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# Common Side Effects With Glaucoma Medications

**Evan Michaelov, MD**

## Introduction

Glaucoma is a progressive optic neuropathy that affects more than 400 000 Canadians[1] and up to 111 million are expected to be afflicted with the disease worldwide by 2040.[2] Despite trends toward increasing utility of laser and surgical interventions for glaucoma treatment, topical medications remain a mainstay of treatment. These medications often comprise the initial treatment alongside selective laser trabeculoplasty (in open angle subtypes). Additionally, given the progressive nature of glaucoma, many patients who undergo laser or surgery treatments may eventually require the use of topical medications. Although glaucoma drops are generally accepted as safe and low risk for patients, each type carries its own side effect profiles and contraindications. No glaucoma drop is completely benign and can significantly affect patient wellbeing if not selected correctly. Therefore, it is important for ophthalmologists and eye care professionals, who will undoubtedly have numerous glaucoma patients in their care, to be aware of common side effects and contraindications associated with ocular anti-hypertensive agents. This article will outline the side effects and contraindications of the ocular anti-hypertensive agents currently available in Canada.

## Prostaglandins

Prostaglandin analogs (PGAs) are often the first choice for the initiation of glaucoma therapy, largely due to their convenient once-daily dosing, superior efficacy, and infrequent side effects.[1] Although the exact mechanism of action is unknown, PGAs are believed to increase uveoscleral outflow, thereby reducing intraocular pressure (IOP). This class of medications typically achieves an IOP lowering in the range of 25-33%.

Conjunctival hyperemia is a common side effect of topical PGAs, occurring in approximately 15% of patients using latanoprost and up to 40% of those using bimatoprost (0.03% concentration).[3] However, if there is no concurrent discomfort or alternative cause of hyperemia, conjunctival hyperemia alone may be acceptable to the patient. It is important for the eye care provider to assess and determine the cause of hyperemia.

PGAs also induce changes in iris pigmentation and lash growth. While these changes are cosmetic in nature, they can be of significance to patients and should be discussed prior to treatment. Iris pigmentation changes are particularly common in patients with hazel or green irides and are least common in those with blue irides.[4] Iris colour changes tend to be permanent, even after cessation of the PGA.

Chronic use of PGAs can result in prostaglandin-associated periorbitopathy, which is characterized by symptoms such as ptosis, deepening of the lid sulcus, mild enophthalmos, and periorbital fat atrophy. These changes usually resolve with cessation of the PGA.

PGAs are relatively contraindicated in patients with a known history of herpetic keratouveitis due to the risk of reactivation. Although there was a belief that PGAs could potentiate cystoid macular edema (CME) and should be avoided in patients at higher risk of CME, recent studies have refuted this claim.[5]

## Beta Blockers

Before the introduction of PGAs, beta adrenergic antagonists were the most commonly used topical medication for the treatment of glaucoma. These medications lower IOP by reducing aqueous production, generally achieving an IOP reduction in the range of 25-30%. They are generally prescribed to be taken twice daily but can usually be equally efficacious with once-daily dosing. When administered once-daily, they should be dosed in the morning as aqueous production is naturally lower over night, making the medication less efficacious during that time. Furthermore, morning dosing may reduce the incidence of nocturnal hypotension and may provide increased benefits for patients with normotensive glaucoma.[6] Most available beta blockers available for glaucoma are non-selective with the exception of betaxolol, which is β-1 selective, but less efficacious in reducing IOP. Patients taking systemic beta blockers may experience a reduced IOP-lowering effect. Additionally, beta blockers have been noted to have a tachyphylactic effect, where efficacy decreases with time due to the upregulation of the target receptor of the drug.

Beta blocker drops can cause blurring of vision and discomfort, however, they are usually well tolerated. Patients with myasthenia gravis may experience a worsening of their ocular symptoms when using beta blocker drops. Additionally, corneal anesthesia has been reported with the use of beta blockers which can lead to neurotrophic sequalae affecting the cornea. Beta blockers may also cause reduced exercise tolerance, decreased libido, and depression.

Contraindications: Most of the issues patients experience with beta blockers stem from their systemic effects. Beta blockers are contraindicated in those with obstructive lung diseases such as asthma and chronic obstructive pulmonary disease, as their systemic effects on the smooth muscle in the lung can cause severe bronchospasm. β-1 selective drops (betaxolol) may reduce the risk of these adverse effects, but they can still occur and should be used with caution. Patients with bradycardia or heart block should avoid this agent as it can lead to an exacerbation of their condition. Individuals with diabetes should be advised that these agents can mask symptoms of hypoglycemia, which can predispose them to hypoglycemic crises. Lastly, rapid withdrawal of the agent can trigger symptoms of hyperthyroidism.

## Carbonic Anhydrase Inhibitors

Carbonic Anhydrase inhibitors (CAIs) are available in both topical and oral forms. While the United States Food and Drug Administration (FDA) has approved topical administration for 3 times daily dosing, most physicians prescribe them twice daily. This class includes 2 medications: brinzolamide, introduced in 1998, and dorzolamide, introduced in 1995. Overall, this class of medications are slightly less potent than other topical medications, typically reducing IOP by approximately 15-20%.

Both classes of CAIs share similar side effect profiles when used as topical agents. These side effects include conjunctival injection, punctate keratopathy, blurring of vision, and pain on administration. Pain tends to be worse with dorzolamide, due to its low pH, while blurring of vision tends to be worse with brinzolamide, because it is a suspension. Topical CAIs should be avoided in patients with endothelial dysfunction, as carbonic anhydrase is an important component in endothelial pump function.[7] If using CAIs is necessary, patients should be frequently asked about any vision changes consistent with corneal edema, and pachymetry should be monitored.

## Systemic Carbonic Anhydrase Inhibitors

Oral CAIs are potent medications for reducing IOP, however, they carry more substantial systemic side effects. Available options include acetazolamide and methazolamide. Common side effects include alterations in taste, especially with carbonated beverages, paresthesia in the fingers and toes, and general malaise. Due to their side effects, these oral agents are usually reserved only for maintaining adequate IOP while awaiting surgery, or for patients who are not suitable candidates for surgical intervention. Dosing should be reduced to the lowest tolerated level that maintains an adequate IOP.

Both agents result in potassium excretion, thus, patients should be monitored for hypokalemia, especially if they are also taking other potassium-wasting medications such as thiazide diuretics. Health care providers will frequently recommend increasing the patient's potassium intake while taking these medications.

Rarely, patients may develop aplastic anemia. They should be advised to consult their primary care physician for blood work if they exhibit signs of such, including petechia and fever.

Patients with chronic kidney disease, or those on dialysis, will require adjusted dosing of CAIs. Patients with hepatic disease should avoid oral CAIs due to the risk of hepatic encephalopathy. Before starting these medications, patients should be screened for sickle cell disease, as these medications may induce a sickle cell crisis.

Allergic reactions from CAIs in those with sulfa allergies are rare and should generally be avoided only in patients with a documented history of anaphylaxis to sulfa drugs.[8] However, CAIs are a known risk for Steven-Johnson Syndrome/Toxic epidermal necrolysis spectrum.

Finally, patients taking CAIs are at risk of developing nephrolithiasis. They should be advised to hydrate adequately to reduce this risk.

## Alpha-Agonists

Alpha-Adrenergic agonists were previously available in both non-selective forms (epinephrine, dipivefrin), and alpha-2 selective forms (brimonidine, apraclonidine). the non-selective forms are no longer in use due to their significant side effect profiles. Alpha-2 selective agonists (α2A) can lower IOP by approximately 20-30% and are typically dosed either three times daily, or more frequently, twice daily. These α2A agents cause conjunctival vasoconstriction, and low concentration forms have been used for reducing vascularity for cosmesis or certain conjunctival-based procedures.[9]

The most common adverse effect of α2A agents is ocular allergy, which usually manifests as a follicular response and/or blepharodermatitis. Among topical glaucoma drops in this class, allergy rates are amongst the highest, with brimonidine causing allergic reactions in approximately 15% of patients after 1 year of use, and the incidence rates increase with continued usage.[10] Apraclonidine has higher allergy rates than brimonidine and is primarily used only in the prophylactic setting during laser procedures. Although alternative formulations with purite preservatives reduce these allergy rates, they remain elevated compared to other topical options.

Common adverse effects of α2A agents include dry mouth, lid retraction, and somnolence. Additionally, apraclonodine may cause mydriasis, whereas brimonidine may cause miosis.

Rarely, brimonidine treatment can cause granulomatous anterior uveitis. This reaction need-not occur immediately after starting the topical agent. It is important to consider discontinuing brimonidine use in glaucoma patients who present with new anterior uveitis.[11]

Alpha agonists are strictly contraindicated in children under the age of 2, as they may cause respiratory distress, hypotension, and central nervous system depression. Even in children older than 2 years, these medications should still be used with caution. Brimonidine is the only topical glaucoma drop that was previously classified under FDA category B for pregnancy, indicating it is presumed safe based on animal studies. It is considered the first-line treatment for pregnant patients. Patients taking tricyclic antidepressants and monoamine oxidase inhibitors should avoid α2A agents due to the risk of systemic hypotension, although this risk appears to be mostly theoretical.

## Miotics

Miotics, once widely used for treating glaucoma for over 100 years, are now rarely used. The most common miotic is pilocarpine, a direct cholinergic agonist. Due to its numerous adverse effects and the need for frequent dosing (three to four times daily), its use has been relegated to niche scenarios including chronic angle closure status-post laser peripheral

iridotomy and aphakic glaucoma. IOP reduction with pilocarpine ranges from 15-25%.

Pilocarpine results in increased tension on the trabecular meshwork and associated structures and increased outflow due to contraction of the longitudinal ciliary muscle fibres. This action also causes anteriorization of the lens-iris diaphragm, which can lead to multiple consequences, including an increased risk of angle closure in phakic individuals (via increased pupil block), induced myopia, and head or brow aches due to ciliary muscle spasm. This effect may also account for the increased rates of retinal tears and detachments observed with pilocarpine use.[12] Therefore, patients should undergo a peripheral retinal exam prior to starting this medication.

Pilocarpine has also been shown to be cataractogenic, and its miotic effects can impact night vision and increase the risk of posterior synechiae formation. Additionally, pilocarpine can compromise the blood-aqueous barrier, making it unadvisable for use in uveitic glaucoma.

Systemically, pilocarpine use can result in increased cholinergic activity, which can include symptoms such as salivation, lacrimation, and abdominal pain.

## Other Considerations of Topical Therapy

Despite the unique side effect profiles of each topical class, all drops are capable of irritation and discomfort for patients. The ongoing burden of using drops and the chronic nature of glaucoma treatment can be disconcerting for patients. In addition, physical constraints, which are common among a large population of glaucoma patients, can make the physical use of drops difficult, and can lead to poor adherence with treatment. Given these concerns, it is no surprise that glaucoma patients often prioritize freedom from, or reduction of, the use of drops.[13] As such, every effort should be made to reduce the use of drops. The LiGHT trial has demonstrated the efficacy of selective laser trabeculoplasty in both primary treatment and treatment escalation, and it should be used as appropriate.[14] When escalating medical treatment, it is important to have a good understanding of the available fixed combination drops to limit overall drop burden. Ideally, patients should be able to achieve maximum medical therapy with only two drops.

When glaucoma patients taking topical agents are ready for cataract surgery, it is important to consider planning additional minimally invasive glaucoma surgery. This approach can help minimize the drop burden and provide a greater buffer before considering more invasive filtering surgery.

When patients experience multiple drop intolerances, efforts should be made to offer preservative-free or alternative drops. Otherwise, optimizing the ocular surface using the standard dry eye management algorithm can sometimes improve tolerance.

Lastly, patients who are new to drops should be instructed on proper drop use techniques. Instruction on punctal occlusion may help prevent systemic absorption.

In conclusion, although topical medications are vital for glaucoma management, their use is not benign. It is important for eye care professionals to have an expert understanding of the available options and their adverse effects to ensure optimal patient care.

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## Financial Disclosures

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