REVIEW ARTICLE

Drug-induced Acute Angle-closure Glaucoma: A Review

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Abstract

Aim: Our goal is to review current literature regarding drug-induced acute angle-closure glaucoma (AACG) and provide ophthalmologists and general practitioners with a thorough understanding of inciting medications and treatment pitfalls to be avoided.

Background: Drug-induced AACG is an ophthalmological emergency that ophthalmologists and general practitioners should be familiar with, given its potentially blinding consequences. Common anatomical risk factors for AACG include a shallow anterior chamber depth, short axial length, plateau iris configuration, thick lens, anteriorly positioned lens, and rarely, intraocular tumor. Demographic risk factors include female sex, Asian ethnicity, family history, and advanced age. In patients with predisposing factors, acute angle closure can be triggered by various classes of medications including adrenergic agonists, anticholinergics, cholinergics, sulfonamides, supplements, and serotonergic medications. Physicians prescribing such inciting medications should be aware of their potentially sight-threatening adverse effects and to inform patients of the warning symptoms. Patients typically present with elevated intraocular pressure (IOP), headache, nausea, blurry vision, and halos around lights.

Review results: There are two main mechanisms of drug-induced AACG, both with different treatment strategies. The first mechanism of drug-induced AACG is pupillary block and iridocorneal angle closure secondary to thickening of iris base with mydriasis. The second mechanism of drug-induced AACG is anterior displacement of the lens–iris diaphragm due to mass effect (e.g., blood, misdirected aqueous humor, and tumors), uveal effusion, or weakened zonules.

Conclusion: This paper reviews drug-induced AACG, high-risk anatomical features, underlying mechanisms, inciting medications, and options for treatment and prevention.

Clinical significance: With proper understanding of the underlying mechanism of drug-induced AACG, physicians can respond promptly to save their patients' vision by employing the correct treatment strategy.

Keywords: Acute angle-closure glaucoma, Acute angle-closure crisis, Adrenergic drugs, Drug-induced, Drug-induced acute angle-closure glaucoma, Iatrogenic, Paradoxical pilocarpine reaction, Pupillary block.

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Background

Drug-induced acute angle-closure glaucoma (AACG) is an ophthalmological emergency that can lead to blindness if not recognized and treated promptly and properly. The medications known to precipitate AACG include adrenergic agonists, anticholinergics, cholinergics, sulfonamides, supplements, and serotonergic medications. Patients typically present with elevated intraocular pressure (IOP), headache, nausea, blurry vision, and halos around lights. Each medication may induce angle closure through a different mechanism; as such, the treatment strategy may be different. It is important for ophthalmologists and general practitioners to avoid prescribing inciting medications to at-risk patients and utilize the appropriate treatment in the case of acute angle closure.

Glaucoma is categorized generally as either an open-angle glaucoma or AACG. Each category is further subdivided into related diagnoses. For example, diagnoses within AACG include primary angle-closure suspect, primary angle-closure, primary AACG, acute angle-closure crisis (AACC), chronic angle-closure, plateau iris syndrome (PIS), and secondary angle-closure variations.[1]

Acute angle-closure crisis occurs when there is a sudden blockage of the trabecular meshwork resulting in a rapid rise in IOP. Symptoms include elevated IOP, mid-dilated and sluggish pupil, corneal edema, congested conjunctival vasculature, and shallow anterior chamber. These symptoms are important to recognize quickly in an urgent care setting. Risk factors and mechanisms for AACG will be reviewed, followed by an in-depth discussion of each of the medication classes implicated in acute angle closure.

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Literature Review

Risk Factors for AACG

Common anatomical risk factors for AACG include a shallow anterior chamber depth, short axial length, plateau iris configuration, thick lens, anteriorly positioned lens, and rarely, intraocular tumor. With the use of ultrasound biomicroscopy (UBM) and optical coherence tomography, many other anatomical and dynamic factors have been discovered to predispose patients to AACG. Static anatomic factors that increased the risk of AACG include small anterior chamber width, thick peripheral iris, and a more curved iris. Dynamic factors include decreased iris volume loss with dilation and increased choroidal volume.[2] Demographic factors include female sex, Asian ethnicity, and advanced age.[3]

Clinical Presentation of AACG

Acute angle-closure glaucoma typically presents with subjective complaints of headache, nausea, vomiting, blurry vision, severe

ocular pain, and halos around lights. The patients' history may also be suggestive of inciting medications or recently entering a dimly lit environment. Upon examination, the physician may find elevated IOP, mid-dilated and sluggish pupil, corneal edema, congested conjunctival vasculature, and shallow anterior chamber.

Pathophysiology of AACG

Acute angle-closure glaucoma occurs when there is an obstruction of aqueous outflow through the trabecular meshwork, leading to increased IOP. The mechanism of AACG could be divided into the following four groups: pupillary block, crowded angle, anterior lens subluxation, and PIS.[4]

Pupillary block is the most common mechanism of AACG and occurs when the functional obstruction between the anterior and posterior chambers takes place at the pupillary segment of the iris and lens. Pupillary block is typically accompanied by the characteristic iris bombe, during which the iris bows forward due to the increased pressure in the posterior chamber.

Crowded angle occurs in patients with thicker iris tissue at the base, resulting in less space for the trabecular meshwork to drain. With mydriasis, the iris dilator muscles contract and the iris is pulled peripherally and crowded into the iridocorneal angle. This crowding of tissue can result in blockage of the trabecular meshwork; interestingly, pupillary block often occurs as the iris is returning to its undilated state after being dilated.

In anterior lens subluxation, the lens is displaced anteriorly which comes into contact with the iris or enters the anterior chamber. This can occur as a result of intrinsic laxity in the zonules that hold the lens in place. Conditions that contribute to zonular laxity can all contribute to this phenomenon, and these include pseudoexfoliation syndrome, Marfan syndrome, homocystinuria, Ehlers-Danlos syndrome, and Weill-Marchesani syndrome. Similar to pupillary block, the connection between the anterior and posterior chambers is obstructed, and aqueous humor is unable to drain through the trabecular meshwork.

Plateau iris syndrome is characterized by a flat iris, relatively normal anterior chamber depth, and a crowded angle. Plateau iris syndrome occurs due to an anatomical variation in which the peripheral iris base inserts more anteriorly on the ciliary body. This results in a narrower iridocorneal angle that is susceptible to obstruction during mydriasis. As a result, patients with PIS are still at risk of AACG even with a patent iridotomy.

Drug-induced AACG occurs by a variety of mechanisms—pupillary block with miosis, angle crowding with mydriasis, and disruption of the iridocorneal angle with ciliochoroidal effusion.

Deviations from the aforementioned list will be emphasized in each of the following sections.

Drugs Implicated in AACG and Treatments

Alpha-adrenergic Agonists

Alpha-adrenergic agonists are found in a wide variety of medications, including mydriatic agents, vasoconstrictors, and over-the-counter (OTC) flu remedies.[5–8] Mydriatic agents (e.g., phenylephrine eye drops) are often used by ophthalmologists and optometrists to dilate the pupil for routine fundus examinations.

Over-the-counter flu medications (e.g., Theraflu) often contain phenylephrine (α_1-agonist) for its use as a nasal decongestant (Table 1).[6] In addition to their vasoconstrictive and decongestant effects, α-1 agonists also cause mydriasis via contraction of the iris dilator muscles. In patients with anatomical risk factors, mydriasis may precipitate AACG via two mechanisms. First, mydriasis causes thickening at the base of the iris which may result in iridotrabecular adhesions and closure of the iridocorneal angle. Second, at mid-dilation the lens is brought in close proximity to the iris, which may result in pupillary block.[2]

Treatment for α-agonist-induced AACG includes acetazolamide, mannitol, topical timolol, topical pilocarpine, and Nd:YAG laser peripheral iridotomy (LPI).[6,7,9] The strategy for treatment is targeted toward relieving the pupillary block and decreasing the IOP. Laser peripheral iridotomy is an effective treatment option for managing AACG caused by pupillary block because it equalizes the pressure differential across the iris and flattens the iris.[2]

Beta$_2$-adrenergic Agonists

Beta$_2$-adrenergic agonists (e.g., albuterol and salbutamol) are most commonly used for the treatment of asthma because of their bronchodilatory effects. Salbutamol is often nebulized or aerosolized for optimal delivery through the respiratory tract. However, nebulized medications have been reported to inadvertently enter the unprotected eye and exert its effects.[10,11] When stimulated, β_2-receptors induce ciliary muscle relaxation, mydriasis, and increased aqueous humor production from ciliary epithelium. Despite the increase in aqueous humor production, salbutamol also increases uveoscleral outflow to an overall net effect of lowered IOP.[12] Ultimately, Coakes' work suggests that exposure to β_2-agonist alone will not cause an increase in IOP nor trigger AACG. However, there is a report of exposure to nebulized albuterol alone that triggered mydriasis and subsequent AACG.[10] This patient was successfully treated with Nd:YAG LPI, prednisolone acetate, brimonidine tartrate, and acetazolamide (Table 1).

Anticholinergic Agents

Anticholinergic medications have applications that span across nearly all specialties of medicine. Overall, drugs with anticholinergic properties cause mydriasis in the eye. Atropine and tropicamide are commonly used as mydriatic agents in ophthalmology and optometry. Benztropine and trihexyphenidyl are antiparkinsonian medications used to decrease dyskinetic and spastic movements. Glycopyrrolate is used to decrease airway secretions and reverse neuromuscular blockade (NMB) in combination with neostigmine. Ipratropium and tiotropium are useful in relieving bronchoconstriction in patients with asthma and chronic obstructive pulmonary disease. Oxybutynin and tolterodine are used by urologists to decrease bladder spasms in urge incontinence. Scopolamine is available for the treatment of motion sickness and postoperative nausea (Table 1). Each medication is described in further detail subsequently.

One of the most commonly used eye drops in the ophthalmology office are anticholinergic drops (e.g., atropine, tropicamide, and cyclopentolate) to induce mydriasis for fundus examination. The risk of AACG after using mydriatic agents in the clinical setting has been reported to be 3 in 10,000.[13] Anticholinergic mydriasis occurs by antagonism at the muscarinic receptors on the iris sphincter muscle. On the contrary, adrenergic mydriasis occurs by stimulation at the α_1-receptors on the iris dilator muscle. Although the targeted muscles are different between α-adrenergic agonists and anticholinergic agents, the end results of mydriasis, iridocorneal angle closure, and pupillary block are the same. Given their subtly different mechanisms, applying both adrenergic and anticholinergic agents to the eye results in a synergistic effect on pupillary dilation.[14]

Table 1: Drugs reported to induce acute angle closure glaucoma

Medication class	*Examples*	*Indications*	*Mechanism of angle closure*	*Ocular effects*
α_1-adrenergic agonists	Phenylephrine	Nasal decongestant, mydriatic, and vasopressor	Pupillary block	Mydriasis
	Ephedrine	Vasopressor		
β_2-adrenergic agonists	Albuterol and salbutamol	Bronchodilator	Pupillary block	Mydriasis and increased aqueous humor production
Anticholinergic agents	Atropine	Mydriatic, cycloplegic, and bradycardia treatment	Pupillary block	Mydriasis and cycloplegia
	Glycopyrrolate	Neuromuscular blockage reversal and decrease in airway secretions		
	Oxybutynin	Urge incontinence		
	Scopolamine	Antinausea		
	Botulinum toxin	Strabismus, blepharospasm, wrinkles, and headaches		
Antihistamines (anticholinergic side effects)	Cetirizine, loratadine	Allergy medication	Pupillary block	Mydriasis
Cholinergic agents	Pilocarpine	Pupillary block angle closure and dry mouth treatment	Anterior displacement of the lens–iris diaphragm	Miosis and anterior rotation of the lens–iris diaphragm
Sulfonamides	Topiramate	Seizure and migraine treatment	Anterior displacement of the lens–iris diaphragm	Choroidal effusion
	Acetazolamide	Antiglaucoma, altitude sickness, Meniere's disease treatment, and diuretic		
	Methyl-sulfonyl-methane (MSM) supplement	Detox supplements		
Serotonergic agents	Venlafaxine and escitalopram	Antidepressant	Pupillary block/anterior displacement of lens–iris diaphragm	Mydriasis and increased aqueous humor production, choroidal effusion
	Triptans	Migraine treatment	Pupillary block	Mydriasis, increased aqueous humor production
	Aripiprazole	Antipsychotic	Pupillary block	Mydriasis, increased aqueous humor production

Benztropine and trihexyphenidyl are used to quell the dyskinesia symptoms from antipsychotics' extrapyramidal side effects and Parkinson's disease. Trihexyphenidyl had a mydriatic effect that is one-third as potent as atropine.[15] In certain studies, investigators did not elicit an increase in IOP or trigger AACG with the use of benztropine and trihexyphenidyl.[16] However, there are case reports of prolonged use of trihexyphenidyl that has led to AACG.[15] These patients did not present with acute angle closure, but rather a chronic AACG that occurred after 1–2 years of continued use of trihexyphenidyl.

Glycopyrrolate is an antimuscarinic agent that is used for reduction of airway secretions and to block the muscarinic effects of neostigmine during NMB reversal. There is report of bilateral AACG 12 hours after glycopyrrolate use for NMB reversal after surgery.[17] The patient had undergone cervical spine surgery, requiring him to be in the prone position for 5 hours and 30 minutes. In conjunction with mydriasis and hyperopia, the gravitational effect of the prone position may have contributed to the IOP spike and AACG.

In the treatment of asthma, β_2-agonists are frequently combined with anticholinergics (e.g., ipratropium and tiotropium) for an additive effect in bronchodilation. As described earlier, there are differing reports in the literature regarding whether β_2-agonist alone will cause AACG or an increase in IOP.[10,12] However, there are numerous reports of AACG occurring in patients exposed to a combination of both nebulized ipratropium and salbutamol.[11,18] These two medications act synergistically to precipitate AACG—ipratropium causes pupillary dilation and salbutamol causes increase in aqueous humor production. Inadvertent exposure to the eye can be avoided with the use of goggles during nebulizer treatments.

Oxybutynin and tolterodine are anticholinergic medications that are commonly used in the treatment of overactive bladder and urge incontinence. These medications inhibit the M3 muscarinic receptors found on the detrusor smooth muscle.[19] In a prospective trial, investigators found no significant increase in IOP after 4 weeks of either oxybutynin or tolterodine use.[20] However, case reports of

unilateral and bilateral AACG after oxybutynin use have also been described[21,22] (Table 1).

Scopolamine is most commonly administered as a transdermal patch to treat motion sickness and postoperative nausea. Like many other anticholinergics, scopolamine causes mydriasis when exposed to the eye. There are reports of bilateral AACG after handling the scopolamine patch and then touching the eye or inserting contact lenses.[23]

Botulinum toxin, derived from *Clostridium botulinum* neurotoxins, inhibits muscle contraction by blocking the release of acetylcholine into the neuromuscular junction. Once a feared cause of food poisoning, botulinum toxin is now commonly used for a wide variety of ailments. Botulinum toxin is used to treat strabismus, blepharospasm, wrinkles, and even headaches.[24] In regard to its intraocular effects, botulinum toxin exerts its anticholinergic effects on the ciliary ganglion or directly on the iris sphincter muscle leading to mydriasis.[25] Several case reports have demonstrated botulinum toxin-induced AACG after injection for blepharospasm.[26,27]

Antihistamines are medications that target the H_1- and H_2-histamine receptors. H_1-receptor antihistamines (e.g., cetirizine and loratadine) are inverse agonists that act to reduce the symptoms of allergies and anaphylaxis. H_2-receptor antihistamines (e.g., ranitidine, cimetidine, and famotidine) are competitive antagonists that target the parietal cells in the stomach to relieve symptoms of dyspepsia and gastroesophageal reflux disease.[28] The H1 receptor is phylogenetically linked with muscarinic receptors, thus explaining the antimuscarinic effects seen with many antihistamines.[28] Antihistamines are found not only as solitary medications but also in flu remedy combinations (e.g., Theraflu). These medications have been reported to cause AACG by their anticholinergic effects of mydriasis and iridocorneal angle closure[6,9] (Table 1).

Anticholinergic-induced AACG has a similar mechanism of action to that triggered by adrenergic mydriasis—pupillary block and closure of the iridocorneal angle. For this reason, similar medical and surgical treatment strategies are effective in anticholinergic-induced AACG (e.g., Nd:YAG LPI, brimonidine tartrate, dorzolamide, timolol, pilocarpine, mannitol, and acetazolamide).

Cholinergic Agents

Cholinergic agents (e.g., pilocarpine, acetylcholine, and carbachol) act on smooth muscle muscarinic receptors and are used to constrict the pupil for intraocular surgery and glaucoma treatment. These medications cause miosis by stimulating the iris sphincter muscle, which pulls the iris away from the trabecular meshwork. Pilocarpine's effect of miosis can be useful in treating AACG caused by mydriasis, pupillary block, and closure of the iridocorneal angle.[29]

However, there are certain cases of AACG in which cholinergic agents may actually exacerbate the problem. Miotic agents (e.g., pilocarpine) can worsen pupillary block by increasing the contact between iris and lens. Cholinergic agents also cause contraction of the ciliary muscles, which leads to looser zonules, lens rounding, and forward displacement of the lens into the anterior chamber.[30] In topiramate-induced AACG, pilocarpine can stimulate further anterior displacement of the lens–iris diaphragm and worsen the iridocorneal angle obstruction[31,32] (Table 1).

The paradoxical adverse effect of pilocarpine is also seen in spherophakia, pseudoexfoliation syndrome, phacomorphic glaucoma, and malignant glaucoma.[33] In spherophakia, the lens is more spherical in shape with a larger anterior–posterior diameter and weaker zonules—leading to greater anterior lens–iris diaphragm movement.[34] In malignant glaucoma (aka ciliary block glaucoma), there is a misdirection of aqueous posteriorly which pushes the lens–iris diaphragm anteriorly. Overall, conditions that share this paradoxical pilocarpine reaction have common features of weakened zonules, enlarged lens, and anterior lens–iris diaphragm displacement.[33] Treatment is based on the underlying mechanism (e.g., lens exchange for spherophakia).[34]

Sulfonamides (Topiramate)

Sulfonamides are a class of medications defined by a particular sulfur-based functional group found in the drug's molecule. Sulfa drugs were initially used for their antifolic properties as an antibacterial agent. Since then, medicinal chemists have discovered a wide variety of clinical uses for the sulfonyl functional group including antidiuretics, anticonvulsants, diabetes medications, and many more.[35] With sulfa drugs permeating through every specialty of medicine, general physicians and ophthalmologists have the difficult task of remaining vigilant when scanning patients' medication lists for AACG triggers. Sulfa-based medications implicated in AACG include topiramate and less commonly acetazolamide, trimethoprim–sulfamethoxazole, zonisamide, chlorthalidone, and hydrochlorothiazide.[36–39]

Topiramate, commonly prescribed for seizures and migraines, is classically associated with AACG[32] (Table 1). Angle closure typically occurs within 2 weeks of starting topiramate, but reports have ranged between 1 days and 262 days.[31] The proposed mechanism is ciliary detachment and ciliary body edema, which causes relaxation of the zonules and thickening of the lens. As the lens enlarges, the lens–iris diaphragm is displaced anteriorly, and the anterior chamber becomes more shallow and increasingly susceptible to angle closure. These anatomical changes have been confirmed with ultrasonography and UBM.[40] It is important to emphasize that obstruction is not a result of pupillary block, but rather due to anterior rotation of the lens–iris diaphragm resulting in a closed angle.

Treatment for topiramate-induced AACG is immediate discontinuation of medication, cycloplegia, topical corticosteroids, and mannitol.[41] By paralyzing and relaxing the ciliary body, the tension on the zonules is increased and the lens–iris diaphragm is pulled posteriorly.[36] Ultimately, this increases the ciliary body diameter, deepens the anterior chamber, and allows the angle to reopen for aqueous drainage. Notably, the mechanism of topiramate-induced AACG does not involve pupillary block—therefore, peripheral iridectomy and cholinergic agents (e.g., pilocarpine) will not ameliorate angle closure. In addition, cholinergic agents may actually worsen the angle closure by inducing further anterior rotation of the lens–iris diaphragm and exacerbate preexisting intraocular inflammation.[31,32] It is important to note that in clinical encounters, a history of topiramate use may not be elicited or reliable, and that LPI should be performed when topical medications fail to break the angle closure. In other words, the pupillary block mechanism should always be ruled out first by performing LPI.

Serotonergic Medications

Serotonin [5-hydroxytryptamine (5-HT)] receptors are found throughout the central nervous system, blood vessels, gastrointestinal tract, and the eye. Serotonergic medications are used to treat depression, obsessive compulsive disorder, and many other psychiatric disorders. Common serotonergic drug classes include selective serotonergic reuptake inhibitors (SSRI), serotonin

and norepinephrine reuptake inhibitors (SNRI), monoamine oxidase inhibitors, tricyclic antidepressants, and triptans. 5-HT_{1A} and 5-HT_7 receptors are found on the ciliary body, choroid, trabecular meshwork, and iris sphincter muscle.[42] Stimulation of the 5-HT_7 receptors causes relaxation of the iris sphincter muscles, mydriasis, and increased production of aqueous humor. In addition to 5-HT receptor activity, SNRIs also affect adrenergic and dopaminergic receptors—causing mydriasis and increased aqueous humor production, respectively[42] (Table 1).

In a large study conducted in Taiwan, researchers found a 5.80-fold increase in risk of AACG in patients taking SSRIs daily.[43] They found that patients who were older, female, and taking a daily SSRI dose greater than 20 mg were also at increased risk of AACG. Numerous reports of AACG occurring with SNRIs (e.g., venlafaxine and duloxetine) have been documented.[44,45] The mechanism of AACG in most SNRI-induced cases is attributed to mydriasis and closure of the iridocorneal angle—which resolves with peripheral iridotomy. Other medications with serotonergic properties (e.g., triptans and aripiprazole) have also been reported to cause AACG via this aforementioned mechanism.[46,47] However, like topiramate-induced AACG, not all serotonergic-induced AACG can be treated with pilocarpine and peripheral iridotomies. Selective serotonergic reuptake inhibitors and SNRIs (e.g., escitalopram and venlafaxine, respectively) have been reported to cause uveal effusions, which results in anterior rotation of the lens–iris diaphragm and obstruction of the iridocorneal angle.[48] In these cases, miotic agents and iridotomies are not effective—instead, offending drugs should be discontinued and patient should be treated with corticosteroids, topical aqueous suppressants, and cycloplegia.[36,48]

Supplements

Supplements have been used to complement or replace conventional medical treatments in many common illnesses. Glaucoma is no exception; supplements have been used with the intention of reducing IOP or improving ocular blood flow. Some studies have shown that flavonoids and gingko biloba extract improve ocular blood flow and forskolin significantly reduces IOP.[49,50] However, not all supplements are beneficial or even benign. Consuming supplemental oxidants (e.g., iron and calcium) above a certain threshold is associated with glaucoma.[51] Some studies have found high levels of caffeine consumption to be associated with increased IOP in susceptible patients.[52]

Methylsulfonylmethane (MSM) is a nutritional supplement that is commonly found in detox products (e.g., cortex and basic detox nutrients). Methylsulfonylmethane is used as an anti-inflammatory, antioxidative, and anti-histamine medication.[53] There is a report of AACG associated with MSM use as a detox supplement.[54] Methylsulfonylmethane has a sulfonyl moiety that is similar to that found on other sulfa-based drugs (e.g., topiramate and hydrochlorothiazide). Like topiramate-induced AACG, MSM-induced AACG is due to uveal effusion and anterior rotation of the lens–iris diaphragm[54] (Table 1). Similarly, treatment with peripheral iridotomy and miotic agents is likely to be ineffective and can worsen the situation.

Conclusion

Drug-induced AACG is a feared complication of prescribing certain medications to at-risk patients. The two major mechanisms of drug-induced angle closure are pupillary block with iridocorneal angle closure and anterior displacement of the lens–iris diaphragm. With proper understanding of the underlying mechanism of AACG, physicians can respond promptly to save their patients' vision by employing the correct treatment strategy.

Clinical Significance

Acute angle closure glaucoma is a significant cause of visual impairment worldwide, most prevalent in populations with high-risk features (e.g., narrow angles, hyperopia, and advanced age). Of the many causes of AACG, one iatrogenic reason is due to commonly prescribed medications (e.g., flu remedies, antihistamines, and supplements). It is crucial for general physicians and ophthalmologists to have a proper understanding of the underlying mechanism of angle closure, as pilocarpine (a common therapy for AACG) may paradoxically exacerbate certain types of drug-induced AACG. This review includes a variety of recent case reports, mechanism of drug-induced glaucoma, discussion of inciting medications, and strategies for treatment.

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