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Expert Perspectives on the Prescription Practice and Management Strategies for Dry Eye Disease in Indian Settings

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Authors' contributions

This work was carried out in collaboration between both authors. Authors MS and KKM contributed equally in managing literature search, designing the study, performed the statistical analysis, wrote the protocol, and the first draft of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Artificial tears have been recognized as the first-line treatment for dry eye disease (DED), however, the clinician's opinion regarding the management of dry eye remains uncertain. This study evaluated the Ophthalmologist's perspectives on the treatment for DED, with a special focus on polyethylene glycol + propylene glycol (PEG + PG) and Lifitegrast in Indian settings.
Methods: The cross-sectional study was conducted using a multiple-response questionnaire distributed electronically to clinicians. It included 30 questions on prevalence, demographics, diagnostic practices, treatment strategies, patient education, treatment adherence pertaining to

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DED, and the perceived benefits of newer treatments like PEG + PG and Lifitegrast. Data analysis was performed using descriptive statistics.

Results: This study involved 350 clinicians and revealed that 57.43% preferred PEG + PG eye drops as the first-line treatment for lipid-deficient dry eyes. Approximately 44% recommended PEG + PG thrice daily for mild cases and 53% reported switching to PEG + PG for patients unresponsive to carboxymethyl cellulose (CMC) 0.5%. Additionally, 65% preferred using PEG + PG for moderate symptoms. Lifitegrast was considered effective by 79.43% for targeting LFA-1/ICAM-1 and reducing ocular inflammation. About 61% believed that Lifitegrast provides significant benefits due to its inhibition of T cell adhesion, with noticeable effects within two weeks. According to 80% of the survey participants, compared to traditional lubricants, Lifitegrast offers longer-lasting relief, targeted action, and reduced application frequency. Furthermore, 78% noted the advantages of Lifitegrast over cyclosporine, such as faster relief, no burning sensation, no refrigeration, fewer side effects, and no drug interactions.

Conclusion: The survey highlighted PEG + PG combination eye drops as the preferred primary treatment for lipid-deficient dry eyes. Lifitegrast effectively targets LFA-1/ICAM-1, offering rapid relief with minimal side effects, and outperforms traditional lubricants and cyclosporine. These findings underscore Lifitegrast as a key therapeutic option for managing DED.

Keywords: Dry eye diseases; polyethylene glycol; propylene glycol; lifitegrast.

1. INTRODUCTION

The economic burden of dry eye disease (DED) is substantial, encompassing direct medical costs for treatments and consultations, as well as indirect costs related to lost productivity and diminished work performance. It affects individuals' daily activities, resulting in decreased productivity and increased healthcare utilization [1]. The global prevalence of DED ranges from 5% to 50%, affecting nearly 344 million people worldwide. In the United States alone, nearly twenty million individuals suffer from DED [2]. A cross-sectional hospital study reported the prevalence of DED in North India to be around 32%, with individuals aged between 21 and 40 years being the most affected. Additionally, the research highlighted associations between increased odds of developing DED and factors such as smoking, and the use of contact lenses [3].

The subjective symptoms and discomfort experienced by patients with DED often do not correlate well with objective clinical tests. Studies have noted that diagnosing and grading DED using symptom-based questionnaires, such as the Ocular Surface Disease Index (OSDI) questionnaire was more reliable than relying solely on clinical tests [4,5]. Artificial tears have been recognized as the first-line treatment for DED, offering relief by reducing ocular surface stress, enhancing contrast sensitivity and optical quality, and improving overall quality of life. They typically include demulcents like carboxymethyl cellulose (CMC) and propylene glycol (PG), which are water-soluble polymers safeguarding and lubricating mucous membrane surfaces, thereby alleviating dryness and irritation [6].

The multifaceted mechanism of action of the polyethylene glycol (PEG) and PG combination helps alleviate DED-associated symptoms, protects against goblet cell loss, and reduces squamous metaplasia. Its lubricating properties enhance the stability and lubrication of the tear film, while its mucoadhesive properties allow it to adhere to the ocular surface and prolong tear contact time. Moreover, its humectant properties aids in attracting and retaining moisture on the ocular surface [7]. Lifitegrast, an LFA-1 antagonist, inhibits the interaction between LFA-1 and its ligand, ICAM-1, reducing lymphocyte adhesion, activation, migration, and cytokine secretion, thus alleviating DED symptoms [8]. It is an FDA-approved drug administered as a 5% (50 mg/ml) ophthalmic solution, with one drop applied to each eye every 12 hours [8].

Although there were several clinical studies available, the clinician’s opinion regarding the management of dry eye remains uncertain. The present cross-sectional survey was intended to evaluate clinicians’ perspectives on prevalence, demographics, diagnostic practices, treatment strategies, patient education, and treatment adherence pertaining to DED, as well as the perceived benefits of newer treatments like Lifitegrast.

2. MATERIALS AND METHODS

A cross sectional, multiple-response questionnaire based survey was carried out

among ophthalmologists specialized in treating DED in the major Indian cities from June 2023 to December 2023.

Simple random sampling method was used in this study. An invitation was sent to leading ophthalmologists in managing DED in the month of March 2023 for participation in this Indian survey. About 350 ophthalmologists from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. The questionnaire booklet titled DESQ-2 (Dry Eye Survey Questionnaire- 2) study was sent to the ophthalmologists who were interested to participate. The DESQ-2 study questionnaire consisted of 30 items on prevalence, demographics, diagnostic practices, treatment strategies, patient education, and treatment adherence pertaining to DED, as well as the perceived benefits of newer treatments like Lifitegrast. Ophthalmologists were requested to complete the questionnaire without discussing with peers. A written informed consent was obtained from each ophthalmologists before initiation of the study.

Descriptive statistics were used for data analysis, presenting categorical variables as percentages to provide a clear overview of their distribution. The frequency and corresponding percentage of each variable were utilized to illustrate their distribution. Microsoft Excel 2013 (version 16.0.13901.20400) was employed to generate graphs and pie charts, facilitating visualization of the distribution of categorical variables.

3. RESULTS

The survey included 350 experts specialized in ophthalmology, and 30% of them observed between 20-30 new cases of DED per month in routine clinical practice. Approximately 63% of clinicians noted an increased occurrence of dry eye symptoms in urban areas, while 25% observed them in suburban areas. Majority of the respondents (61%) indicated an equal prevalence of DED in both genders. Nearly half of the experts (51%) reported that the age group 25-40 years had the highest prevalence of DED.

Approximately 56% of the experts stated that individuals with digital screen exposure are the most affected by dry eyes in routine practice. Majority of the clinicians (41.71%) reported using slit lamp examination as the primary diagnostic strategy for dry eyes. A significant proportion of clinicians (56.86%) reported using the OSDI questionnaire rarely in their day-to-day examination of dry eyes. Most clinicians (56.57%) indicated that 26-50% of their patients are diagnosed with aqueous deficient dry eyes. Around 71% and 57% of the clinicians reported a burning sensation in the eyes as the most common symptom observed in patients with aqueous deficient dry eyes, and evaporative dry eyes, respectively.

Nearly 60% of the respondents noted 26-50% as the proportion of patients diagnosed with evaporative dry eyes in routine practice. Majority of the clinicians (83.71%) preferred using both periodic screening and regular awareness for the early diagnosis of dry eyes. CMC eye drops 0.5% and 1.0% are the preferred first-line choice of treatment for patients diagnosed with aqueous-deficient dry eyes as reported by 38% and 33% of the clinicians respectively.

More than half (57.43%) of the clinicians responded that the first-line choice of treatment for patients diagnosed with lipid-deficient dry eyes is PEG + PG combination eye drops (Fig. 1). Almost 84% of the clinicians responded that regular use of prescribed medication, minimizing digital screen exposure, following the 20-20-20 rule, and diet and exercise are the approaches that can lead to good clinical outcomes. As reported by 44% of the participants, the dose of PEG + PG was recommended thrice daily for mild dry eye patients (Fig. 2).

More than half (53.43%) of the clinicians opined that one-to-one patient education is the model that will work better for patients' education. The patient educator session should be conducted once in three months to increase the awareness of dry eyes according to 46% of the respondents. About 53% of the clinicians reported that switching to PEG +PG was the preferred strategy for patients who fail to respond to CMC 0.5% for managing dry eyes (Fig. 3). Majority (64.57%) of the clinicians responded that PEG + PG combination is generally recommended for patients with moderate dry eye symptoms (Fig. 4).

According to 57% of the clinicians, sodium hyaluronate was normally recommended to patients with severe dry eye conditions. As indicated by 44% of the clinicians, nearly 11-20% of DED patients have chronic inflammation. A substantial majority (72.57%) of the respondents stated that they understand the role of

lymphocyte function-associated antigen-1 (LFA-1): intercellular adhesion molecule-1 (ICAM-1) interaction in ocular surface inflammation in DED patients, recognizing that ICAM-1 was highly expressed on epithelial, endothelial, and immune function cells during inflammation. They also acknowledged that increased ICAM-1 expression and T cell infiltration occur in the conjunctiva and lacrimal glands of DED patients and that ICAM-1 was the cognate ligand of LFA-1. Most (83.71%) of the ophthalmologists reported that the formation of immunological synapses by LFA-1/ICAM-1 binding facilitates T-cell proliferation/activation, cytokine release, and recruitment of more T-cells at the inflammatory sites.

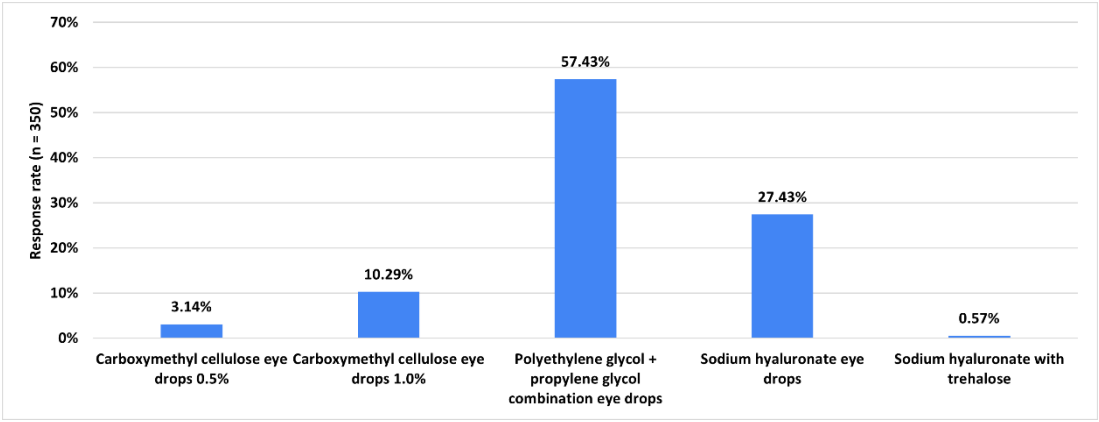

Fig. 1. Distribution of response to the preferred first line of treatment for patients diagnosed with lipid-deficient dry eyes

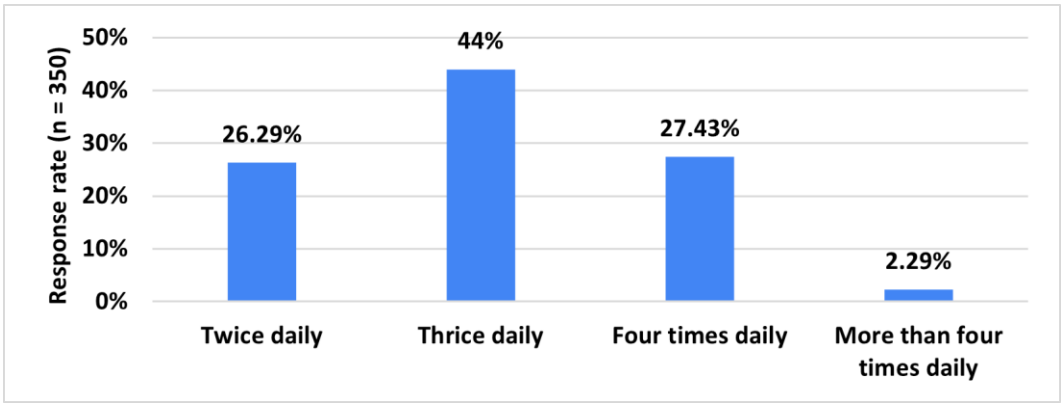

Fig. 2. Distribution of response on the dose of PEG + PG recommended for mild dry eye patients

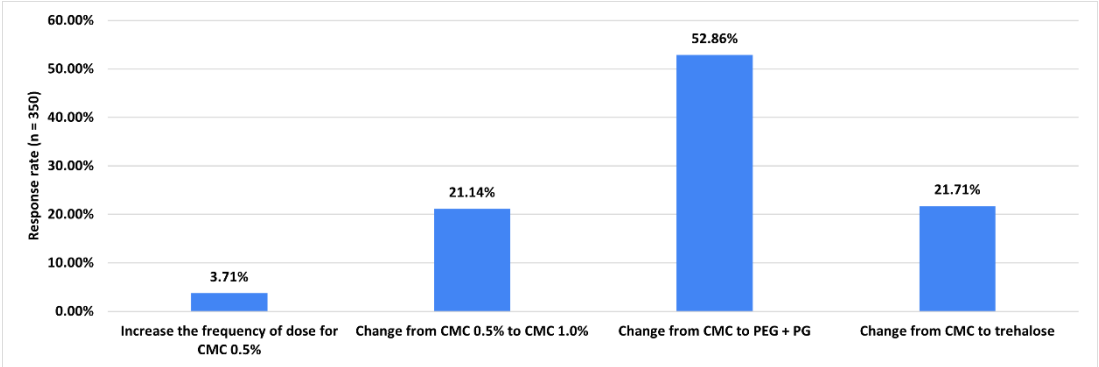

Fig. 3. Distribution of response on the preferred strategy for patients who fail to respond to CMC 0.5% eye drops for managing dry eyes

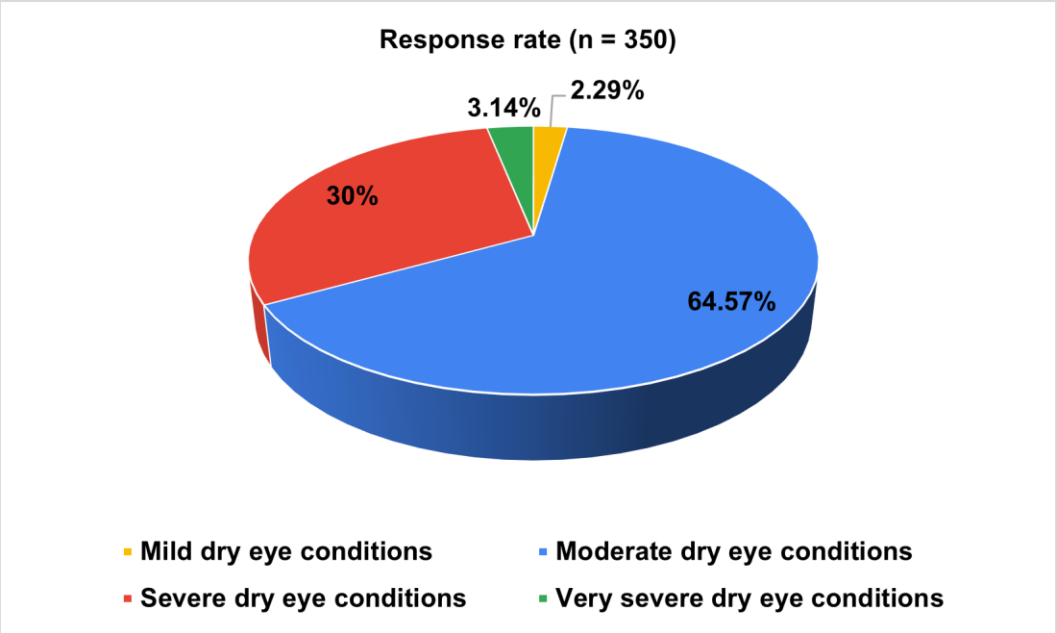

Fig. 4. Distribution of response on the type of patients generally recommended with PEG + PG combination

Majority of the participants (79.43%) reported that Lifitegrast was an effective first-class targeting of LFA-1/ICAM- 1, including inhibition of T-cell activation, cytokine release, formation of the immunological synapse, and a decrease in the ocular inflammatory cycle (Table 1). Approximately 61% of clinicians believed that Lifitegrast eye drops provide significant benefits due to their strong inhibition of T cell adhesion to ICAM-1 expressing surfaces. These drops have a faster onset of action, with effective outcomes observed as early as two weeks (Table 2).

As reported by 80% of the survey participants, Lifitegrast offers several advantages over traditional lubricants, including longer-lasting relief, targeted action, and reduced frequency of application. Nearly 78% of the clinicians stated that compared to cyclosporine, Lifitegrast provides faster relief, causes no burning sensation, requires no refrigeration, has fewer side effects, and poses no risk of drug interactions (Tables 3 and 4). According to 55% of the participants, lack of patient education is the primary reason for non-adherence to medication among DED patients.

Table 1. Distribution of response on the effects of Lifitegrast on immune responses

Effect on immune response	Response rate (n = 350)
Inhibits T-cell activation	3.71%
Inhibits cytokine release	4.86%
Inhibits formation of immunological synapse	6.57%
Decreases ocular inflammatory cycle	5.43%
All of the above	79.43%

Table 2. Distribution of response on the benefits of Lifitegrast eye drops

Benefits of Lifitegrast eye drops	Response rate (n = 350)
Strong inhibition of T cell adhesion to ICAM-1 expressing surfaces, faster onset of action, effective outcomes seen as early as 2 weeks	60.57%
Improves overall quality of life (QoL), reduces the impact of symptoms on daily activities such as reading	23.71%
Improves driving	4.57%
Reduces the impact of using a computer	11.14%

Table 3. Distribution of response on the advantages of Lifitegrast over other lubricants

Advantages	Response rate (n = 350)
Targeted action	5.43%
Longer lasting relief	12.29%
Fewer applications	2.29%
All of the above	80%

Table 4. Distribution of response on the advantages of Lifitegrast over cyclosporine

Advantages over cyclosporine	Response rate (n = 350)
Faster relief	7.14%
No burning sensation	7.14%
No need for refrigeration	1.71%
Fewer side effects	4.86%
No drug interactions	0.86%
All of the above	77.71%
Not sure	0.29%

4. DISCUSSION

The present survey emphasized the significant preference of PEG + PG combination eye drops for the management of DED. Majority of the respondents preferred PEG+ PG combination eye drops as the first-line therapy for lipid-deficient dry eyes. In line with this, Panigrahi et al. reported that PEG + PG combination-based topical formulations are effective in alleviating the symptoms related to DED by adding moisture to the eyes and keeping them lubricated [7]. Similarly, Labetoulle et al. concluded that PEG + PG combinations reduced ocular surface damage, and were effective, convenient, and well tolerated [9]. Shirsat and Trailokya indicated that artificial tears are the first line of therapy for the treatment of all types of DED and PEG + PG combinations are effective in relieving the ocular surface inflammation and irritation by forming a protective layer over the ocular surface [10]. PEG+PG combination lubricating eye drops have been effectively used as a treatment option in the case of DED patients. It has been reported that it alleviates the symptoms related to DED, protects against goblet cell loss, and reduces squamous metaplasia [7].

Aguilar et al. found that administering a combination of PEG and PG artificial tears three times daily for 90 days led to a decrease in conjunctival impression cytology scores, reduced corneal and conjunctival staining, and an increase in tear film break-up time in patients with DED [11]. Another study by Pflugfelder et al. showed that regular administration of a combination of PEG + PG combination thrice daily usage significantly improved ocular surface health and patient comfort [12]. Gifford et al. indicated that using a combination of PEG and PG three times a day provided optimal hydration and symptomatic relief for dry eye patients. It highlighted the importance of consistent dosing to maintain tear film integrity [13]. The current study also highlighted similar findings.

Most clinicians prefer switching to PEG for managing dry eyes in patients who do not respond to CMC 0.5%. Consistent with these findings, a comparative study by Shilpy and Patel evaluated the clinical effectiveness of different artificial tear formulations, including CMC 0.5% and PEG/PG. The results indicated that PEG/PG had a superior clinical profile in terms of improving both the signs and symptoms of DED in patients who were previously inadequately managed with CMC 0.5% [14]. Another comparative study by Maharana et al. revealed that PEG/PG combinations provide both immediate and lasting relief in objective and subjective measures, surpassing the effects of CMC 0.5% tear substitutes [15]. Studies have demonstrated that patients with moderate to severe DED who did not respond to CMC 0.5% experienced significant improvements in both subjective symptoms and objective measures of dry eye severity when switched to a PEG and PG formulation. These studies highlighted the superior moisturizing and protective properties of PEG/PG formulations compared to CMC alone. This enhanced efficacy was attributed to the dual mechanism of PEG and PG, which not only lubricate the ocular surface but also help retain moisture more effectively [9,16].

Majority of the clinicians in the present survey responded that the PEG + PG combination was generally recommended for patients with moderate dry eye symptoms. Studies have shown that PEG/PG with hydroxypropyl guar (HP guar) significantly reduced both corneal and conjunctival staining, as well as improved the overall ocular surface health in patients with DED over six weeks. A significant improvement in dry eye symptoms and ocular surface staining in patients treated with PEG/PG lubricant eye drops [17,11,18].

The survey respondents recommended Lifitegrast as an effective agent that targets LFA-1/ICAM-1, leading to inhibition of T-cell activation, cytokine release, formation of the immunological synapse, and a reduction in the ocular inflammatory cycle. According to Pflugfelder et al., blocking LFA-1/ICAM-1 binding with Lifitegrast presents a novel strategy for mitigating ocular surface inflammation in this condition [19]. Similarly, Holland et al. concluded that treatment with Lifitegrast ophthalmic solution, 5%, may benefit participants with moderate to severe signs and symptoms of DED [20]. The Ocular Pain and Dryness Study (OPUS) trials series of phase III clinical studies, have shown that Lifitegrast significantly improves patient-reported symptoms of eye dryness compared to placebo. Lifitegrast-treated patients reported significant reductions in eye dryness score (EDS) and improvements in other DED symptoms. It confirmed the efficacy of Lifitegrast in reducing symptoms of DED, with significant improvements observed in EDS compared to placebo. This trial emphasized the positive effects of Lifitegrast in reducing ocular discomfort and dryness, reinforcing its role in inhibiting inflammatory pathways involved in DED [21-23]. Semba et al. highlighted that Lifitegrast disrupts the immunological synapse formation, a critical step in T-cell activation and proliferation, thus mitigating the inflammatory response at the ocular surface [24]. Abidi et al. concluded that Lifitegrast is a novel integrin antagonist that inhibits the interaction between LFA-1 and ICAM-1, thereby preventing T-cell activation and recruitment as well as the release of inflammatory mediators. This action effectively reduces the inflammatory responses associated with DED [25].

The respondents emphasized that Lifitegrast confers several benefits over traditional lubricants, such as longer-lasting relief, targeted action, and reduced application frequency. The SONATA study provided long-term safety and efficacy data for Lifitegrast. Patients treated with Lifitegrast for one year exhibited sustained improvement in DED symptoms with a favorable safety profile, supporting its use as a long-term therapeutic option for managing DED [23,22]. A study reported that Lifitegrast is a highly effective drug demonstrated in various clinical trials for alleviating both the signs and symptoms of DED. It exhibited a rapid onset of action and provided good therapeutic efficacy as ophthalmic drops. Lifitegrast effectively protected corneal surfaces and was well tolerated both locally and systemically. Consequently, the FDA approved its use for DED in the form of 5% eye drops to be administered twice daily [25].

The current survey findings revealed that in contrast to cyclosporine, Lifitegrast offers quicker relief, induces no burning sensation, does not necessitate refrigeration, presents fewer side effects, and carries no risk of drug interactions. The pivotal Phase III trials, OPUS I and II, showcased significant enhancement of both DED symptoms and signs within just 14 days of commencement of Lifitegrast treatment compared to a placebo. These trials further showed swift onset of symptom alleviation of Lifitegrast, indicating notable enhancements in eye dryness scores and visual-related function within a two-week timeframe of usage [21,22,26].

Haber et al. reported that Lifitegrast was well-tolerated and the action was rapid. Although some patients experienced mild to moderate instillation site irritation, the incidence of severe burning sensation was low compared to cyclosporine [8]. In terms of side effects, Lifitegrast has shown a favorable safety profile. Common adverse events include dysgeusia (altered taste sensation) and mild ocular irritation, which are generally well-tolerated. This contrasts with cyclosporine, which can cause more frequent and severe ocular burning and stinging [8,27]. Studies reported that Lifitegrast, being a topical medication, has minimal systemic absorption, thereby posing a negligible risk for systemic drug interactions. This was supported by pharmacokinetic studies indicating low systemic exposure levels [25,28].

The current survey results may assist clinicians in enhancing management strategies for DED, in Indian settings. Major strengths of the current survey are the larger sample size and the utilization of a well-designed and validated questionnaire to collect data from clinicians.

However, it is important to acknowledge certain limitations of the survey. The results may be subject to bias due to reliance on expert opinion, which can be influenced by diverse perspectives and preferences among clinicians. It was essential to keep these limitations in mind when interpreting the findings. Additionally, the survey may not fully account for emerging evidence or evolving trends in DED management. To address these limitations, it was recommended to conduct prospective trials or real-world observational studies to validate the survey results and provide a more comprehensive understanding of optimal treatment approaches.

5. CONCLUSION

The survey indicated that clinicians prefer PEG + PG combination eye drops for lipid-deficient dry eyes. Lifitegrast, known for targeting LFA-1/ICAM-1, is favored for its rapid relief, minimal side effects, and advantages over traditional treatments like lubricants and cyclosporine. Lifitegrast benefits include a faster onset, no burning sensation, ease of storage, and lower risk of drug interactions, establishing it as a preferred therapy for DED due to its effectiveness, and safety.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

As per international standards or university standards, respondents' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

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.

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COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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