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"ARTIFICIAL TEAR SUPPLEMENTS: A SYSTEMATIC REVIEW"

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ABSTRACT

Background: Artificial tears are fundamental in managing dry eye disease (DED), providing symptomatic relief and supporting ocular surface health. Beyond lubrication, they promote corneal healing, reduce inflammation, aid in treating keratitis and conjunctivitis, and facilitate contact lens rewetting and foreign body removal. Variability in formulations, dosing regimens, and patient responses necessitates a systematic evaluation of their clinical effectiveness.

Methods: A comprehensive literature search was conducted using PubMed, Scopus, and the Cochrane Library to identify studies published between 2015 and 2024. Eligible studies assessed the efficacy of artificial tears in DED patients, reporting outcomes such as symptom relief, objective clinical measures, formulation characteristics, dosing regimens, and treatment responses across various DED subtypes.

Results: Artificial tears consistently yielded significant improvement in subjective symptoms within one month, with most studies recommending four-times-daily dosing. Objective measures, including ocular surface staining and tear film stability, showed progressive improvement with continued use. Combination formulations demonstrated greater efficacy than single-agent products. Polyethylene glycol-based tears outperformed those containing carboxymethylcellulose or hydroxypropyl methylcellulose. High-concentration liposomal formulations were particularly effective in patients with evaporative DED. However, heterogeneity in study design, classification criteria, disease severity grading, and adherence reporting limited the generalizability of findings.

Conclusion: Artificial tears provide effective short-term symptom relief and may improve objective clinical signs with sustained use. Treatment should be individualized based on DED subtype and patient-specific factors. If symptoms persist beyond one month, escalation to alternative or adjunctive therapies is recommended.

Keywords: artificial tears, dry eye disease, tear film instability, tear deficiency, ocular surface, contact lenses, symptom relief

INTRODUCTION

Dry Eye Disease (DED) affects millions worldwide and is a prevalent, multifactorial disorder characterized by tear film instability and disruption of ocular surface homeostasis. This chronic

condition causes ocular pain and visual disturbances, significantly diminishing quality of life by impairing daily activities and work performance [1–3]. Artificial tears remain the cornerstone of first-line therapy due to their accessibility, ease of use, diverse formulations, and excellent safety profile [4]. DED results from either inadequate tear production or excessive evaporation, leading to tear hyperosmolarity. This hyperosmolar state activates inflammatory pathways—including cytokine release and matrix metalloproteinase upregulation—that perpetuate a vicious cycle of ocular surface damage [5]. Common symptoms such as dryness, burning, stinging, photophobia, itching, and fluctuating vision can severely impact well-being if untreated [6,7].

Epidemiological data consistently demonstrate a disproportionate burden of DED among women, particularly those over 50. In India, prevalence rates in this group range from 5% to 30%, mirroring trends across Asia [8–10]. For example, a Spanish cross-sectional study of 1,947 peri- and postmenopausal women found that 37.7% reported severe DED symptoms [6]. This sex disparity is primarily attributed to menopausal hormonal changes—especially reductions in estrogen and androgen—that impair lacrimal and meibomian gland function [11].

Despite its prevalence and impact, clinicians often underdiagnose and undertreat DED, with over half of affected individuals receiving suboptimal care [12]. First-line management generally includes behavioral and environmental modifications such as reducing screen time, avoiding dry environments, discontinuing contact lens use, and dietary adjustments. Nonetheless, artificial tears remain the primary intervention for symptomatic relief and ocular surface protection [11].

Given these complexities, the wide array of artificial tear formulations—varying in composition, viscosity, and delivery mechanisms—poses a significant challenge for optimal product selection. This challenge is compounded by a scarcity of rigorous comparative data, as many studies fail to stratify outcomes by DED subtype or severity, limiting their relevance for personalized treatment. Consequently, clinicians and patients frequently face uncertainty when answering the common question, "Which is the best drop for dry eyes?"—often without an evidence-based response [13,14].

This systematic review aims to fill this critical knowledge gap by rigorously evaluating the clinical efficacy, safety, and patient-reported outcomes of various artificial tear formulations. By addressing this unmet need, the review provides evidence-based guidance to support personalized treatment strategies and improve therapeutic outcomes for individuals living with Dry Eye Disease. compare the efficacy, safety, tolerability, and acceptability

Materials and Methods

Protocol and Reporting Standards

In compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 standards, this systematic review was carried out. To maintain scientific rigor, transparency, and consistency throughout the review process, the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist was used in the development of the review protocol.

Literature Search Strategy

Studies assessing the efficacy of artificial tears in the treatment of DED were found through a thorough and methodical search. The electronic databases listed below were searched:

- **PubMed (MEDLINE)**
- **Embase**
- **Cochrane Library**
- **Web of Science**
- **Scopus**
- **Wiley Online Library**
- **Google Scholar**

Search terms included both **Medical Subject Headings (MeSH)** and free-text keywords, using Boolean operators where appropriate. Key terms included: *"Artificial tears," "tear substitutes,"*

"ocular lubricants," "dry eye disease," "keratoconjunctivitis sicca," "tear film," "eye drops," "lubricating eye drops," and "topical ophthalmic treatments."
The search included both observational studies and randomized controlled trials (RCTs), and was restricted to English-language publications dated between January 2014 and December 2024.

Eligibility Criteria
Inclusion Criteria:
- RCTs or observational studies
- Studies evaluating artificial tears or ocular lubricants in patients with DED
- Full-text articles published in English
- Studies reporting on at least one of the following: **clinical efficacy**, **safety**, or **patient-reported outcomes**
- Studies involving **adult participants** (≥18 years), irrespective of sex

Exclusion Criteria:
- Studies with incomplete or inaccessible full texts
- Duplicate publications
- Animal or in vitro studies
- Studies published prior to 2014

RESULTS

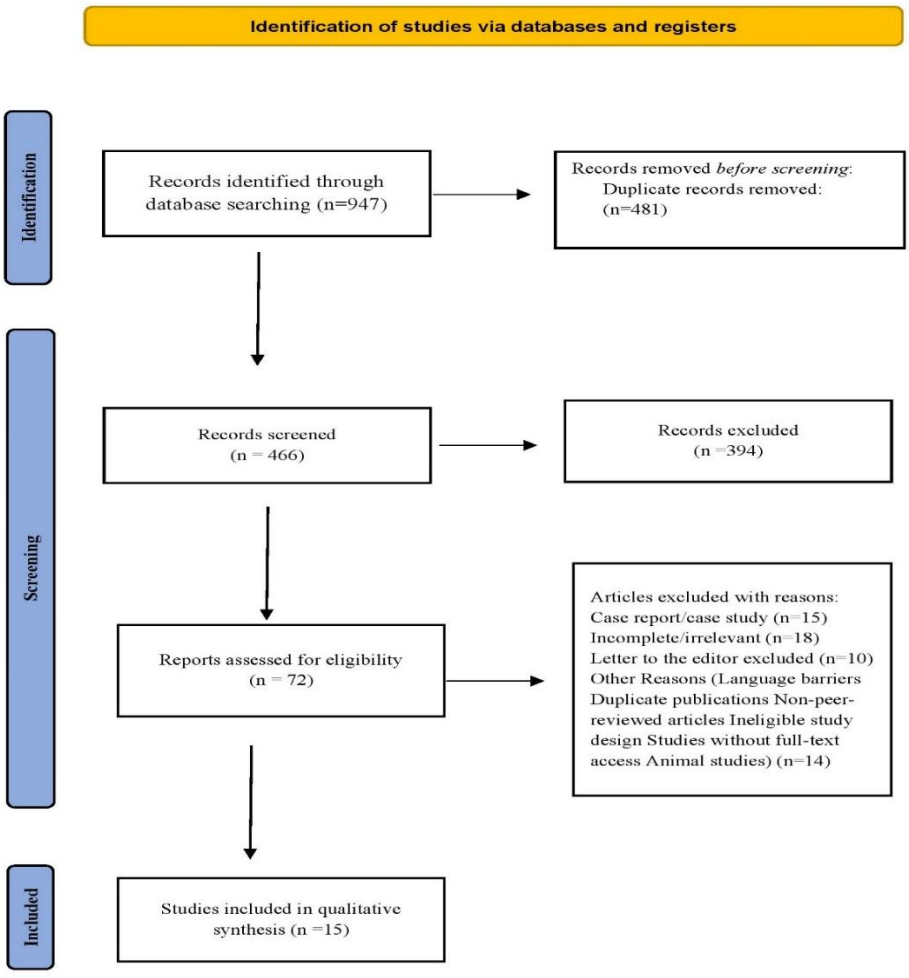

Figure 1. PRISMA flow diagram depicting the study selection process, including the databases searched as detailed in the article.

STUDY SELECTION:

After the removal of 481 duplicate entries, 466 unique records remained for initial screening. During the title and abstract screening phase, 394 records were excluded for not meeting the predefined inclusion criteria. The full texts of 72 articles were retrieved and assessed for eligibility.

Of these, 15 studies were excluded as case reports or case series, 18 due to incomplete data or lack of relevance to the review objectives, and 10 as letters to the editor. An additional 15 articles were excluded for reasons including non-English language, previously unidentified duplicate publications, non-peer-reviewed sources, ineligible study designs (e.g., in vitro or animal studies), or unavailability of full-text access.

Following this rigorous selection process, 15 studies met the inclusion criteria and were incorporated into the qualitative synthesis. The detailed screening and selection process is illustrated in the PRISMA flow diagram (Figure 1). A comprehensive overview of the characteristics of the included studies is presented in Table 1

Table 1. Randomized Controlled Trials Assessing the Efficacy of Artificial Tears

Sr. No.	Author (Year)	Study Design	Country	Sample Size	Artificial Tear Type	Mean Age (Years)	Duration & Dosing	General Outcome
1	**Ahmadi H, et al. (2024) [15]**	Prospective, randomized	Iran	N = 70	Cyclosporine 0.05%	64.15 ± 9.17	1 month (4x/day)	Significant TBUT improvement (P = 0.004); no significant change in Schirmer's test (P = 0.095), VAS (P = 0.374), or visual acuity.
2	**Zhou Y, et al. (2023) [16]**	Prospective cohort	USA	N = 66	Carboxymethylcellulose vs. Polyethylene glycol	41.2 ± 17.8 / 40.0 ± 13.4	7 days (dosing not specified)	No significant difference in OSDI or microbiome diversity; CMC altered microbiome (↑ Enterobacteriaceae).
3	**Maity M, et al. (2022) [17]**	Randomized, double-masked, multicenter	India	N = 100 (20 per group)	0.5% CMC, 1% CMC, SH-trehalose, PEG-PG formulations	40.24 ± 11.55	Single drop, 1-hour follow-up	All formulations improved NIBUT vs. control; SH-based formulations showed better subjective symptom relief than CMC.
4	**Craig JP, et al. (2021) [14]**	Randomized, double-masked, multicenter	AUS, CAN, NZ, UK	N = 49 / N = 50	Systane Ultra vs. Systane Complete	43 ± 17 / 45 ± 16	6 months (4x/day or more)	Significant improvements in LWE, lipid layer, staining, and symptoms. Lipid-based drops more effective in lipid layer grade < 3.
5	**Downie LE, et al. (2020) [18]**	Randomized, double-masked, multicenter	USA	N = 120 / N = 122	OM3 vs. Refresh Optive Advanced	54.3 ± 17.3 / 52.8 ± 16.7	90 days (2x/day or more)	Adverse events: OM3 (0%) vs. ROA (4.1%). Trial registered (NCT02553772).
6	**Aragona P, et al. (2020) [19]**	Randomized, double-masked, multicenter	USA	N = 180 / N = 184	Optive Fusion UD vs. Refresh Optive UD	59.4 ± 13.8 / 57.5 ± 13.7	90 days (2x/day)	10% minor adverse events. Clinical trial not registered.
7	**Diaz-Llopis M, et al. (2019) [20]**	Randomized, investigator-masked, multicenter	Spain	N = 60 / N = 60	Seawater spray (Quinton) vs. CMC 0.5% (Viscofresh)	68.1 ± 6.3 / 66.8 ± 8.4	12 weeks (5x/day)	Results not detailed; trial not registered.

8	**Fogt JS, et al. (2019) [21]**	Randomized, observer-masked, crossover	USA	N = 19	Omega-3 (Refresh Optive MEGA-3) vs. Refresh Optive	46.5 ± 8.7	Single dose (60 minutes)	Limited data reported; 15-minute data missing. Trial registered (NCT03380624).
9	**Essa L, et al. (2018) [22]**	Randomized, investigator-masked, crossover	UK	N = 50	SH (0.15%, 0.4%), liposomal spray, CMC-based drops	60.8 ± 14.2	4 weeks (avg. 2–3x/day)	All treatments effective; osmolarity-balanced drops better for low tear volume; liposomal spray better for lipid deficiency. Trial: NCT02420834.
10	**Fondi K, et al. (2018) [23]**	Randomized, patient-masked, crossover	Austria	N = 40	Thealoz Duo vs. Thealoz Duo Gel	43.7 ± 12.3	1 week (avg. 3.2x/day vs. 1.9x/day)	Trial registered (NCT02980913); specific outcomes not detailed.
11	**Chiambaretta F, et al. (2017) [24]**	Randomized, investigator-masked, multicenter	France	N = 52 / N = 49	HA-trehalose vs. HA	60.0 ± 12.2 / 58.5 ± 13.4	84 days (3–6x/day)	More adverse events with HA (24 cases) vs. HA-trehalose (3 cases). Trial: NCT02023268.
12	**Safarzadeh M, et al. (2017) [25]**	Randomized, patient-masked	Iran	N = 41 / N = 47	Tears Naturale vs. Tearlose (Dextran-HPMC formulations)	44.1 ± 6.3 / 45.8 ± 8.4	4 weeks (2x/day)	Only fluorescein staining assessed. Clinical trial not registered.
13	**Robert PY, et al. (2016) [26]**	Randomized, investigator-masked, multicenter	France	N = 37 / N = 37	Cationic emulsion vs. SH 0.18% (Vismed)	60.0 ± 14.6 / 65.3 ± 11.1	3 months (4x/day)	AEs: Cationic emulsion (18%) vs. Vismed (27%). >10% dropout. Trial: EudraCT 2011-A00955-36.
14	**Simmons PA, et al. (2015) [27]**	Randomized, investigator-masked, multicenter	USA	N = 105 / 103 / 51 / 56	Various CMC formulations	53–56	30 days (2x/day or more)	No significant differences in efficacy, safety, or acceptability. Trial: NCT01459588.
15	**Amrane M, et al. (2015) [28]**	Randomized, open-label, multicenter	France	N = 44 / N = 35	Cationorm vs. PVA–Povidone (Refresh)	61.3 ± 15.4 / 61.9 ± 12.5	4 weeks (4x/day)	Subgroup analysis performed in MGD participants. Clinical trial not registered.

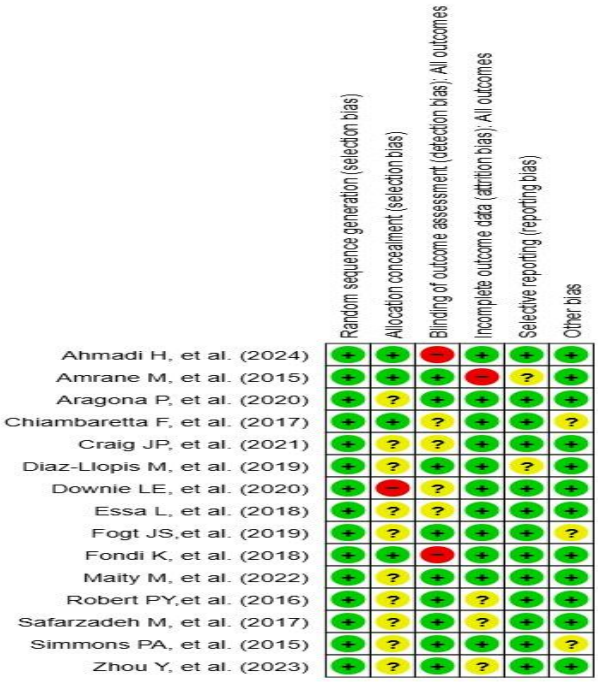

Fig 2: Summary of risk of bias: Each study was evaluated for the risk of bias associated with its specific items.

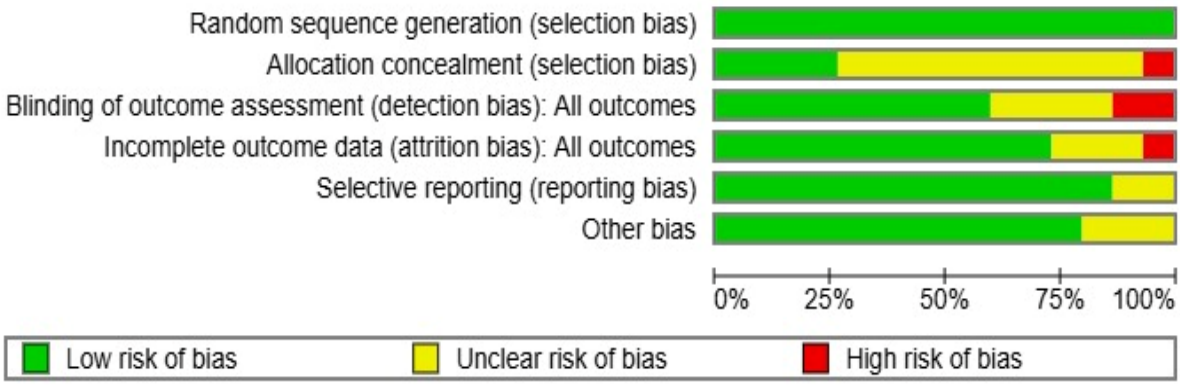

Figure 3: The author's assessment of each risk of bias item is represented as percentages across all articles in the risk of bias graph.

Quality Assessment of Included Studies

The methodological quality of included RCTs was assessed using the **Cochrane Risk of Bias Tool (RoB 1.0)** in **Review Manager (RevMan) version 5.4**. The following domains were evaluated:

- **Selection bias** (random sequence generation, allocation concealment)
- **Performance bias** (blinding of participants and personnel)
- **Detection bias** (blinding of outcome assessment)
- **Attrition bias** (completeness of outcome data)
- **Reporting bias** (selective outcome reporting)
- **Other bias** (any other potential threats to validity)

Each domain was rated as **low risk (−), unclear risk (?)**, or **high risk (+)** of bias.

7. Data Synthesis and Analysis

Due to significant **clinical and methodological heterogeneity** including variability in artificial tear formulations, dosing regimens, study designs, and outcome measures—a **meta-analysis was not conducted**. Instead, a **descriptive (narrative) synthesis** was performed. Key findings were summarized narratively and presented in tabular form where applicable.

Risk of bias assessments and synthesis were independently conducted by two reviewers. Any discrepancies were resolved through discussion or, when necessary, consultation with a third reviewer.

Eligible Study Characteristics

A total of 15 studies met the inclusion criteria and were included in this systematic review, each evaluating the safety and therapeutic efficacy of various artificial tear formulations in patients with DED.

The included studies employed a range of methodological designs, including RCTs, prospective cohort studies, and crossover trials, reflecting a robust and diverse evidence base. These studies were conducted across multiple countries, including the United States, Iran, India, Australia, Canada, the United Kingdom, France, Spain, and Austria, thereby offering a broad international perspective on the management of DED.

Sample sizes ranged from 19 to 184 participants per study arm, indicating variability in study power and scope. The intervention durations varied considerably—from single-dose assessments with follow-up at one hour to long-term trials extending up to six months.

While the overall methodological quality was acceptable, several studies demonstrated a high risk of bias, particularly in areas such as participant selection and outcome assessment. These limitations were primarily attributed to retrospective elements or insufficient reporting, which may affect the internal validity and generalizability of the findings. A comprehensive overview of the study

characteristics, including design, sample size, duration, and primary outcomes, is provided in Table 1.

Key Findings and Comparative Efficacy

- **Combination formulations** generally outperformed single-agent drops:
  - Carboxymethyl cellulose (CMC) combined with hyaluronic acid (HA) showed superior outcomes compared to either agent alone [19, 27].
  - Trehalose enhanced the efficacy of sodium hyaluronate and HA [24].
- **Predictive value of early response**:
  - Consistent use of artificial tears over one month predicted long-term benefit in approximately one-third of patients [14].
- **Formulation-specific benefits**:
  - Individual tear film layer–targeted formulations were comparably effective overall; however, the optimal choice may depend on baseline tear film classification [27].
  - Phospholipid-containing drops were particularly effective in evaporative DED [14, 22].
  - Osmoprotectants were beneficial for patients with high tear film osmolarity [22].
  - Cationic formulations demonstrated superior efficacy in reducing objective symptoms compared to polyvinyl alcohol and sodium hyaluronate–based drops [26, 28].

Risk of Bias Assessment

This systematic review employed the Cochrane *Risk of Bias* tool (RoB 2.0), specifically designed for RCTs. The tool evaluates bias across five key domains:

- **Randomization process**
- **Deviations from intended interventions**
- **Missing outcome data**
- **Measurement of outcomes**
- **Selection of the reported results**

Based on this structured assessment, **71.11%** of the included studies were rated as having a **low risk of bias**, indicating a robust study design with reliable randomization and minimal risk of systematic error. These studies demonstrated appropriate methods of assigning participants to intervention groups, strengthening the credibility of their findings.

Approximately **22.44%** of studies were rated as having high risk (previously referred to as "unclear" risk), often due to **incomplete reporting or insufficient methodological detail**, which could introduce bias but not necessarily invalidate the results.

A smaller subset, **4.44%**, was judged to have a **high risk of bias**, typically due to methodological flaws such as inadequate blinding, incomplete data, or inconsistent outcome reporting, which may compromise the validity of their conclusions.

DISCUSSION

Artificial tears remain a fundamental component in the treatment of DED, providing symptom relief across the full spectrum of disease severity. Strong clinical evidence favors the use of preservative-free or minimally preserved formulations for long-term management, as these offer enhanced ocular surface tolerability and reduced toxicity. High-liposome concentration formulations have shown particular efficacy in evaporative DED, a subtype commonly associated with meibomian gland dysfunction (MGD). Typically, a regimen of four instillations per day for one month is recommended to evaluate initial therapeutic response, with modifications made based on individual outcomes. Notably, while subjective symptom relief may occur early, objective improvements in ocular surface health may take up to four months, emphasizing the importance of patient education, sustained use, and regular follow-up.

Over time, the formulation of artificial tears has advanced significantly. Contemporary multi-ingredient preparations—especially those incorporating polyethylene glycol (PEG)—demonstrate greater efficacy than earlier monotherapies. These products aim to improve lubrication, extend

retention time, and support epithelial repair. Nevertheless, treatment success hinges not only on the formulation itself but also on patient-specific factors. Manual dexterity, comfort with instillation techniques, and the design of the delivery system (e.g., traditional dropper bottles versus spray applicators) can significantly impact compliance and, by extension, clinical outcomes [29].

Beyond symptomatic management, artificial tears are now being explored for their utility in asymptomatic individuals with ocular surface disease. Preoperative administration before refractive or cataract surgery may enhance tear film stability, thereby improving surgical accuracy and comfort. Röggla et al. (2021) [30] highlighted this potential use, though further robust, large-scale studies are necessary to define standardized protocols for such indications.

Most artificial tears are formulated with an aqueous base and incorporate viscosity-enhancing agents to improve tear film stability and extend retention on the ocular surface. Commonly used ingredients include carbomer 940, carboxymethylcellulose (CMC), dextran, hyaluronic acid, sodium hyaluronate, hydroxypropyl guar (HP-guar), hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol, polyvinylpyrrolidone, and polyethylene glycol (PEG) [4]. These compounds are frequently combined with osmoprotectants, antioxidants, pH buffers, electrolytes, and low-toxicity preservatives to maintain biocompatibility and ensure product shelf stability.

Although aqueous-based formulations primarily target the muco-aqueous layer of the tear film, their broad efficacy across various DED subtypes makes them a practical first-line therapy [31]. At the same time, lipid-based artificial tears have gained recognition for their ability to replenish the tear film's lipid layer and reduce evaporation, particularly in evaporative dry eye related to MGD. Randomized controlled trials, including that by Agarwal et al. (2019) [34], have demonstrated the superior effectiveness of lipid-based drops in these contexts.

Lipid-containing artificial tears are now available in innovative forms, including nano-emulsion eye drops and liposomal sprays, which are applied to the closed eyelid. These are especially helpful for patients with physical limitations that make traditional drop instillation difficult. Additionally, newer water-free lipid formulations, such as perfluorohexyloctane-based drops, offer preservative-free solutions ideal for patients requiring chronic use or those with sensitivities to preservatives.

Despite these advancements, several gaps remain in the current body of evidence. A major limitation is the lack of standardized diagnostic criteria for DED across studies, which hampers direct comparisons and meta-analytical interpretation. Variability in patient demographics, disease severity, and outcome measurement further complicates the synthesis of findings. Moreover, there is insufficient data on patient adherence to artificial tear regimens—a critical factor influencing both perceived symptom relief and actual clinical effectiveness.

Future research should focus on the development of uniform diagnostic and outcome assessment standards, long-term efficacy evaluations, and personalized treatment strategies based on individual patient profiles. The integration of smart delivery systems, AI-driven adherence monitoring, and patient-centered designs may further enhance treatment success and long-term management of chronic DED.

CONCLUSION

Artificial tears remain the cornerstone of DED management and provide valuable adjunctive benefits in conditions such as corneal abrasions, ocular surface wound healing, inflammation, conjunctivitis, keratitis, contact lens discomfort, and foreign body removal. Evidence from 15 randomized controlled trials supports their efficacy in alleviating DED symptoms within one month when used approximately four times daily. However, objective improvements in ocular signs often require sustained use over several months, underscoring the importance of long-term management and routine follow-up.

Not all patients experience adequate relief with artificial tears alone. For those unresponsive after one month, alternative or adjunctive therapies should be explored. Combination formulations generally yield superior outcomes compared to single-agent preparations, with PEG-based drops demonstrating better efficacy than CMC or HPMC variants. In patients with evaporative DED particularly those

with meibomian gland dysfunction high-concentration liposomal formulations offer enhanced therapeutic benefit.

ABBREVIATION

AE – Adverse Event
CMC – Carboxymethylcellulose
CE – Cationic Emulsion
CT – Computed Tomography
HA – Hyaluronic Acid
HP-guar – Hydroxypropyl guar
HPMC – Hydroxypropyl Methylcellulose
HT – Thealoz Duo (Sodium Hyaluronate and trehalose)
HTC-gel – Thealoz Duo Gel (Hyaluronic Acid, trehalose, and carbomer)
LWE – Lid Wiper Epitheliopathy
NIBUT – Non-Invasive Break-Up Time
OM3 – Omega-3 Artificial Tear Formulation
OSDI – Ocular Surface Disease Index
PEG – Polyethylene Glycol
PG – Propylene Glycol
ROA – Refresh Optive Advanced
SH – Sodium Hyaluronate
TBUT – Tear Break-Up Time
VAS – Visual Analog Scale

REFERENCES

1. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tsubota K, Stapleton F. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017 Jul;15(3):276-283. doi: 10.1016/j.jtos.2017.05.008. Epub 2017 Jul 20. PMID: 28736335.
2. Sullivan DA, Rocha EM, Aragona P, Clayton JA, Ding J, Golebiowski B, Hampel U, McDermott AM, Schaumberg DA, Srinivasan S, Versura P, Willcox MDP. TFOS DEWS II Sex, Gender, and Hormones Report. Ocul Surf. 2017 Jul;15(3):284-333. doi: 10.1016/j.jtos.2017.04.001. Epub 2017 Jul 20. PMID: 28736336.
3. Tsubota K, Yokoi N, Shimazaki J, Watanabe H, Dogru M, Yamada M, Kinoshita S, Kim HM, Tchah HW, Hyon JY, Yoon KC, Seo KY, Sun X, Chen W, Liang L, Li M, Liu Z; Asia Dry Eye Society. New Perspectives on Dry Eye Definition and Diagnosis: A Consensus Report by the Asia Dry Eye Society. Ocul Surf. 2017 Jan;15(1):65-76. doi: 10.1016/j.jtos.2016.09.003. Epub 2016 Oct 8. PMID: 27725302.
4. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. Ocular Surface. 2017;15(3):575–628. doi: 10.1016/j.jtos.2017.05.006
5. Baudouin C, Aragona P, Messmer EM, Tomlinson A, Calonge M, Boboridis KG, Akova YA, Geerling G, Labetoulle M, Rolando M. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf. 2013 Oct;11(4):246-58. doi: 10.1016/j.jtos.2013.07.003. Epub 2013 Aug 9. PMID: 24112228.
6. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, Na KS, Schaumberg D, Uchino M, Vehof J, Viso E, Vitale S, Jones L. TFOS DEWS II Epidemiology Report. Ocul Surf. 2017 Jul;15(3):334-365. doi: 10.1016/j.jtos.2017.05.003. Epub 2017 Jul 20. PMID: 28736337.
7. Garcia-Alfaro P, Garcia S, Rodriguez I, Vergés C. Dry eye disease symptoms and quality of life in perimenopausal and postmenopausal women. Climacteric. 2021 Jun;24(3):261-266. doi: 10.1080/13697137.2020.1849087. Epub 2020 Dec 7. PMID: 33283560.
8. Matossian C, McDonald M, Donaldson KE, Nichols KK, MacIver S, Gupta PK. Dry Eye Disease: Consideration for Women's Health. J Womens Health (Larchmt). 2019 Apr;28(4):502-514. doi: 10.1089/jwh.2018.7041. Epub 2019 Jan 29. PMID: 30694724; PMCID: PMC6482917.

9. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007 Apr;5(2):93-107. doi: 10.1016/s1542-0124(12)70082-4. PMID: 17508117.
10. Cai Y, Wei J, Zhou J, Zou W. Prevalence and Incidence of Dry Eye Disease in Asia: A Systematic Review and Meta-Analysis. Ophthalmic Res. 2022;65(6):647-658. doi: 10.1159/000525696. Epub 2022 Jun 27. PMID: 35760054.
11. Mateo-Orobia AJ, Del Prado Sanz E, Blasco-Martínez A, Pablo-Júlvez LE, Farrant S, Chiambaretta F. Efficacy of artificial tears containing trehalose and hyaluronic acid for dry eye disease in women aged 42-54 versus ≥ 55 years. Cont Lens Anterior Eye. 2023 Aug;46(4):101845. doi: 10.1016/j.clae.2023.101845. Epub 2023 Apr 26. PMID: 37117131.
12. Verjee MA, Brissette AR, Starr CE. Dry Eye Disease: Early Recognition with Guidance on Management and Treatment for Primary Care Family Physicians. Ophthalmol Ther. 2020 Dec;9(4):877-888. doi: 10.1007/s40123-020-00308-z. Epub 2020 Oct 22. PMID: 33090327; PMCID: PMC7708574.
13. Essa L, Laughton D, Wolffsohn JS. Can the optimum artificial tear treatment for dry eye disease be predicted from presenting signs and symptoms? Cont Lens Anterior Eye. 2018 Feb;41(1):60-68. doi: 10.1016/j.clae.2017.07.007. Epub 2017 Aug 12. PMID: 28811095.
14. Craig JP, Muntz A, Wang MT, Luensmann D, Tan J, Huarte ST, Xue AL, Jones L, Willcox MD, Wolffsohn JS. Developing evidence-based guidance for the treatment of dry eye disease with artificial tear supplements: A six-month multicentre, double-masked randomised controlled trial. The ocular surface. 2021 Apr 1;20:62-9.
15. Ahmadi H, Tahmasbian S, Janbazi M, Amiri A, Heidari Z. Evaluation of cyclosporine 0.05% and artificial tears for the management of dry eye disease following cataract surgery: a randomized controlled trial. Annals of Medicine and Surgery. 2024 Apr 1;86(4):1983-8.
16. Zhou Y, Sidhu GS, Whitlock JA, Abdelmalik B, Mayer Z, Li Y, Wang GP, Steigleman WA. Effects of carboxymethylcellulose artificial tears on ocular surface microbiome diversity and composition, A randomized controlled trial. Translational vision science & technology. 2023 Aug 1;12(8):5-.
17. Maity M, Allay MB, Ali MH, Basu S, Singh S. Effect of different artificial tears on tear film parameters in dry eye disease. Optometry and Vision Science. 2022 Dec 28:10-97.
18. Downie LE, Hom MM, Berdy GJ, El-Harazi S, Verachtert A, Tan J, Liu H, Carlisle-Wilcox C, Simmons P, Vehige J. An artificial tear containing flaxseed oil for treating dry eye disease: A randomized controlled trial. The Ocular Surface. 2020 Jan 1;18(1):148-57
19. Aragona P, Benítez-del-Castillo JM, Coroneo MT, Mukherji S, Tan J, Vandewalle E, Vingrys A, Liu H, Carlisle-Wilcox C, Vehige J, Simmons PA. Safety and efficacy of a preservative-free artificial tear containing carboxymethylcellulose and hyaluronic acid for dry eye disease: a randomized, controlled, multicenter 3-month study. Clinical Ophthalmology. 2020 Oct 1:2951-63.
20. Diaz-Llopis M, Pinazo-Duran MD, Diaz-Guiñon L, Rahhal-Ortuño M, Perez-Ramos M, Bosch R, Gallego-Pinazo R, Dolz-Marco R, Diaz-Guiñon T, Diaz M, Romero FJ. A randomized multicenter study comparing seawater washes and carmellose artificial tears eyedrops in the treatment of dry eye syndrome. Clinical Ophthalmology (Auckland, NZ). 2019 Mar 12;13:483.
21. Fogt JS, Fogt N, King-Smith PE, Liu H, Barr JT. Changes in tear lipid layer thickness and symptoms following the use of artificial tears with and without omega-3 fatty acids: a randomized, double-masked, crossover study. Clinical Ophthalmology. 2019 Dec 20:2553-
22. Essa L, Laughton D, Wolffsohn JS. Can the optimum artificial tear treatment for dry eye disease be predicted from presenting signs and symptoms?. Contact Lens and Anterior Eye. 2018 Feb 1;41(1):60-8.
23. Fondi K, Wozniak PA, Schmidl D, Bata AM, Witkowska KJ, Popa-Cherecheanu A, Schmetterer L, Garhöfer G. Effect of hyaluronic acid/trehalose in two different formulations on signs and symptoms in patients with moderate to severe dry eye disease. Journal of ophthalmology. 2018;2018(1):4691417.

24. Chiambaretta F, Doan S, Labetoulle M, Rocher N, El Fekih L, Messaoud R, Khairallah M, Baudouin C, HA-trehalose Study Group. A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome. European Journal of Ophthalmology. 2017 Jan;27(1):1-9.
25. Safarzadeh M, Azizzadeh P, Akbarshahi P. Comparison of the clinical efficacy of preserved and preservative-free hydroxypropyl methylcellulose-dextran-containing eyedrops. Journal of optometry. 2017 Oct 1;10(4):258-64.
26. Robert PY, Cochener B, Amrane M, Ismail D, Garrigue JS, Pisella PJ, Baudouin C. Efficacy and safety of a cationic emulsion in the treatment of moderate to severe dry eye disease: a randomized controlled study. European journal of ophthalmology. 2016 Nov;26(6):546-55.
27. Simmons PA, Carlisle-Wilcox C, Vehige JG. Comparison of novel lipid-based eye drops with aqueous eye drops for dry eye: a multicenter, randomized controlled trial. Clinical Ophthalmology. 2015 Apr 15:657-64.
28. Amrane M, Creuzot-Garcher C, Robert PY, Ismail D, Garrigue JS, Pisella PJ, Baudouin C. Ocular tolerability and efficacy of a cationic emulsion in patients with mild to moderate dry eye disease–a randomised comparative study. Journal francais d'ophtalmologie. 2014 Oct 1;37(8):589-98.
29. Drew T, Wolffsohn JS. Usability of prostaglandin monotherapy eye droppers. Br J Ophthalmol. 2015 Sep;99(9):1251-4. doi: 10.1136/bjophthalmol-2014-306291. Epub 2015 Mar 11. PMID: 25761745.
30. Röggla V, Leydolt C, Schartmüller D, Schwarzenbacher L, Meyer E, Abela-Formanek C, Menapace R. Influence of Artificial Tears on Keratometric Measurements in Cataract Patients. Am J Ophthalmol. 2021 Jan;221:1-8. doi: 10.1016/j.ajo.2020.08.024. Epub 2020 Aug 21. PMID: 32828877.
31. Pucker AD, Ng SM, Nichols JJ. Over the counter (OTC) artificial tear drops for dry eye syndrome. Cochrane Database Syst Rev. 2016;2016(2):Cd009729. doi: 10.1002/14651858.CD009729.pub2
32. Lee SY, Tong L. Lipid-containing lubricants for dry eye: a systematic review. Optom Vis Sci. 2012 Nov;89(11):1654-61. doi: 10.1097/OPX.0b013e31826f32e0. PMID: 23096494.
33. Moshirfar M, Pierson K, Hanamaikai K, Santiago-Caban L, Muthappan V, Passi SF. Artificial tears potpourri: a literature review. Clin Ophthalmol. 2014 Jul 31;8:1419-33. doi: 10.2147/OPTH.S65263. PMID: 25114502; PMCID: PMC4124072.
34. Agarwal P, Khun D, Krösser S, Eickhoff K, Wells FS, Willmott GR, Craig JP, Rupenthal ID. Preclinical studies evaluating the effect of semifluorinated alkanes on ocular surface and tear fluid dynamics. Ocul Surf. 2019 Apr;17(2):241-249. doi: 10.1016/j.jtos.2019.02.010. Epub 2019 Mar 2. PMID: 30831252.