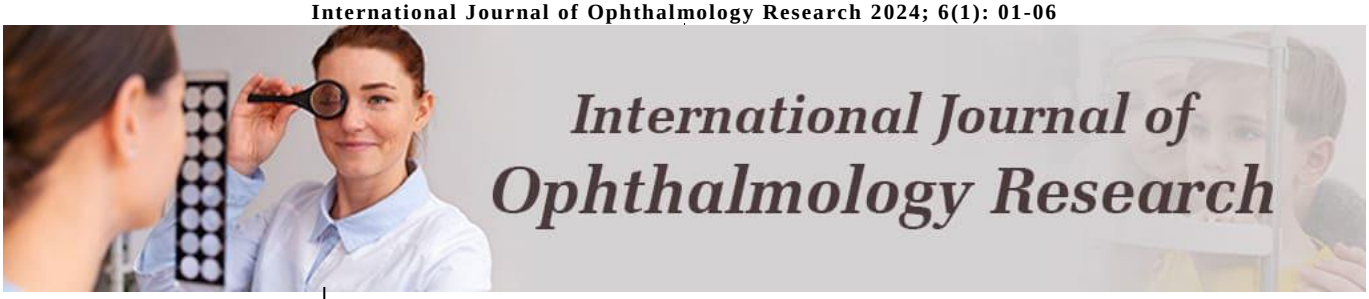

ISSN Print: 2618-1495
ISSN Online: 2618-1509
IJOR 2024; 6(1): 01-06
www.ophthalmologyjournal.in
Received: 05-11-2023
Accepted: 09-12-2023

Dr. Manjula S
Sr. Vice President, Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

Krishna Kumar M
Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

Corresponding Author:
Dr. Manjula S
Sr. Vice President, Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

Perspectives and preferences on preservative-free therapies for managing glaucoma and ocular surface disease among ophthalmologists in Indian settings

Dr. Manjula S and Krishna Kumar M

DOI: https://doi.org/10.33545/26181495.2024.v6.i1a.24

Abstract
Objective: This survey-based study was to gather expert opinion regarding the perspective and preference of preservative-free therapies in managing glaucoma and ocular surface disease (OSD) in Indian settings.
Methodology: This cross-sectional study used a multiple-response questionnaire comprising 20 questions designed to collect feedback, clinical observations, and experiences from specialists regarding the management of glaucoma and ocular surface dryness by using preservative-free compositions in routine settings. The questionnaire was structured to capture insights on the frequency of use, perceived efficacy, adverse effects, and preferences for preservative-free compositions. Data analysis was conducted using descriptive statistics.
Results: The survey included 227 experts, and about 55% of the clinicians attributed age as the reason for the association between dry eye and newly diagnosed glaucoma patients. For newly diagnosed patients with both glaucoma and OSD, around 53% of the clinicians recommended preservative-free anti-glaucoma medication. As reported by 44% of clinicians, tear substitutes with less or no preservative on the ocular surface could be an ideal tear substitute for managing OSD in glaucoma patients. More than half (58.59%) of the clinicians responded that all glaucoma patients generally preferred a preservative-free anti-glaucoma medication. Approximately 69% of clinicians sometimes chose a fixed-dose combination over monotherapy for newly diagnosed glaucoma patients. According to 42% of clinicians, the primary advantage of fixed-dose combination eye drops was the reduction in the total number of drops and preservatives used daily.
Conclusion: This study highlighted a preference for preservative-free medications to minimize ocular surface damage, particularly in patients with OSD. Fixed-dose combinations were favored for convenience and reduced preservative exposure, improving patient compliance and outcomes. Age was commonly cited as a factor linking dry eyes to newly diagnosed glaucoma.

Keywords: Expert opinion**,** glaucoma, ocular surface disease, preservative-free medications

Introduction
Glaucoma is a multifaceted eye condition marked by increased intraocular pressure (IOP). It is the primary cause of irreversible blindness and the second leading cause of blindness globally. This condition encompasses a cluster of progressive optic nerve disorders characterized by the deterioration of retinal ganglion cells and nerve fibers, leading to alterations in the optic nerve head. The damage inflicted on the optic nerve due to IOP lies at the heart of glaucoma, resulting in the depletion of retinal ganglion cells [1, 2]. The two most prevalent types of glaucoma are primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG), with POAG being about seven times more common than PACG in the United States and Europe [3, 4]. Globally, approximately 3 to 5% of individuals aged 40 and above are affected by glaucoma, with projections indicating a surge to 112 million cases by 2040. The rapid aging of the global population largely fuels this increase [4, 5].
India accounts for the highest regional burden of global blindness, contributing 23.5% to the worldwide total. Glaucoma ranks as the third leading cause of blindness in India, following cataracts and refractive errors. India faces a significant challenge with 11.9 million individuals affected by glaucoma and 8.9 million experiencing blindness [6, 7]. Topical medical therapy is the most common initial treatment for glaucoma.

About 49 to 59% of glaucoma patients using topical anti-glaucoma medications experience ocular surface disease (OSD) [8, 9]. In glaucoma patients, OSD can either be a pre-existing condition exacerbated by topical therapy or a new condition that develops after the initiation of treatment. The prevalence of OSD increases with age, making it a common comorbidity in glaucoma patients, and effective management was crucial for treatment success [9-11]. Chronic OSD is likely due to toxicity from preservatives or the active compounds in the medications. Using preservative-free medications can help reduce the risk of chronic OSD [12-13].

Recognizing the challenges associated with preservatives in anti-glaucoma medications, preservative formulations have been developed to mitigate the risk of OSD and enhance patient outcomes [14]. Single-dose units have become the most commonly used form of preservative-free eye drops to avoid the risk of potentially severe eye infections and to maintain the integrity of the formulation. Preservative-free medications offer a valuable treatment strategy for the lifelong management of glaucoma. By eliminating preservative toxicity, preservative-free formulations provide significant clinical benefits, improving tolerability and adherence. This, in turn, positively impacts long-term IOP control, benefiting glaucoma patients worldwide [15-16].

The present survey-based study aims to obtain clinicians' perspectives and preferences regarding preservative-free anti-glaucoma medications in the management of glaucoma and associated OSD in Indian settings.

Methodology

A cross sectional, multiple-response questionnaire based survey was carried out among ophthalmologists specialized in treating glaucoma and associated OSD using preservative-free compositions in the major Indian cities from June 2023 to December 2023.

Questionnaire

The questionnaire booklet titled GODRY (Glaucoma management and ocular surface dryness) study was sent to the ophthalmologists who were interested to participate. The GODRY study questionnaire comprised 24 questions designed to gather feedback, clinical observations, and experiences from specialists regarding the treatment of glaucoma and associated OSD using preservative-free compositions in routine settings. It was structured to capture insights into the frequency of use, perceived efficacy, adverse effects, and preferences for specific compositions. The study was conducted after getting approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

Participants

An invitation was sent to leading ophthalmologists in managing glaucoma and associated OSD in the month of March 2023 for participation in this Indian survey. About 227 ophthalmologists from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Ophthalmologists had the option to skip any questions they preferred not to answer and were instructed to complete the survey independently, without consulting their colleagues. Written informed consent was obtained from all participants before the study's commencement.

Statistical analysis

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide a clear insight into their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, graphs, and pie charts were created using Microsoft Excel 2013 (Version 16.0.13901.20400).

Results

Of the 227 clinicians involved in the survey, 49% practiced comprehensive ophthalmology. As reported by 46% of the clinicians, on average, < 10 individuals were newly diagnosed with glaucoma monthly, while 41% reported that about 11 to 40 individuals are diagnosed monthly on average. According to 41% of the participants, individuals from suburban areas mostly suffer from glaucoma. As indicated by the majority (62.56%) of the participants, glaucoma was equally prevalent in both men and women. Approximately 41% of the clinicians reported that individuals between the ages of 51 to 60 years mostly suffer from glaucoma. Half of the clinicians (50.22%) indicated that < 25% of newly diagnosed patients had pre-existing OSD at the time of glaucoma detection.

Around 51% of the clinicians opined that they administer dry-eye questionnaires like the Ocular Surface Disease Index (OSDI), Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED) and Dry Eye Questionnaire (DEQ) only if the patients complain of dry-eye symptoms. Age was reported as the reason by about 55% of clinicians for the association between dry eye and newly diagnosed individuals with glaucoma (Fig. 1).

As opined by 42% of the respondents, the long-term use of anti-glaucoma products may cause OSD in about 26 to 50% of the patients. Majority of the respondents (61%) indicated age and other comorbidities, the anti-glaucoma drug itself, preservatives in the drug, and multiple drops as the most important reasons for developing OSD with long-term anti-glaucoma products.

Nearly 36% of the participants reported frequent follow-up with complaints of discomfort as the impact of developing OSD in patients using anti-glaucoma drugs for a long time. Around 53% of the clinicians preferred preservative-free anti-glaucoma medication for newly diagnosed glaucoma patients who also have OSD (Table 1).

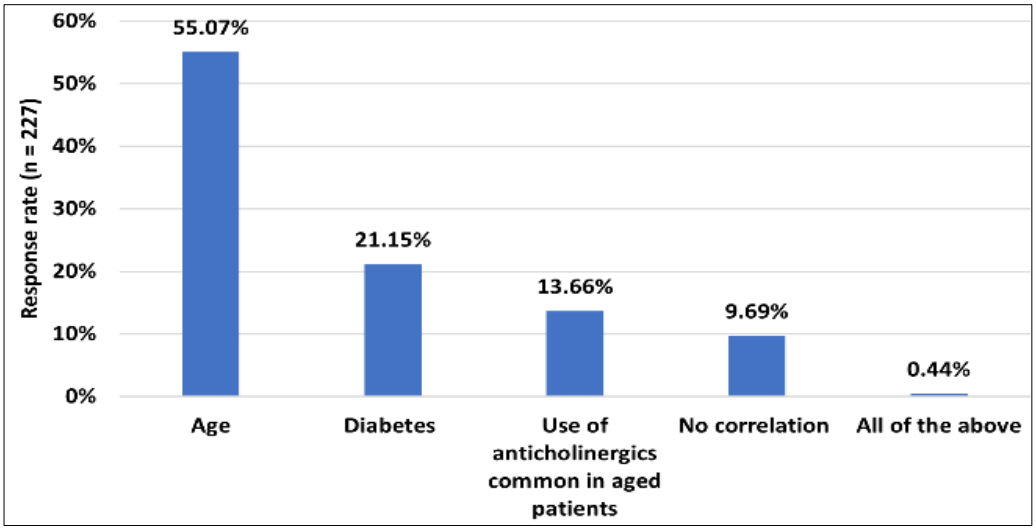

Fig 1: Distribution of response on the reason for dry eye being associated with glaucoma in newly diagnosed glaucoma cases

Table 1: Distribution of response on the management options for newly diagnosed glaucoma patients with OSD

Management	Response rate (n= 227)
Preservative-free anti-glaucoma medication	52.86%
Fixed-dose combinations to reduce preservative load	18.5%
Prescribe a tear substitute	18.94%
Use preserved drugs due to low concentrations and risk	5.73%
Along with anti-glaucoma medication	2.2%

According to 62% of the participants, shifting to preservative-free eye drops as much as possible was a better strategy for glaucoma patients who develop OSD during the course of treatment. As reported by 44% of clinicians, tear substitutes with fewer or no preservatives on the ocular surface could be an ideal tear substitute for managing OSD in glaucoma patients (Table 2). Approximately 35% of the clinicians opined that one should continue the tear substitute in OSD that was associated with glaucoma as long as the patient received anti-glaucoma medication. More than half (58.59%) of the clinicians responded that they normally prefer a preservative-free anti-glaucoma medication in all glaucoma patients, while 38% of them reported preferring it in patients with pre-existing signs and symptoms of OSD (Fig. 2).

Table 2: Distribution of response on the ideal tear substitute for managing OSD in glaucoma patients

Tear substitute	Response rate (N=227)
Any tear substitute	7.93%
Preservative-free tear substitute	44.49%
High-viscosity tear substitute	19.38%
Muco-mimetic tear substitute	11.45%
Water-retaining tear substitute	15.86%
Tailored to patient's needs	0.44%
Counselling and meditation	0.44%

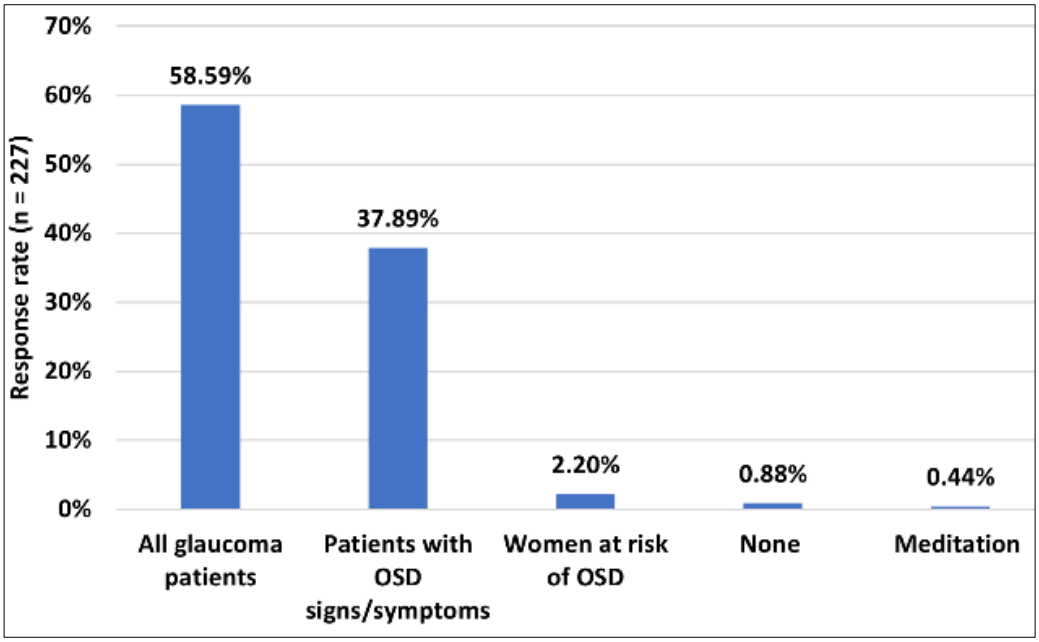

Fig 2: Distribution of response to the preference for preservative-free anti-glaucoma medication among different patient groups

Majority (92.95%) of the clinicians expressed their preference to transition a glaucoma patient from their current treatment containing preservatives to a preservative-free therapy using the same medication, provided that the IOP was adequately managed. Approximately 69% of clinicians opined that they sometimes prefer a fixed-dose combination over monotherapy in newly diagnosed glaucoma patients (Fig. 3).

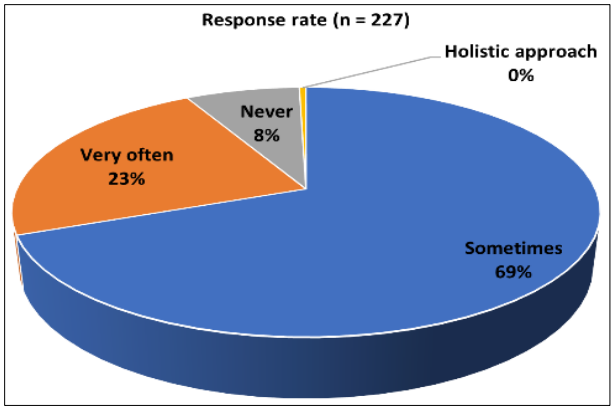

Fig 3: Distribution of response to the preference for fixed-dose combination over monotherapy in newly diagnosed glaucoma patients

As indicated by 35% of the clinicians, the alternative preservative systems like ionic buffer solution (IBS) were good but completely preservative-free would have been better, while 33% of the clinicians reported that IBS was good, and patients have experienced better results when switched from preserved anti-glaucoma drugs in terms of ocular surface health. The advantage of fixed-dose combination eye drops in glaucoma medication, as opined by 42% of the clinicians, was a reduction in the total number of drops and preservatives instilled per day (Table 3).

Table 3: Distribution of response to the advantages of fixed-dose combination eye drops in glaucoma medication

Advantages	Response rate (N=227)
Fewer drops and preservatives per day	41.85%
Improves compliance	21.15%
Prevents washout effect from rapid-sequence instillation	2.2%
Reduces risk of ocular surface damage	5.73%
Cost-benefit to the patients	0.88%
Easier addition of another drug class	7.05%
All of the above	21.15%

Discussion

The survey results provide valuable insights regarding the preference for preservative-free anti-glaucoma medication in managing both glaucoma and OSD in routine practice and its potential benefits**.** The present study highlights age as a key factor linking dry eye and newly diagnosed glaucoma. This finding aligns with the study by Stefano Barabino, which indicated that aging affects tear production and ocular surface health. As individuals age, the function of meibomian and lacrimal glands declines, leading to reduce tear production and stability-crucial factors in the development of dry eye disease [17]. Additionally, a cross-sectional comparative study noted that most glaucoma patients are over 60 years old [18]. Studies have shown that glaucoma and OSD were mostly prevalent in the elderly with a mean age of 54.39 years [19-21].

The preference for preservative-free anti-glaucoma medications by the majority of clinicians for patients with both newly diagnosed glaucoma and OSD underscores the importance of minimizing ocular surface irritation and toxicity. Preservatives like benzalkonium chloride (BAK), commonly used in glaucoma medications, have been shown to exacerbate dry eye symptoms by disrupting the tear film and damaging the ocular surface [22]. Jandroković *et al*. demonstrated that patients using preservative-free formulations experience less ocular surface damage and better overall tolerability [23]. Similarly, Hutnil *et al*. concluded that preservative-free combinations do not increase eye discomfort and significantly reduce IOP in patients with open-angle glaucoma or ocular hypertension [24]. Studies have indicated that preservative-free medications represent innovative solutions aimed at mitigating the detrimental effects of preservatives on ocular tissues. The utilization of preservative-free drops has been associated with a reduced prevalence of symptoms and signs. Furthermore, the majority of adverse reactions induced by preservatives in glaucoma medication demonstrate reversibility upon their removal ($p<0.001$) [25, 26, 23]. Additionally, preservative-free anti-glaucoma medications have been shown to promote improved treatment adherence compared to those containing preservatives [27].

Preservative-free artificial tears are less likely to cause additional irritation and inflammation, which are common problems noted in patients with both glaucoma and dry eye disease [28]. Lester *et al*. concluded that in cases of OSD resulting from preserved anti-glaucoma treatment, cytoprotective tear substitutes demonstrate superior efficacy compared to 0.9% saline solution in relieving both signs and symptoms [29]. This aligns with the current study findings, suggesting that tear substitutes with minimal or no preservatives are ideal for managing OSD in glaucoma patients.

The preference for preservative-free anti-glaucoma medication by the majority of clinicians, particularly for all glaucoma patients and specifically for those with pre-existing OSD, reflects a growing awareness of the adverse effects of preservatives among experts. Long-term use of preserved medications can lead to chronic inflammation, an increased risk of OSD, and poorer patient outcomes [30, 22]. There are several reasons to choose a preservative-free topical therapy for glaucoma over preservative-added treatment like improvements in the patient's quality of life, better adherence, and persistence with therapy, and improving the outcome of trabecular surgery [16].

The use of fixed-dose combination eye drops, preferred by approximately 69% of clinicians for newly diagnosed glaucoma patients, contributes to optimizing therapeutic outcomes in glaucoma management. In line with this finding, Dixit *et al*. reported that fixed-dose combination produced a greater reduction in IOP in glaucoma patients.[31] Fixed-dose combinations simplify treatment regimens by combining multiple active agents into a single bottle, thereby reducing the total number of drops a patient needs to administer. This can lead to improved compliance and better treatment outcomes [32]. According to Shirai *et al*., individuals with glaucoma showed a preference for fixed-combination therapies over unfixed-combination therapies.

The utilization of fixed-combination therapies was found to enhance adherence to treatment regimens [33].

The primary advantage of fixed-dose combination eye drops, highlighted in the present survey, was the reduction in the total number of drops and preservatives used daily. This reduction minimizes the exposure to potentially harmful preservatives, which can otherwise contribute to ocular surface damage and exacerbate dry eye symptoms. Khouri *et al*. highlighted several potential advantages of fixed-combination medications compared to using individual components separately. These benefits include reducing the total number of drops and preservatives administered daily, cost savings, improved tolerability, and compliance, and preventing the washout effect caused by the rapid-sequence instillation of multiple drops [32]. Denis P *et al*. also emphasized better therapeutic compliance and a lesser effect of dilution of the initial eye drops by the second as the main advantages of fixed combinations [34].

The survey findings may guide future strategies for optimizing glaucoma and OSD management and improving patient outcomes. The major strengths of the study include its larger sample size and the use of a carefully designed and validated questionnaire to gather expert opinions. However, it was important to acknowledge that personal perspectives and inclinations could have influenced the conclusions, and the reliance on expert judgments increases the likelihood of bias. Consequently, it was essential to interpret the results with these limitations in mind. Further research was needed to confirm and expand upon the findings of the current survey.

Conclusion

The study findings highlighted the clinicians' preference for preservative-free medications to minimize ocular surface damage while managing glaucoma, especially in patients with OSD. Moreover, tear substitutes with minimal preservatives were strongly preferred. The experts also favored fixed-dose combinations due to their convenience and reduced preservative exposure, which enhanced patient compliance and outcomes. Additionally, age was cited as a factor connecting dry eyes to newly diagnosed glaucoma.

Acknowledgement

We would like to thank all the ophthalmologists participated in this study.

Conflict of Interest

Nothing to disclose

Funding Support

Nil

References

1. Allison K, Patel D, Alabi O. Epidemiology of Glaucoma: The Past, Present, and Predictions for the Future. Cureus. 2020;12(11):e11686.
2. Harasymowycz P, Birt C, Gooi P, Heckler L, Hutnik C, Jinapriya D, *et al*. Medical Management of Glaucoma in the 21st Century from a Canadian Perspective. J Ophthalmol. 2016;2016:6509809.
3. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006 Mar;90(3):262-7.
4. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040. Ophthalmology. 2014 Nov;121(11):2081-90.
5. Lin Y, Jiang B, Cai Y, Luo W, Zhu X, Lin Q, *et al*. The global burden of glaucoma: findings from the global burden of disease 2019 study and predictions by Bayesian age-period-cohort analysis. Journal of Clinical Medicine. 2023 Jan;12(5):1828.
6. Jacob A, Thomas R, Koshi SP, Braganza A, Muliyil J. Prevalence of primary glaucoma in an urban South Indian population. Indian Journal of Ophthalmology. 1998 Jun;46(2):81.
7. Seth PK, Senthil S, Das AV, Garudadri C. Prevalence of glaucoma types, clinical profile and disease severity at presentation: Tertiary Institute based cross-sectional study from South India. Indian Journal of Ophthalmology. 2023 Oct;71(10):3305.
8. Leung EW, Medeiros FA, Weinreb RN. Prevalence of Ocular Surface Disease in Glaucoma Patients. Journal of Glaucoma. 2008 Aug;17(5):350.
9. Zhang X, Vadoothker S, Munir WM, Saeedi O. Ocular Surface Disease and Glaucoma Medications: A Clinical Approach. Eye Contact Lens. 2019 Jan;45(1):11-8.
10. Fechtner RD, Godfrey DG, Budenz D, Stewart JA, Stewart WC, Jasek MC. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. Cornea. 2010 Jun;29(6):618.
11. Kaštelan S, Tomić M, Soldo MK, Rabatić SJ. How Ocular surface disease impacts the glaucoma treatment outcome. Biomed Res Int. 2013;2013:696328.
12. Baudouin C, Renard JP, Nordmann JP, Denis P, Lachkar Y, Sellem E, *et al*. Prevalence and risk factors for ocular surface disease among patients treated over the long term for glaucoma or ocular hypertension. European Journal of Ophthalmology. 2013 Jan 1;23(1):47-54.
13. Srivastava K, Bhatnagar KR, Shakrawal J, Tandon M, Jaisingh K, Pandey L, *et al*. Ocular surface changes in primary open-angle glaucoma on anti-glaucoma medications versus treatment-naïve patients. Indian J Ophthalmol. 2024 Mar;72(3):374-80.
14. Baudouin C, Labbé A, Liang H, Pauly A, Baudouin BF. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res. 2010 Jul;29(4):312-34.
15. Konstas AG, Labbé A, Katsanos A, Gibbons MF, Irkec M, Boboridis KG, *et al*. The treatment of glaucoma using topical preservative-free agents: An evaluation of safety and tolerability. Expert Opinion on Drug Safety. 2021 Apr 3;20(4):453-66.
16. Thygesen J. Glaucoma therapy: Preservative-free for all? Clin Ophthalmol. 2018 Apr 13;12:707-717.
17. Barabino S. Is dry eye disease the same in young and old patients? A narrative review of the literature. BMC Ophthalmology. 2022 Feb 22;22(1):85.
18. Sahlu M, Giorgis AT. Dry eye disease among Glaucoma patients on topical hypotensive medications, in a tertiary hospital, Ethiopia. BMC Ophthalmology. 2021 Mar 30;21(1):155.
19. Uchino M, Dogru M, Yagi Y, Goto E, Tomita M, Kon T, *et al*. The features of dry eye disease in a Japanese elderly population. Optom Vis Sci. 2006 Nov;83(11):797-802.

20. Palikhey A, Koiree S, Mehta RK, Shrivastava AK. Dry Eye Disease among patients with glaucoma under topical Antiglaucoma agents in a tertiary care centre: A Descriptive cross-sectional study. JNMA J Nepal Med Assoc. 2022 Sep;60(253):800-4.
21. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: Design and baseline data. Ophthalmology. 1999 Nov;106(11):2144-53.
22. Nijm LM, Schweitzer J, Gould Blackmore J. Glaucoma and Dry Eye Disease: Opportunity to Assess and Treat. Clin Ophthalmol. 2023 Oct 17;17:3063-3076.
23. Jandroković S, Pauk VS, Gaćina LD, Skegro I, Tomić M, Masnec S, *et al*. Tolerability in glaucoma patients switched from preserved to preservative-free prostaglandin-timolol combination: A Prospective Real-Life Study. Clin Ophthalmol. 2022 Sep 28;16:3181-92.
24. Hutnik C, Neima D, Ibrahim F, Scott R, Vaillancourt J, Haine D, *et al*. Tolerability and effectiveness of preservative-free dorzolamide-timolol (preservative-free COSOPT®) in patients with open-angle glaucoma or ocular hypertension. Clin Ophthalmol. 2010;4:581-90.
25. Holló G, Katsanos A, Boboridis KG, Irkec M, Konstas AGP. Preservative-free prostaglandin analogs and prostaglandin/Timolol fixed combinations in the treatment of glaucoma: Efficacy, Safety and Potential Advantages. Drugs. 2018 Jan;78(1):39-64.
26. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol. 2002 Apr;86(4):418-23.
27. Kim DW, Shin J, Lee CK, Kim M, Lee S, Rho S. Comparison of ocular surface assessment and adherence between preserved and preservative-free latanoprost in glaucoma: A parallel-grouped randomized trial. Sci Rep. 2021 Jul 22;11(1):14971.
28. Lubricating Eye Drops for Dry Eyes - American Academy of Ophthalmology [Internet]. [Cited 2024 May 20]. Available from: https://www.aao.org/eye-health/treatments/lubricating-eye-drops
29. Iester MM, Figus M, Fogagnolo P, Frezzotti P, Oddone F, Ferreras A. Artificial tear substitutes and ocular surface in glaucoma patients with chronic treatment. Investigative Ophthalmology & Visual Science. 2017 Jun 23;58(8):4600.
30. El Ameen A, Vandermeer G, Khanna RK, Pisella PJ. Objective ocular surface tolerance in patients with glaucoma treated with topical preserved or unpreserved prostaglandin analogues. Eur J Ophthalmol. 2019 Nov;29(6):645-53.
31. Dixit A, Ashish A, Sharma R. A comparative study on efficacy of fixed combination Timolol/Brinzolamide versus travoprost monotherapy in drug-naïve open-angle glaucoma patients. Ther Adv Ophthalmol. 2020 Apr 28;12:2515841420909666.
32. Khouri A, Realini T, Fechtner R. Use of fixed-dose combination drugs for the treatment of glaucoma. Drugs & aging. 2007 Feb 1;24:1007-16.
33. Shirai C, Matsuoka N, Nakazawa T. Comparison of adherence between fixed and unfixed topical combination glaucoma therapies using Japanese healthcare/pharmacy claims database: A retrospective non-interventional cohort study. BMC Ophthalmology. 2021 Jan 21;21(1):52.
34. Denis P. Attitudes pratiques. Intérêt des traitements par combinaisons fixes [Practical measures. Advantages of fixed combination treatments]. J Fr Ophtalmol. 2006 May;29 Spec No 2:45-8.