly prevalent among the elderly population.¹⁶⁹ Polypharmacy can be problematic given that it puts

patients at increased risk for adverse drug reactions. Case reports, case series, and population-based studies have identified multiple commonly used systemic medications that may modulate IOP and glaucoma risk; however, the full extent of their effects is not well appreciated. More research is needed to better understand the harms as well as the potential protective effects of taking these systemic medications with respect to risk of glaucoma and disease progression.

Basic science research has demonstrated that various commonly used systemic medications can affect optic nerve perfusion, retinal ganglion cell survival, and aqueous humor outflow facility, suggesting these medications may modulate risk for OAG or disease progression. Over the past decade, a number these drugs have been found in large retrospective population-based studies to potentially modulate the risk of OAG, including metformin, statins, beta blockers, calcium channel blockers, SSRIs, bupropion, and postmenopausal hormones, although discordant findings exist in the literature, highlighting the need for well-designed prospective randomized controlled trials to best examine the relationships between these systemic medications and risk for glaucoma.

Iatrogenic AACCC is uncommon but can present bilaterally and may lead to profound visual morbidity if not recognized and treated in a timely manner. Most attacks of pupillary block occur among individuals with narrow iridocorneal angles who are unaware they are at higher risk of AACCC. Prudent history taking in the primary care setting can identify individuals with risk factors for AACCC such as hyperopia, personal or family history of glaucoma, or Asian ethnicity. Patients with these risk factors should be considered for referral for ophthalmologic evaluation prior to initiation of drugs with potential to induce AACCC. Moreover, primary care physicians and healthcare professionals who routinely prescribe medications known to increase the risk of AACCC should be familiar with this condition and alert patients to seek emergent care

by an eye care professional if such symptoms develop soon after starting therapy with one of these medication classes. If recognized early, devastating visual consequences can be avoided by discontinuation of the offending agent and prompt reduction in IOP.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. Dr. Pasquale is a consultant for Bausch+Lomb, Eyenovia and Verily.

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