

Review

The impact of topical intraocular pressure lowering medications on the ocular surface of glaucoma patients: A review

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Abstract

Purpose: To assess the literature on the effects of topical intraocular pressure (IOP)-lowering medications on the ocular surface. Ocular surface assessment in these patients is seldom a priority for most clinicians since the ultimate goal of management is to preserve vision.

Methods: A literature search of articles (English only) on the subject matter was conducted and their findings summarized.

Results: This review assesses the prevalence of dry eye symptoms in glaucoma patients on topical IOP-lowering medications. We extensively reviewed the effects of the preservatives and active ingredients in these medications on the ocular surface. In particular, the effects of benzalkonium chloride (BAK), a widely used preservative, on meibomian glands are explored. Also mentioned in this review is the association between duration of therapy and severity of dry eye symptoms. The role of the pH of medications in the development of ocular surface disease is also reviewed. Finally, we probed the occurrences of ocular allergic reactions with the use of topical IOP-lowering medications.

Conclusions: The preservatives and active agents in most topical glaucoma medications are implicated in the prevalence of ocular surface discomfort. Whilst clinicians involved in glaucoma care are encouraged to assess the ocular surface routinely, further studies are needed to demonstrate the contributions of other physiochemical properties of these medications to the development of ocular surface disease in these patients.

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Keywords: Glaucoma; Dry eye; Meibomian glands; Topical anti-glaucoma medications; Benzalkonium chloride; Ocular surface

Introduction

Glaucoma is a progressive optic neuropathy that is not all the time but frequently associated with raised intraocular pressure (IOP). The most widely prescribed therapy for patients with glaucoma is pharmacological management with topical IOP-lowering medications.^{1–3} Studies have shown that topical IOP-lowering medications are the mainstay of treatment in countries^{4,5} with a higher prevalence of glaucoma. Beta-blockers and prostaglandin analogs (PGAs) are

preferably the first-line medications.^{1,2} Some glaucoma patients administer multiple topical medications for an effective IOP control.^{1,3} The practice of polypharmacy and frequent dosing increase patients' exposure to higher doses of preservatives.¹ Deleterious effects on the conjunctiva, cornea, and trabecular meshwork can occur subsequent to long-term exposure to the preservatives in the formulation of topical IOP-lowering medications.^{6,7} Furthermore, the contribution of the active pharmaceutical agents to these deleterious effects on the ocular surface cannot be understated. Although, there have been a couple of observational dry eye studies^{7–11} in patients with glaucoma, virtually all of them demonstrated a higher prevalence of dry eye symptoms and signs among glaucoma patients compared to the general population. From the

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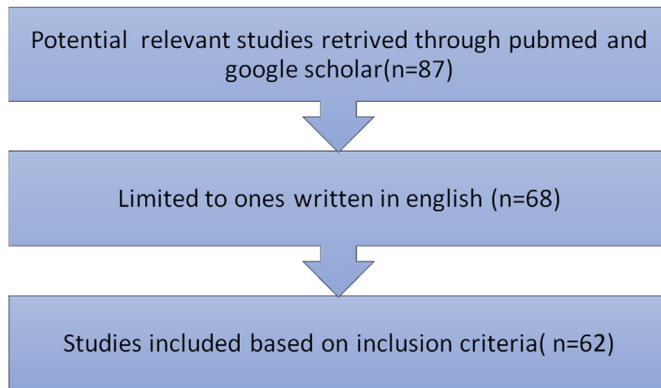


Fig. 1. Flowchart showing how publications were included in the study.

published literature, it is evident that patients with glaucoma exhibit a predictable and progressive ocular surface disease (OSD), the incidence and severity of which is unfortunately underestimated.^{1,11} Many a time in challenging cases, clinicians make glaucoma treatment decisions without recourse to the subsequent effects on the ocular surface, perhaps due to the emphasis placed on vision preservation. There is evidence suggesting that OSDs can terribly affect patients' quality of life.¹ Second and more importantly, OSD may interfere with therapeutic compliance and possible surgical outcomes thereby influencing overall glaucoma prognosis.¹ Glaucoma management can be enhanced by obtaining a comprehensive knowledge of OSD in glaucoma patients and by instituting a few simple diagnostic tests in clinical practice.¹ The purpose of this review is to present the prevalence of dry eye symptoms in glaucoma patients using topical IOP-lowering medications, the occurrence of meibomian gland dysfunction in these patients, the impact of IOP-lowering medications on the clinical signs of dry eye, impact of preservatives and active pharmaceutical agents on the ocular surface, and incidence of allergic reactions with topical IOP-lowering medication.

Methods

A PubMed and Google scholar search was performed using the following search terms: topical anti-glaucoma medications" or "ocular surface" or "dry eye" or "meibomian gland dysfunction" or "effects of benzalkonium chloride" and "glaucoma" to retrieve English language articles published from January 1999 to April 2018. All article types were included. We meticulously reviewed the titles and abstracts of all retrieved papers to determine their eligibility for inclusion. Publications were included, if the study subjects were glaucoma patients and if they reported any effects of topical anti-glaucoma medications on the ocular surface. A total of 62 papers met the inclusion criteria, 7 of which were review articles and 55 original articles. The selection process is summarized in Fig. 1.

Results

Prevalence rates of dry eye symptoms among glaucoma patients on topical IOP-lowering medications in various regions

Several studies^{7–14} have attempted to document the frequency of dry eye symptoms among glaucoma patients and healthy controls (Table 1). The majority of these studies used the ocular surface disease index (OSDI) to document these dry eye symptoms thereby allowing comparison between studies. In Croatia, the prevalence of dry eye symptoms via the OSDI among glaucoma patients on topical IOP-lowering medications was 75%, whilst the prevalence among healthy controls was 30%.⁷ In Brazil, it is reported that the prevalence of dry eye symptoms via the OSDI in glaucoma patients (using a single topical anti-glaucoma medication) is approximately 62.7%.¹² In another study in the same country, the charts of 175 patients with glaucoma (on topical IOP-lowering

Table 1
Prevalence of dry eye symptoms in glaucoma patients in various regions of the world.

Authors	Number of subjects	Prevalence	Diagnostic cut off (OSDI)	Country
Barisic et al. (2014)	Glaucoma group: 110 Control group: 50	Glaucoma group; 75% Control group:35%	≥13	Croatia
Skalicky et al. (2012)	Glaucoma group: 101 Control group: 23	Glaucoma group; 47.6% Control group:21.7%	≥13	Australia
Leung et al. (2008)	Glaucoma group: 101 Control group: none	Glaucoma group; 59% Control group: none	≥13	the United States
Ramli et al. (2015)	Glaucoma group: 105 Control group: 102	Glaucoma group; 39% Control group:26%	≥13	Malaysia
Ruangvaravate et al. (2018)	Glaucoma group: 109 Control group: none	Glaucoma group; 38.5% Control group: none	≥13	Thailand
Costa et al. (2013)	Glaucoma group: 158 Control group: none	Glaucoma group; 62.7 Control group: none	≥13	Brazil
Garcia-Feijoo et al. (2010)	Glaucoma group:448 Control group: none	Glaucoma group; 59.2% Control group: none	≥13	International multicenter study
Fechtner et al. (2010)	Glaucoma group:630 Control group: none	Glaucoma group; 48.4% Control group: none	≥13	United States

medications) and 175 age-matched controls were reviewed.¹⁰ The investigators found that more patients with glaucoma ($n = 92$; 52.6%) used artificial tears compared to age-matched controls ($n = 31$; 17.7%). At the end of the study, the authors concluded that the usage of topical IOP-lowering medication is a risk factor for the use of artificial tears.¹⁰ The prevalence of dry eye symptoms among glaucoma patients in Germany is reported to be 53%¹³ and between 48% and 59% in the United States.^{11,14} In the United States, Leung et al., reported 59% of 101 patients with glaucoma had symptoms of dry eye.¹¹ In Malaysia, Ramli et al. reported 39% and 26% prevalence of dry eye symptoms in 105 glaucoma patients (using topical IOP-lowering medications) and 102 normal controls, respectively.¹⁵ Again, Ruangvaravate et al.¹⁶ recently reported 38.5% prevalence of dry eye symptoms via the OSDI among 109 glaucoma patients (on topical IOP medications) in Thailand. In Australia, the OSDI was used to estimate dry eyes symptoms among 101 glaucoma patients (on topical IOP-lowering medication) and 23 healthy controls.⁸ The study reported 47.6% prevalence of dry eye symptoms in patients with glaucoma and 21.7% prevalence among the healthy controls.⁸ This implies that whether studies were conducted in Europe, Asia, Australia, South America, or North America, the findings were universally the same indicating more dry eye symptoms in patients with glaucoma (on topical IOP-lowering medications) compared to the general population.

Using the OSDI, Fechtner and colleagues assessed the prevalence of dry eye symptoms among 630 glaucoma patients on topical IOP-lowering medications.¹⁴ They observed that 48.4% of the patients reported mild to severe dry eye symptoms.¹⁴ In a non-interventional study, subjects using one or more topical IOP-lowering medications completed the OSDI.⁹ Patients were recruited from twelve study centers situated in Europe, Australia, Asia, and Latin America. Out of the 448 patients, the prevalence of dry eye in the eligible subjects was 59.2%, with 25.7%, 13.2%, and 20.3% of the subjects reporting mild, moderate, or severe dry eye symptoms, respectively.⁹ These studies provide compelling evidence that dry eye symptoms are more common in glaucoma patients using topical IOP-lowering medications compared to the general population, irrespective of geographical location and/or race. Clinicians, therefore, need to be attentive to complaints of ocular surface discomfort by glaucoma patients and take proactive steps to ameliorate them.

Meibomian gland dysfunction and changes in glaucoma patients on topical IOP-lowering medications

The meibomian glands are the main source of lipids for the tear film. Any adverse effects affecting them can cause significant evaporation of tears and subsequently hyperosmolarity of tears and eventually dry eye symptoms. Agnifili et al. conducted a study involving 80 patients with glaucoma, and 20 healthy subjects as controls.¹⁷ According to the number of topical IOP-lowering medications they were using, subjects were selected into one of three groups: Group one (30 eyes), one drug; Group two (23 eyes), two drugs; Group three (27

eyes), three or more drugs. Laser scanning confocal microscopy revealed lower mean acinar area and mean acinar density, greater secretion reflectivity and glandular orifice area in groups two and three than in controls.¹⁷ They also showed that preserved PGAs caused more definite changes on all measured variables compared to preservative-free PGAs.¹⁷ No such observations or differences were found between preserved and preservative-free beta-blockers.¹⁷

Similarly, Arita et al.¹⁸ evaluated 71 glaucoma patients (Group 1) receiving one type of topical IOP-lowering medication, 61 glaucoma patients (Group 2) receiving two types of topical IOP-lowering medications, 30 glaucoma patients (Group 3) receiving three types of topical IOP-lowering medications, and 75 healthy volunteers serving as controls. Compared to the controls, superficial punctate keratopathy, lid margin abnormality, meiboscore, and meibum scores were significantly higher in patients with glaucoma.¹⁸ The researchers reiterated that long-term usage of topical IOP-lowering medications is associated with changes in the structure and function of the meibomian glands. Kim et al.¹⁹ reported 82% of meibomian gland dysfunction in 50 patients with glaucoma (on topical IOP-lowering medications) and 52.5% in a control group. Again, the study showed a significant difference in Marx line and breakup time according to the presence of meibomian gland dysfunction between the cases and controls.¹⁹ Cho and colleagues reported that patients with glaucoma had significantly worse meibum quality, thinner lipid layer thickness, and lower meibomian gland secretion compared to healthy controls.²⁰

In another study, involving 70 glaucoma subjects on long-term (>1 year) topical IOP-lowering medications, meibomian gland dysfunction was found in 56 (80.0%) subjects.²¹ Forty-seven patients (67.1%) had obstructive and 9 (12.9%) had atrophic type of meibomian gland dysfunction.²¹ In a recent study, Lee et al. evaluated three clinical signs of meibomian gland dysfunction: lid margin abnormality score, meibum expressibility, and the level of meibomian gland dropout examined with the Keratograph 5M.²² They found that the glaucoma group had significantly worse meibum scores and lid margin scores in comparison with those of the control group. It is evident from these clinical studies that long-term usage of topical IOP-lowering medications precipitates meibomian gland dysfunction.

Other experimental studies have also documented the effects of topical IOP-lowering medications on the cells of the meibomian glands. For instance, Zhang and colleagues²³ showed that timolol and pilocarpine caused a dose-dependent decrease in the survival of immortalized human meibomian gland epithelial cells. They demonstrated that concentrations that are utilized clinically are toxic and could cause poor adherence and cell death.²³ They also suggested that pilocarpine and timolol have adverse effects on human meibomian gland epithelial cells that may impact their anatomy and proliferative capacity. On the other hand, Han et al.²⁴ showed that the application of brimonidine causes a dose-dependent decrease in the proliferation of immortalized human meibomian gland epithelial cells. Notwithstanding,

brimonidine also facilitated a dose-dependent differentiation of immortalized human meibomian gland epithelial cells.²⁴ These studies support the claim that the long-term usage of topical IOP-lowering medications can alter the anatomy and physiology of the meibomian glands.

Clinical signs of dry eye in glaucoma patients using topical IOP-lowering medications

Baudouin et al., in an expert review reported that topical IOP-lowering medications preserved with benzalkonium chloride (BAK) induces tear film instability, conjunctival hyperemia, ocular surface alterations, subconjunctival fibrosis, and epithelial apoptosis.^{6,25} In a comparative study, Saini et al. prospectively assessed the ocular surfaces of 25 patients who have used two or more anti-glaucoma medications for at least 6 months and 25 healthy subjects.²⁶ The researchers observed that central subbasal nerve fiber layer density was decreased in the glaucomatous eyes. The central subbasal nerve fiber layer density correlated significantly with ocular surface staining scores, fluorescein breakup time, and OSDI values.²⁶

Another study reported reduction in tear film breakup time following three hours and three days of administering carteolol preserved with BAK.²⁷ Subjects who received BAK-preserved timolol had lower Schirmer test values, reduced goblet cell densities, shorter tear breakup time, and a greater amount of squamous epithelial cell metaplasia when compared with healthy age-matched controls.²⁸ Arici et al. also observed the negative impact of BAK on tear breakup time and Schirmer tests scores.²⁹ Another clinical study found that frequent dosing of preserved timolol induced changes to the ocular surface, mostly the mucoid layer of the tear film.³⁰ Ramli et al. reported that more subjects with glaucoma (on topical IOP-lowering medications) had abnormal Schirmer test and corneal staining scores compared to the age-matched controls.¹⁵ This clearly shows that topical IOP-lowering medications affects the ocular surface, and it is fairly easy to use common clinical tests to detect these changes on the ocular surface. Furthermore, in another study, subjects were divided into six groups according to their topical treatment regimen. Subjects on preserved medication demonstrated reductions in Schirmer I scores, tear breakup time, superficial corneal epithelial cell density, and the number of subbasal nerves compared to the normal controls and subjects on non-preserved topical medications.³¹ Wong and colleagues recently reported that topically treated eyes of glaucoma patients had poorer non-invasive tear film breakup time, tear film osmolarity, bulbar conjunctival hyperemia, eyelid margin abnormality grade, tear meniscus height, and anesthetized Schirmer value compared with fellow untreated eyes.³²

Duration of anti-glaucoma therapy and severity of dry eye symptoms

There is evidence in the literature confirming the tendency of worsening dry eye symptoms with the increasing duration of treatment with topical glaucoma medications. In a study

conducted by Garcia-Feijoo and colleagues, subjects who had used topical anti-glaucoma medications for a longer period had a higher mean OSDI score compared to those who had used these medications for a shorter period.⁹ This is in accordance with the findings of Barisic et al. that showed that the OSDI score increases with the duration of glaucoma therapy.⁷ Many other studies have also reported increasing severity of symptoms with increasing duration of therapy.^{8,11}

Effects of preservatives on the ocular surface of glaucoma patients

BAK is the most widely used preservative in ophthalmic medications. BAK is a quaternary ammonium that acts as a detergent to disrupt the membrane of cells, thus destroying microorganisms. BAK is an efficacious microbicidal with broad-spectrum activity against Gram-negative bacteria, Gram-positive bacteria, and fungi.^{1,33}

Effects of benzalkonium chloride on the cornea, tear film, and conjunctiva

BAK's characteristic detergent properties interfere with the lipid layer of the tear film, resulting in decreased tear film breakup time and increased aqueous tear evaporation.³⁴ BAK has also been implicated in the reduction in the density of goblet cells. This decrease in the density of goblet cells impairs mucin production and affects tear film stability.³⁵ These adverse effects on the tear film homeostasis usually result in dry eye symptoms in glaucoma patients. Even in subjects who do not experience discomfort, corneal epithelial damage and signs of tear film instability can be found.³⁰ Again, BAK has been shown to cause alterations in the corneal stroma, when the integrity of the epithelium is compromised.^{30,36} Martone and colleagues did an *in vivo* confocal microscopy analysis of the adverse effects of preserved topical anti-glaucoma medications on corneal morphology and innervations. The density of superficial epithelial cells was diminished in all subjects with glaucoma, apart from the preservative-free group.³¹

BAK can induce inflammation within the conjunctival tissue which may ultimately result in dry eye symptoms.³⁶ Several inflammatory mediators are implicated in BAK-induced conjunctival inflammation. These comprise tumor necrosis factor-alpha, interleukins 1, 10, and 12, and C-reactive protein.³⁷ More importantly, BAK has been implicated in the increased expression of the CCR4 chemokine receptor, a marker for the T-helper 2 pathway. BAK can enter into the cells of the conjunctiva and remained there up to a week.³⁸

Apart from BAK's effects on tear film homeostasis or indirect damage to the cornea and conjunctiva, BAK also causes a direct effect on the cells of the cornea.³⁶ In experimental studies, BAK has been demonstrated to have a dose-dependent adverse effects on the corneal epithelium resulting in loss of microvilli at epithelial cell edges, cell wrinkling, and exposure of the cell layers beneath.^{39,40} The concentration of BAK in eye drops usually ranges from 0.004% to 0.02%, which falls within the range of causing toxic effects. BAK usually result in

inflammation and increase release of matrix metalloproteinase-9 by trabecular meshwork cells. This enzyme has been implicated in the pathophysiology of dry eye.^{36,41–43}

Interventional studies on benzalkonium chloride

In a randomized trial, using the OSDI, BAK-free travoprost 0.004% was compared with BAK preserved latanoprost 0.005% among well-controlled IOP patients. These patients' OSDI scores were less than 13 and were assessed again after six and 12 weeks.⁴⁴ After twelve weeks, the mean OSDI score was significantly lower in the BAK-free travoprost 0.004% group compared to the BAK preserved latanoprost 0.005% group. Changing from BAK preserved latanoprost 0.005% to BAK-free travoprost 0.004% resulted in significant reductions in the symptoms of dry eye per the OSDI score.⁴⁴ This study further affirmed the known effect of BAK on dry eye symptom worsening.

In a clinical trial, subjects experienced reduction in ocular symptoms with preservative-free timolol when compared to subjects on preserved timolol.⁴⁵ The use of unpreserved timolol has been demonstrated to improve the tear film homeostasis in glaucoma patients with altered integrity of the ocular surface.⁴⁵

Comparison of benzalkonium chloride to other preservatives used in IOP-lowering medications

In an effort to alleviate the toxic effects of BAK, several other preservatives have been developed.⁴³ Purite is a preservative with oxidative properties that is utilized in brimonidine topical drops. A study with brimonidine-purite 0.15% found the incidence of adverse effects such as conjunctival hyperemia to be very mild.^{33,46}

Polyquad[®] (polyquarternium-1) is a polycationic preservative that is included in the preparation of artificial tears.⁴⁷ Labbe et al. demonstrated that Polyquad causes less toxicity than BAK in vivo.⁴⁸ BAK-preserved travoprost 0.004% ophthalmic solution led to a safety disadvantage for the ocular surface compared with subjects receiving topical medications preserved with Polyquad[®].⁴⁹ According to Labbe et al., apart from concentrations of 0.5%, Polyquad[®] did not induce ocular surface damage.⁴⁸ However, BAK caused significant toxic effects at mild to high concentrations with destruction of goblet cells. Liang et al.⁵⁰ compared a new formulation of travoprost 0.004% ophthalmic solution preserved with Polyquad with available formulations of BAK-preserved travoprost 0.004% ophthalmic solution in rabbits. BAK-preserved travoprost 0.004% ophthalmic solution led to more alterations of the ocular surface compared with subjects receiving topical medications preserved with Polyquad[®].

SofZia[®] is a preservative with oxidative properties, that disintegrates into non-toxic by-products after coming into contact with cations on the ocular surface.^{51,52} A randomized multicenter single-masked study recruited 220 patients who had been treated with BAK preserved latanoprost 0.005%

monotherapy for at least three months.⁵² After changing to SofZia-preserved travoprost 0.004%, the occurrence of epitheliopathy significantly decreased in the travoprost SofZia-preserved group.⁵² Tear breakup time and superficial punctate keratitis scores significantly improved in the travoprost group.

Effects of pharmaceutical agents in antiglaucoma drugs on the ocular surface

Even though preservatives in topical IOP-lowering medications are known to adversely affect the ocular surface, there is mounting evidence that also suggests the involvement of the active pharmaceutical agents. In a cross-sectional, observational case series involving 31 glaucoma patients, all were on topical treatment in only one eye for more than 1 year. Thirteen subjects were on PGAs alone, eight on beta-blockers alone, and ten receiving combination treatment with untreated contralateral eyes that served as controls.⁵³ The eyes on treatment had significantly higher scores for superficial punctate keratitis, lid margin abnormality, meiboscore than control eyes. Schirmer values and tear film breakup time were significantly lower in the treated eyes than in the control eyes. Subgroup analysis also indicated a significantly higher meibo-score in eyes treated with either PGAs or beta-blockers alone than in the corresponding controls.⁵³

In another study, preservative-free timolol solution had a favorable effect on the tear turnover in patients with glaucoma or ocular hypertension than those patients on BAK-preserved timolol, even though the integrity of the precorneal tear film persisted to be affected in those using timolol without BAK.⁵⁴ Kurna et al. observed that preserved and non-preserved beta-blockers induce more damage on the ocular surface compared to PGA and brimonidine-purite.⁵⁵ Chen et al. studied 2065 dry eye patients aged 65 years and older, 63.3% of which were female, and 48.9% were male. After adjusting for potential confounding factors, an increased risk of dry eye was observed for all glaucoma medications with the exception of the alpha-agonists.⁵⁶ The adjusted odds ratio of having dry eye increased with the number of glaucoma medications used. Beta-blockers had the highest risk for dry eye, with similar trends occurring in both females and males. In a recent single-center, open-label trial of 32 newly diagnosed glaucoma patients who were randomized to one of four PGAs namely bimatoprost preserved with BAK, latanoprost preserved with BAK, polyquad preserved travoprost, and preservative-free tafluprost.⁵⁷ Clinical assessment were made at presentation, 1, 3, and 6 months follow-up, and dry eye symptoms were also assessed at presentation and follow-up visits using the OSDI. The travoprost group had the least mean OSDI scores whilst latanoprost group had the highest scores.⁵⁷ Even though tafluprost was preservative-free, it appears that travoprost preserved with polyquad had a lower mean OSDI score.⁵⁷ This shows that apart from preservatives the active pharmaceutical agents play a role in the occurrence of dry eye symptoms in glaucoma patients on topical IOP-lowering medications. The evidence

elucidated above suggests that beside preservatives, the active substances may also induce ocular surface changes and worsen dry eye symptoms.

Effects of pH of anti-glaucoma medications on the ocular surface

Level of pH is an important physiochemical property of topical ocular medication due to the potential of causing ocular surface injury and drug compliance. pH has become the focus of a recent push for a combination topical beta-blocker and carbonic anhydrase inhibitor.⁵⁸ A patient preference study revealed more comfort with the pH of the brinzolamide-based suspensions compared to the more acidic dorzolamide-based solutions. The study concluded that improvement in ocular comfort with brinzolamide-based solutions were due to the pH.^{58,59}

Topical IOP-lowering medications and allergic reaction on the ocular surface

Topical anti-glaucoma medications can incite different allergic reactions on the ocular surface. Although quite rare, allergic reactions can be clinically devastating; however, their incidence is actually lower compared to non-allergic effects induced by the long-term use of topical IOP-lowering medications.¹ The incidence of allergic reactions differs, depending on the medication in question. Instantaneous allergic reactions are less common with timolol compared with other topical IOP-lowering medications.⁶⁰ One study reported an incidence of 1.5% of allergic reactions with latanoprost, when used as an adjunct therapy.⁶¹ Allergic reactions with brimonidine have been reported to be between 4.2% and 25.7%.⁶² The preservatives and active agents in these topical IOP-lowering medications initiate an allergic reaction by acting as a hapten.³⁴

Discussion

It is evident from the literature that different topical anti-glaucoma medications have different levels of impact on the health of the ocular surface. Generally, preservative-free medications have fewer adverse effects compared with preserved medications. Topical beta-blockers, whether preserved or unpreserved, have been shown to have the greatest adverse effects on the ocular surface compared to other medications, hence should be used cautiously in patients with moderate to severe dry eye.^{17,54,56} Also, among the prostaglandin analogs, it appears travoprost, even with preservatives, has less impact on the ocular surface compared to latanoprost, bimatoprost, and even non-preserved tafluprost.⁵⁷ Again, in the choice of an adjunctive therapy for a glaucoma patient, on either beta-blockers or prostaglandins analogs, alpha agonist appears to have less risk for dry eye compared to carbonic anhydrase inhibitors and miotics like pilocarpine.⁵⁶

In conclusion, the review of the current literature showed that dry eye symptoms are more prevalent in glaucoma

patients compared to the general population. The main driver for this observation is the presence of preservatives in topical IOP-lowering medications. The contribution of the active pharmaceutical agents to both dry eye symptoms and signs is substantively justified in literature. Even though the literature confirms BAK as having more adverse effects on the ocular surface compared to other preservatives, several other issues need to be resolved with convincing evidence. Firstly, it is unknown whether the concentration of preservatives has a linear relationship with the severity dry eye symptoms and signs. Secondly, a robust investigation is needed to ascertain the contribution of other physiochemical properties of topical medications such as osmolarity, tonicity, and pH to the development of dry eye symptoms and signs. Topical IOP-lowering medications are implicated in the development dry eye among glaucoma patients. Hence, clinicians need to take proactive steps in managing glaucoma patients for ocular surface disease.

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