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REVIEW

Management of Dry Eye Disease with Artificial Tears Containing Hyaluronic Acid and Trehalose: A Narrative Review

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Abstract: Dry eye disease (DED) is a growing global public health concern. The market for over-the-counter artificial tears, the mainstay treatment for DED, is also experiencing growth, driven by the rising prevalence of the condition and advancements in therapeutic formulations. The treatment landscape for DED is rapidly evolving, and currently marketed artificial tears vary in their active ingredients, use of preservatives, and formulations. Therefore, it is imperative to understand the breadth of management options and the evidence base of formulations to inform treatment decisions and treatment guidelines. In our narrative review, we provide an overview of the development and regulation of artificial tear formulations in the United States. We evaluate their active ingredients, formulations, and use of preservatives. Increasingly, preservative-free formulations are being developed that contain combinations of well-established active ingredients. In this context, a key focus of the narrative review is to critically analyze the novel, preservative-free, multidose formulation of hyaluronic acid and trehalose in artificial tears. We highlight its formulation and mechanism of action and its involvement in autophagy regulation and inflammatory response. We describe the strong and growing evidence base supporting the effectiveness and safety of this combination formulation of artificial tears in managing DED, and we also describe its use in postcataract surgery and in the real world.

Keywords: artificial tears, dry eye, trehalose, hyaluronic acid, combination, safety, efficacy

Introduction

Dry eye disease (DED) is a common, multifactorial, chronic inflammatory disease of the ocular surface and tear film with a global prevalence of approximately 5% to 50%.[1] An estimated 16.4 million American adults have diagnosed DED, and an estimated additional 6 million adults have reported DED symptoms but have not received a formal diagnosis.[2] The primary treatment for DED is artificial tears,[3,4] which aim to stabilize the tear film, reduce inflammation, and protect the ocular surface to alleviate symptoms.[3,5–7] The market for over-the-counter (OTC) artificial tears is increasing due to the rising prevalence of DED, which has been attributed to the growing aging population[1] and prolonged screen use in adult and pediatric populations.[8–10] An estimated 117 million Americans reported the use of eyedrop products in 2020, and this number was projected to increase to 123 million by 2024.[11] Artificial tears formulations are rapidly advancing, with newer formulations containing novel active ingredients, novel combinations of well-established ingredients, advancements in preservative-free options, and improved compositions.[12] This narrative review provides an overview of the development and regulation of artificial tears for managing DED in the United States. We evaluate their active ingredients, formulations, and use of preservatives. Increasingly, preservative-free formulations are being developed that contain combinations of well-established active ingredients, such as hyaluronic acid and trehalose.[13] We describe the formulation and mechanism of action of this combination treatment and its involvement in autophagy regulation and

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inflammatory response. There is a strong and growing evidence base supporting the effectiveness and safety of this combination formulation of artificial tears in managing DED as well as in postcataract surgery and the real world.

Burden of DED

Dry eye disease is a sexually dimorphic condition, with females at higher risk than males due to biological sex, hormonal differences, and gender factors.[14] Other key risk factors associated with DED include advancing age (over 50 years), systemic and autoimmune diseases,[1,10] and the use of medications such as diuretics, antihistamines, antidepressants, and anxiolytic medications.[15] Additionally, the use of preservative-containing eyedrops, contact lens use, certain lifestyle choices (eg, excessive screen use, tobacco use), environmental exposures, and ophthalmic procedures such as cataract and refractive laser surgery further contribute to the development of DED symptoms in both adults and children.[8,10,16,17] Meibomian gland atrophy, characterized by duct obstruction and changes in the glandular secretion, is also a significant contributor to DED and is commonly observed among adult and pediatric populations.[18–20]

The overall burden of DED is rising due to the growing aging population[1] and due to the prolonged use of digital devices such as computers, laptops, smartphones, and tablets in adult and pediatric populations; the use of these devices was exacerbated during the COVID-19 pandemic.[8–10] Visual screen use reduces the blinking rate and increases incomplete blinking, leading to accelerated tear evaporation, tear film instability, ocular surface damage, and dry eye symptoms.[1,21,22] A 2025 study indicates that there are ocular surface disease signs present in young adults regardless of dry eye status.[23] In this prospective, longitudinal study including 50 participants aged 18–25 years, 56% met criteria for DED, over 90% had at least one diagnostic sign (even if not fulfilling DED criteria), and 48% had at least 25% meibomian gland loss in either lid by age 25.[23] Disease state awareness is growing among patients, prompting them to self-treat or seek treatment more frequently and earlier in the disease course. Content creators such as nonphysician medical providers, nonmedical providers, licensed physicians, and private companies use social media platforms such as TikTok and Instagram to discuss DED, covering topics from educational content, treatment options, homeopathy, and personal experiences.[24]

The burdensome symptoms of DED (eg, pain, discomfort, fluctuating or blurry vision)[1,25,26] negatively affect quality of life (QoL), including aspects of physical, social, and psychological functioning, daily activities, and workplace productivity.[10,27–29] The severity of DED symptoms positively correlates with patient-reported depression, anxiety, and stress scores.[10] The diminished QoL experienced by patients with moderate-to-severe DED is comparable to the QoL impairments experienced in patients undergoing dialysis or those with severe angina.[30,31] DED also imposes a substantial economic burden,[1,29,32–34] including direct costs involving the use of eyedrops, lubricants, physician visits, and supplements as well as indirect costs[33] related to productivity loss due to absenteeism or presenteeism,[29,32,33] that increases with DED severity.[32,34]

Ingredients Used in Artificial Tears

Various artificial tear treatments are now available to alleviate the symptoms in DED by enhancing tear film stability, reducing inflammation, and safeguarding the ocular surface.[3,5–7] Artificial tears are the mainstay management option in all stages of DED management.[3,4] Artificial tear formulations contain various active ingredients and biologically active excipients and may contain preservatives.[35] Demulcent agents are water-soluble polymers that enhance viscosity, increase tear film thickness, and provide lubrication to the ocular surface.[36–38] Currently marketed artificial tears in the United States are formulated with a demulcent (Table 1)[39] as the active ingredient and often contain a combination of other biologically active excipients (or inactive ingredients). Most marketed artificial tears are demulcents (also referred to as viscosity-enhancing agents);[36] however, artificial tears may also incorporate osmoprotectants to counteract tear film hyperosmolarity, humectants, oils, carbomers, or poloxamers (Table 1).[3,36–38] Viscosity and pH are also important factors that impact patient compliance with DED treatment; formulations that have high viscosity and have a pH close to that in normal tears (within the range of 6.5 to 7.8) are associated with better tear film distribution and ocular comfort, respectively.[40,41]

A summary of currently marketed artificial tears in the United States by active ingredient(s) and types of ingredient(s) for preserved formulations is presented in Table 2 and for preservative-free formulations is presented in Table 3. Currently available preserved artificial tears are preserved by OcoPure® (sodium chlorite), Purite® (Stabilized Oxychloro Complex), or Polyquad® (polyquaternium-1), and these formulations were first marketed from 2008. The preservative-free formulations are newer and were first marketed in 2016 and contain key active ingredients (eg, sodium

Table 1 Summary of Ingredients Used in Artificial Tears

Demulcent Agents (Active Ingredient)	**Examples: Cellulose Derivatives, Dextran, Gelatin, Polyols, Polyvinyl Alcohol, or Povidone**
Biologically active excipients (inactive ingredients)	Osmoprotectants Examples: trehalose, sorbitol, erythritol, L-carnitine, betaine, and glycerin Humectants Examples: HA and SH Oils Examples: castor, mineral, or flaxseed Carbomers Poloxamers

Abbreviations: HA, hyaluronic acid; SH, sodium hyaluronate.

Table 2 Currently Marketed Preserved Artificial Tear Formulations in the United States

Product	**Active Ingredient(s)**	**Key Inactive Ingredient(s) with Biological Activity**	**Preservative Type**	**Year Marketed in the United States**
Blink® Tears Lubricating Eye Drops	Polyethylene Glycol 400 0.25%	Sodium Hyaluronate	Sodium Chlorite (OcuPure® brand)	2008
Blink®Gel Tears Lubricating Eye Drops	Polyethylene Glycol 400 0.25%	Sodium Hyaluronate	Sodium Chlorite (OcuPure® brand)	2008
Refresh Optive® Gel Drops Lubricant Eye Gel	CMC 1%, Glycerin 0.9%	–	Purite® (Stabilized Oxychloro Complex)	2015
Systane® Complete Lubricant Eye Drops	Propylene Glycol 0.6%	Hydroxypropyl Guar, Mineral Oil	POLYQUAD® (polyquaternium-1)	2018
Blink® Triple Care Lubricating Eye Drops	Polyethylene Glycol 400 0.25%	Castor Oil, Sodium Hyaluronate	Sodium Chlorite (OcuPure® brand)	2022

Abbreviation: CMC, carboxymethylcellulose.

Table 3 Currently Marketed Preservative-Free Artificial Tear Formulations in the United States

Product	**Active Ingredient(s)**	**Key Inactive Ingredient(s) with Biological Activity**	**Year Marketed in the United States**
Refresh® PM PF Lubricant Eye Ointment	Mineral Oil 42.5%, White Petrolatum 57.3%	–	2016
Blink® Tears PF Lubricating Eye Drops	Polyethylene Glycol 400 0.25%	Sodium Hyaluronate	2016
Refresh® Digital PF Lubricant Eye Drops	CMC 0.5%, Glycerin 1%, Polysorbate 80 0.5%	Castor Oil	2020
Systane® Hydration PF Lubricant Eye Drops	Polyethylene Glycol 400 0.4%, Propylene Glycol 0.3%	Hydroxypropyl Guar, SH	2020
iVIZIA® Sterile Lubricant Eye Drops	Povidone 0.5%	HA, Trehalose	2021
iVIZIA® Lubricant Eye Gel	Povidone 0.5%	HA, Trehalose, Carbomer	2021
Refresh Optive Mega-3® PF Lubricant Eye Drops	CMC 0.5%, Glycerin 1%, Polysorbate 80 0.5%	Flaxseed & Castor Oils, Trehalose	2021
Systane® Complete PF Lubricant Eye Drops	Propylene glycol 0.6%	Hydroxypropyl Guar, Mineral Oil	2022
Optase® MGD Advanced Dry Eye Drops	Glycerin 0.9%	Sacha Inchi Seed Oil, SH, Trehalose	2022
Refresh® RELIEVA® PF Xtra Lubricant Eye Drops	CMC 0.5%, Glycerin 0.9%	SH, Trehalose	2024
Blink® Nourish Lubricating Eye Drops	Glycerin 0.75%	SH, Trehalose	2025
Systane® Pro PF Lubricant Eye Drops	Propylene glycol 0.6%	SH	2025

Abbreviations: CMC, carboxymethylcellulose; HA, hyaluronic acid; SH, sodium hyaluronate.

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hyaluronate [SH], hyaluronic acid [HA], trehalose) or combinations of well-established active ingredients (eg, HA + trehalose, HA + trehalose + carbomer).

Use of Preservatives in Artificial Tears

Artificial tears are typically formulated with preservatives to ensure sterility and to extend shelf life.[4,42] The most common preservative in topical drops is benzalkonium chloride (BAK).[43,44] Although BAK is an effective antimicrobial agent, it is associated with toxicity and limitations (Table 4).[43,45–47] BAK alternatives (eg, Purite®, Polyquad) provide less toxicity; however, there are certain disadvantages to their use (Table 4).[46]

Preservative-free ophthalmic formulations have been developed to address the limitations of using preservatives and to avoid preservative-induced adverse effects. The global availability of preservative-free artificial tears is expanding, driven by growing awareness of the adverse impact of preservatives and advancements in technology and innovation that enhance product development. Preservative-free artificial tears reduce signs and symptoms of DED more effectively than BAK-containing agents.[48]

Regulation of Artificial Tears in the United States

In the United States, most artificial tears are marketed as OTC drugs.[39] These products are regulated by the U.S. Food and Drug Administration (FDA) under an OTC monograph, essentially a "rule book" that sets standards for safety, effectiveness, and labeling. The monograph defines which ingredients, concentrations, and labeling are considered safe and effective. The following specifications for artificial tears are provided in the Ophthalmic Drug Products for OTC Human Use (Monograph M018):[49]

- Permitted active ingredients and concentration ranges:

  a. Cellulose derivatives: carboxymethylcellulose (CMC) sodium: *0.2–2.5*%, hypromellose: *0.2–2.5*%, hydroxyethyl cellulose: *0.2–2.5%, and* methylcellulose: *0.2–2.5%.*
  b. Polyols (sugar alcohols): glycerin: *0.2–1*%, polyethylene glycol 300 or 400: *0.2–1%, and* propylene glycol: *0.2–1%.*
  c. Other lubricants: Dextran 70: *0.1%* (when combined with another polymeric demulcent), polyvinyl alcohol: *0.1–4%, and* povidone: *0.1–2%.*

- Indication: Temporary relief of dryness and irritation of the eye.
- Labeling requirements: Directions for use, warnings (eg, discontinue if pain or vision changes occur), and storage instructions.

Products that comply with these conditions are considered "generally recognized as safe and effective" (GRASE) and do not require individual FDA approval. Manufacturers are responsible for ensuring compliance, and the FDA primarily monitors safety after products reach the market. This framework was modernized under the CARES Act (2020) to allow faster updates when safety concerns arise.

Table 4 Advantages and Disadvantages to BAK and BAK Alternatives

	BAK	BAK Alternatives (Purite®, Polyquad®)
Benefits	Effective antimicrobial agent	Less toxicity than BAK
Disadvantages	Associated with ocular surface disease and cytotoxic effects on the ocular surface in conjunctival and corneal cells, leading to exacerbated DED symptoms, especially following chronic use[43,45–47]	Can exert cytotoxic, proinflammatory, and structural damage effects on the ocular surface[46]

Abbreviations: BAK, benzalkonium chloride; DED, dry eye disease.

HA in Artificial Tears for the Treatment of DED

Formulation and Mechanism of Action

Hyaluronic acid (or its derivative, SH), a naturally occurring glycosaminoglycan, is an active ingredient that is frequently used in artificial tears.[5,7,50] HA is essential for joint and tendon lubrication, is distributed in connective, epithelial, and neural tissues,[5,7] and is found in vitreous and aqueous humor, cornea, and tear film.[50] Studies have shown multiple mechanisms of action of HA in the treatment of DED. In vitro studies demonstrate that HA inactivates the CD44 adhesion molecule, a receptor that is overexpressed in the cornea and the conjunctiva of patients with DED,[51] which promotes cellular migration and reepithelization.[52,53] HA has a role in regulating localized inflammation in patients with keratoconjunctivitis sicca.[54] Mechanical damage to the cornea is reduced with HA through viscoelastic properties that lubricate the ocular surface during blinking and ocular movements, thereby preventing damage from the eyelid.[55] Lastly, with an affinity of 1000-fold its weight, the water-retentive properties of HA facilitate ocular surface wettability by acting as a reservoir for the slow release of water molecules[56] and reducing tear evaporation.[52] HA has also been shown to increase the number of goblet cells,[57] decrease the apoptosis of corneal epithelial cells,[57,58] and increase corneal wound healing.[57,58]

HA concentration, drop frequency, and the molecular weight of HA vary widely in clinical trials.[50] Higher concentrations of HA (>0.2%) in eyedrops provide more extended tear film stability; however, blurry vision becomes more prominent as HA concentrations increase.[7] The molecular weight of HA varies based on the number of disaccharide units forming the molecule and ranges from <100 kilodaltons (kDa) to >1000 kDa.[59] Generally, high-molecular-weight HA has anti-inflammatory properties and is more viscous. In contrast, low-molecular-weight HA displays proinflammatory properties and has lower viscosity, allowing for greater distribution and protection of the ocular surface.[5,56,60,61] In a pivotal study using an environmental dry eye stress model, high-molecular-weight HA eyedrops provided significantly enhanced protection against mechanical damage and ocular surface inflammation compared with their low-molecular-weight counterparts.[58] This therapeutic superiority was attributed to the robust anti-inflammatory properties intrinsic to high-molecular-weight HA, underscoring its potential in managing ocular surface disorders.

Clinical Evidence Base

HA is recognized as a safe and effective therapeutic agent for DED, with a well-established role in enhancing tear film stability, reducing inflammation, and promoting ocular surface protection.[7,50,52,62,63] In a comprehensive review of 53 studies evaluating the safety and efficacy of HA (concentrations ranging from 0.1% to 0.4%) in artificial tears compared with baseline measures and placebo, significant improvements in symptoms and objective measures such as total ocular surface staining (in 40/53 treatment arms) and improved tear film break-up time (TBUT) (in 29/48 treatment arms) were demonstrated.[7] Schirmer's test scores improved in fewer studies (in 15 of 37 treatment arms).[7] No major complications or serious adverse events were associated with HA use.[7] In another review of 23 studies (30 treatment arms) comparing HA with other single-ingredient eyedrops, CMC showed better subjective outcomes in some studies.[50] In both studies, lack of comparative studies and varied treatment regimens limited the ability to recommend one formulation over another.[7,50] In a recent double-masked, controlled study in patients with moderate DED (N = 100), Maity et al (2024) reported significant improvements in TBUT that were maintained until 1 hour after drop instillation across five different formulations of CMC, SH, and polyethylene glycol–based artificial tears; however, none of the formulations were superior to the other formulations for TBUT changes at any time from baseline.[64] Together, these findings highlight the need for more robust and consistent research to understand HA's potential relative to other artificial tears fully and to optimize its use in clinical practice.

Meta-analyses evaluating the efficacy and safety of HA in treating DED demonstrate HA formulations are effective for tear production (as measured by Schirmer's test) and tear film stability (TBUT) compared with saline or non-HA formulations (Table 5).[52,63] In a meta-analysis of high or low concentrations of HA for DED, high concentrations (0.3%) of HA significantly improved the outcome of corneal fluorescein staining (CFS) according to random effect modeling (SMD −3.37, 95% CI −5.25 to −1.48, P = 0.0005); however, the Schirmer's I test, TBUT, the dry eye symptom score, and ocular surface disease index (OSDI) were not statistically significant (Table 5).[65] These findings suggest that high concentrations of HA were more effective than lower concentrations of HA in improving CFS, but variations in molecular weight and other properties can affect its overall viscosity and clinical application.[65]

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Table 5 Meta-Analyses Evaluating HA

Study	Schirmer's Test	TBUT	CFS	OSDI/Symptom Improvement
Ouyang et al (2024)[65] 10 RCTs comparing high or low concentrations of HA	No significant difference between low vs high concentration HA WMD 0.57 (95% CI −0.15 to 1.29), p = 0.12	No significant difference between low vs high concentration HA WMD 0.98 (95% CI −1.09 to 3.04), p = 0.35	Significant improvement with high vs low concentration HA SMD −3.37 (95% CI −5.25 to −1.48), p = 0.0005	No significant difference in OSDI for low vs high concentration HA SMD −0.24 (95% CI −0.75 to 0.27) p = 0.36
Yang et al (2021)[63] 19 studies comparing HA vs non-HA artificial tears	Significant improvements with HA vs non-HA SMD 0.18 (95% CI 0.03 to 0.33)	No significant difference between low vs high concentration HA SMD −0.00 (95% CI −0.10 to 0.11) Significant improvement with HA vs saline SMD 0.28 (95% CI 0.03 to 0.52)	Similar improvements for HA vs non-HA SMD −0.01 (95% CI −0.17 to 0.16)	No significant difference in OSDI for HA vs non-HA SMD −0.14 (95% CI −0.30 to 0.02) Significant improvement with HA vs saline SMD −0.61 (95% CI −1.12 to −0.10)
Ang et al (2017)[52] 18 studies comparing HA vs non-HA artificial tears	Significant improvements with HA vs non-HA SMD 0.238 (95% CI 0.107 to 0.369), p < 0.001	HA showed less improvement compared with non-HA SMD −0.566 (95% CI −1.099 to -0.0336), p = 0.037	HA showed superiority over non-HA artificial tears in 12 datasets, with 7 showing statistical significance	HA showed superiority over non-HA artificial tears in 10 datasets, with 6 showing statistical significance

Abbreviations: CFS, corneal fluorescein staining; CI, confidence interval; HA, hyaluronic acid; OSDI, Ocular Surface Disease Index; RCT, randomized controlled trial; SH, sodium hyaluronate; SMD, standardized mean difference; WMD, weighted mean difference.

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Trehalose in Artificial Tears for the Treatment of DED

Formulation and Mechanism of Action

Trehalose, a naturally nonreducing disaccharide consisting of 2 glucose molecules,[66,67] is a bioprotectant widely found in nature in bacteria, fungi, plants, and some invertebrates.[68,69] Trehalose is widely known for its ability to protect proteins and other biomolecules by upregulating in response to environmental stress.[70] Perhaps, the most well-known natural example of trehalose is the Rose of Jericho (*Selaginella lepidophylla)*, a resurrection plant that produces trehalose. The plant can survive years of desiccation through the action of trehalose, which replaces water in the organism by rearranging the cellular water structure.[71,72] As an osmoprotectant,[5,73,74] trehalose maintains osmotic balance and prevents water leakage from the cytoplasm. Trehalose prevents protein degradation and denaturation by binding to and protecting proteins and cell membranes, allowing them to retain their integrity and shape during periods of stress and quickly return to normal function.[63,73,74] Early in vivo and in vitro studies helped demonstrate the usefulness of trehalose as a treatment for DED.[75–77]

Clinical Evidence Base

Although trehalose has been used in artificial tears for decades, trehalose-containing artificial tears only recently became available in the United States.[66] Trehalose is an osmoprotectant known for its lubricating, hydrating, and protective properties in patients with DED.[66,67] Randomized controlled trials (RCTs) evaluating patients with DED demonstrate improved TBUT with trehalose compared with saline[78] and significant improvements in fluorescein and Rose Bengal scores of the ocular surface along with improved TBUT compared with hyaluronan or hydroxycellulose.[79]

Novel Artificial Tears Formulations

Although supplementation with artificial tears is a central part of DED management, providing ocular surface protection and possibly reducing inflammation, many patients continue to experience symptoms.[80] A significant challenge in treating ocular surface disorders is poor patient compliance, which is associated with persistent symptoms, demanding dosing regimens, adverse events, and treatment costs.[47,81] Another primary concern in managing DED is the iatrogenic effects associated with preservative-containing artificial tears, which have been addressed by preservative-free ophthalmic formulations.

New formulations of artificial tears are being developed to overcome the limitations and to address the challenges of conventional formulations. Some novel formulations of artificial tears combine well-established active ingredients, such as HA + trehalose, with anti-inflammatory molecules like n-acetyl-aspartyl-glutamic acid [NAAGA].[13] In a systematic review conducted by Semp et al in 2023, the efficacy of different formulations of artificial tears was examined, including 64 prospective studies that compared 2 or more formulations of artificial tears.[4] The investigators concluded that combination formulations were more effective than single-active ingredient artificial tears.

Most recently, efforts have been made to improve the lubrication properties of contact lenses. For example, self-lubricating, living contact lenses have been developed to contain self-replenishable reservoirs that autonomously produce and release HA to provide long-term comfort.[82]

HA + Trehalose Combination in Artificial Tears for the Treatment of DED

Formulation and Mechanism of Action

HA is an established safe and effective treatment for DED that benefits tear film stability, and trehalose is well established for its lubricating, hydrating, and protective properties in patients with DED.[66,67] Formulations that contain both HA + trehalose benefit from synergistic mechanisms of action, characterized by the lubrication properties of HA and the bioprotectant properties of trehalose.[5] A novel, preservative-free, multidose formulation of artificial tears has been developed for moderate-to-severe DED formulated with the well-established active ingredients of trehalose (3%) and HA (0.15%) (Thealoz® Duo). The gel formulation adds carbomer (0.25%), a polymer that enables longer-acting dispersion of the therapeutic ingredients (Thealoz® Duo Gel) and requires less frequent instillation.

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Efficacy of HA + Trehalose in Autophagy

Autophagy regulates inflammation in ocular surface homeostasis by degrading unwanted cellular organelles due to cells under starvation or environmental stresses.[83] Results of a recent study comparing HA + trehalose vs hydrocortisone and HA (I/HA) on clinical signs and inflammatory markers in a mouse DED model showed greater improvements with HA + trehalose vs I/HA.[84] Following 21 days of treatment with HA + trehalose, clinical signs of DED improved and inflammatory markers were reduced to a greater extent than with I/HA. The effect of HA + T on the reduction of corneal damage was demonstrated at 7 days, and the reduction in corneal damage was reduced by 50% at the endpoint, while the I/HA reduction was relatively stable throughout the study duration.

Clinical Evidence Base

There is strong evidence to support the use of trehalose-containing artificial tears, namely HA + trehalose and HA + trehalose + carbomer, for the safe and effective treatment of DED. Research collectively demonstrates that treatment of DED with HA + trehalose improves the signs and symptoms of DED[85–91] and improves ocular surface and tear film stability;[85–88,90,91] these studies also provide evidence that HA + trehalose is as effective or better than HA[85,86,88,89,91] or other treatments.[87,90] Patients with DED treated with HA + trehalose show improved patient satisfaction[85] and increased patient preference[86] compared with HA alone. Studies demonstrate that single instillation of HA + trehalose[92] and HA + trehalose + carbomer[93] results in longer corneal residence than HA. The HA + trehalose + carbomer formulation is as effective as HA in reducing DED symptoms, more effective than HA for OSDI and TBUT outcomes, and results in greater global patient satisfaction vs HA alone.[94] HA + trehalose[85,86,91] and HA + trehalose + carbomer[93,94] formulations are well-tolerated. Supplemental Table 1 summarizes the study design, results, and conclusions of studies evaluating the efficacy and safety of HA + trehalose and HA + trehalose + carbomer in patients with DED. These studies are highlighted in the sections below.

Efficacy of HA + Trehalose in DED

The noninferiority of HA + trehalose compared with HA alone was established in an RCT conducted in patients with moderate-to-severe DED (N = 105) in 2017.[85] Noninferiority of HA + trehalose (n = 52) to HA (n = 53) was established in terms of the change from baseline at day 35 of global ocular staining according to the Oxford grading score.[85] Secondary performance variables (ie, Schirmer's test at day 35, TBUT at day 35, van Bijsterveld score at days 35 and 84, and conjunctival hyperemia at day 84) were similarly improved with HA + trehalose and HA treatment.[85] Investigator and patient assessments at day 35 of global performance were significantly better among patients treated with HA + trehalose vs HA.[85] Administration of HA + trehalose resulted in significantly fewer ocular symptoms at instillation and fewer ocular adverse events vs the HA formulation.[85] Post-hoc analysis results demonstrate significantly more patients had OSDI <19 on day 84 with the combination formulation (HA + trehalose) vs HA alone (78.8% vs 58.5%, P = 0.025).[95] Similar to the findings of Chiambaretta et al,[85] other studies demonstrate improvements in tear film stability with artificial tears containing HA + trehalose.[91]

HA + trehalose is at least as effective as polyethylene glycol 400, propylene glycol, hydroxypropyl guar, polyquaternium-1 0.001% preservative, and purified water (Systane®) and, based on some outcomes, is more effective than this established treatment in patients with DED.[86] In a randomized, single-center, open-label crossover study of 17 patients with moderate-to-severe DED who were randomized to treatment with HA + trehalose or Systane®, patient satisfaction improved significantly during treatment with HA + trehalose and the difference in improvements between treatments was statistically significant in favor of HA + trehalose (P = 0.043).[86] HA + trehalose was at least as effective as Systane® in several secondary efficacy variables, including OSDI, staining, ocular signs, Schirmer's test, TBUT, patient satisfaction/global efficacy, and patient preference.[86] In another study, patients with DED treated with twice-daily HA + trehalose showed increased tear stability as demonstrated by significant improvements in the noninvasive tear break-up time and TBUT compared to treatment with carmellose control.[87]

HA + trehalose has a longer corneal residence time and results in significantly longer increases in tear film thickness (TFT) vs HA alone.[92] In a randomized, double-masked, controlled study, Schmidl et al showed a significantly different time course of TFT following a single instillation of SH + trehalose, HA, and sodium chloride (NaCl).[92] SH + trehalose

and HA significantly increased TFT 10 minutes after instillation. The increase in TFT remained up to 240 minutes after administration of SH + trehalose; however, the increase in TFT after administration of HA was statistically significant only up to 40 minutes after instillation. There was no significant change was observed following NaCl instillation.[92]

Efficacy of HA + Trehalose in Cataract Surgery

HA + trehalose is also effective in reducing dry eye signs and symptoms after cataract surgery.[88–90] Studies demonstrate significantly fewer dry eye symptoms (ie, lower postoperative OSDI scores)[88–90] and significantly increased TBUT[88–90] following the instillation of HA + trehalose. Mencucci et al randomized 120 patients to 3 treatment groups. In group 1, HA + trehalose was administered 3 times/day preoperatively; in group 2, HA + trehalose was administered for 5 weeks postoperatively; group 3 did not receive artificial tears.[88] Patients treated with HA + trehalose preoperatively and postoperatively showed lower OSDI on the day of surgery and at postoperative visits compared with patients treated with HA + trehalose only postoperatively and the control group. In another study, Cagini et al examined HA + trehalose vs unpreserved NaCl, administered twice a day for 4 weeks in 135 patients with healthy ocular surface, subclinical, or mild dry eye undergoing cataract surgery.[90] In addition to the positive effects of HA + trehalose in OSDI and TBUT, Schirmer's test and CFS showed improvements for the group administered HA + trehalose but not in the group administered NaCl. In a third study, 98 patients with healthy ocular surfaces were randomly assigned to receive HA + trehalose, HA, or no treatment.[89] In this study, patients treated with HA + trehalose showed significant and progressively decreased tortuosity and reflectivity of the subbasal plexus at 4-month follow-up.[89] In contrast, these properties increased at 1-month follow-up and became normal at 8 months follow-up in patients treated with HA and in patients who received no treatment.[89]

Efficacy of HA + Trehalose + Carbomer in DED

Results of a single-center, prospective, randomized case-control study in 60 patients with very mild to severe DED demonstrate that HA + trehalose + carbomer is as effective as HA in reducing DED symptoms and more effective than HA for OSDI and TBUT outcomes.[94] A significantly greater global patient satisfaction score was demonstrated among patients treated with HA + trehalose + carbomer treated with HA (mean±SD, 97.3±4.95 vs 87.4±8.96, respectively, $P < 0.001$).[94] OSDI from baseline to day 30 was decreased with HA + trehalose + carbomer from 31.19 at baseline to 5.05 at day 30 and was decreased with HA from 21.3 at baseline to 14.37 on day 7 and to 11.24 on day 30 ($P < 0.0001$). Mean TBUT was significantly improved with HA + trehalose + carbomer from baseline (3.47 s) to day 7 (6.3 s) and day 30 (6.67 s) (both values, $P < 0.001$). In the HA group, mean TBUT was 4.13 s at baseline, 4.77 s at day 7, and 5.13 s at day 30; there was a statistically significant improvement in TBUT with HA + trehalose + carbomer vs HA ($P < 0.0001$).[94]

HA + trehalose + carbomer results in significantly longer increases in TFT vs HA or polyethylene glycol + propylene glycol, indicating a longer residence time on the cornea.[93] In an analysis of the effect of different artificial tears on TFT as measured by ultrahigh-resolution optical coherence tomography, single instillation of HA + trehalose + carbomer, HA (0.2%), and polyethylene glycol + propylene glycol were compared. Patients with mild-to-moderate DED had a pronounced increase in TFT 10 minutes after instillation in all three study groups. Notably, a significant increase in TFT was observed with HA + trehalose + carbomer but not the other formulations 60 to 120 minutes after administration, demonstrating that the combination of HA + trehalose + carbomer achieves a more prolonged increase in TFT.[93] Results of another study report that HA remains on the ocular surface longer than HA + trehalose + carbomer.[96] In this prospective study of 122 patients with mild-to-moderate DED, tear meniscus height (TMH) and tear meniscus depth showed a significant increase with both formulations; however, the effect remained significant for up to 60 minutes with HA + trehalose + carbomer vs up to 120 minutes for HA (0.3%).[96] The investigators suggest that the longer corneal residence time with HA observed in their study could be explained by the higher concentration of HA (0.3%) that was used[96] compared to Wozniak et al (0.2% HA).[93]

Meta-Analyses Comparing the Efficacy and Safety of HA + Trehalose and HA + Trehalose + Carbomer

In 2023, Ballesteros-Sanchez et al conducted the first systematic review and meta-analysis of 10 RCTs evaluating the effects of trehalose-containing artificial tear therapies in patients with DED.[4,67] The meta-analysis findings showed that compared with control groups, the use of trehalose (HA + trehalose or HA + trehalose + carbomer) formulations results

in higher improvements than control groups (HA, NaCl, or no tear substitute) in all reported variables. Mean differences between both groups favored trehalose-containing artificial tears in OSDI score (−8.5±7 points), TBUT (1.9±1 s), TFT (0.25±0.1 μm), TMH (0.02±0.02 mm), Schirmer's test (0.8±1.4 mm), CFS (−0.7±0.1 points), and visual acuity (0.3±2.1 letters), compared with control treatments in patients with DED.[67] The meta-analysis also indicated that trehalose-containing formulations were beneficial in patients who underwent cataract surgery during the preoperative and post-operative periods.[67] No adverse events were reported in the included studies after administering artificial tears with trehalose.[67] The investigators concluded that there was insufficient evidence to suggest that trehalose-containing formulations improve TMH and the Schirmer I test.[67]

Efficacy of HA+ Trehalose in DED in the Real World

The TEARS (ThEaloz® Duo sAtisfaction in oculaR Surface) study was conducted to assess the effect of HA + trehalose on dry eye signs and symptoms and patient satisfaction in the real world.[97] In this multicenter, international, prospective, observational study, patients with DED were treated with HA + trehalose (N = 312); HA + T improved symptoms of DED as assessed by the OSDI, which significantly decreased from a mean±SD of 41.7±20.6 at baseline to 27.3±19.8 ($P < 0.0001$). Moreover, the percentage of patients with an initial severe OSDI score decreased from 60.3% to 34.3% during the study. HA + trehalose significantly reduced ocular surface damage and improved tear film stability after 84 days, as demonstrated by significant improvements in ocular staining, in the Schirmer's test, and in TBUT ($P < 0.001$ for all values). Patient satisfaction was also increased, as was demonstrated with higher overall treatment satisfaction scores from baseline to day 28 and after 84 days of HA + trehalose treatment, which was accompanied by a greater percentage of patients recommending HA + trehalose from after 28 days of use to after 84 days of use (76.0% to 78.4%, respectively). This study supports findings from clinical trials in the real world and provides reinforcement that HA + trehalose is a safe and effective treatment for DED.

Conclusions

Formulations containing both HA + trehalose benefit from their synergistic effects of HA + trehalose. HA provides well-established lubricating and protective properties, and trehalose offers proven bioprotective properties. Studies in vitro and in vivo have shown that formulations combining HA + trehalose can regulate autophagy and reduce inflammation in DED. A robust evidence base supports the finding that HA + trehalose is at least as effective, and in some cases, more effective than HA alone, Systane®, or carmellose in treating DED. HA + trehalose has also been shown to provide significant protective and therapeutic benefits for managing postoperative DED after cataract surgery, especially when started before surgery and continued afterward. HA + trehalose + carbomer is effective for rapid symptom relief and tear film stabilization. Its use is associated with greater patient satisfaction and more significant reductions in symptoms of DED and improvements in tear film stability. Combination formulation artificial tears are more effective than single active ingredient artificial tears in treating DED, afforded by their complimentary mechanisms of action.

Future Directions

The market for OTC artificial tears is experiencing growth, driven by the rising prevalence of the condition and advancements in therapeutic formulations. Artificial tears vary in their active ingredients, use of preservatives, and formulations. There has been an increased uptake of sterile, preservative-free combination multidose formulations such as HA + trehalose. A strong and growing evidence base supports the effectiveness and safety of this combination formulation of artificial tears. Combination formulations afford greater efficacy than single-ingredient formulations. Formulations that can be administered with fewer drops have a positive impact on patients and providers, with the potential to improve compliancy. The use of multidose formulations versus single-use vials also reduces the amount of discarded plastic and environmental waste. With an evolving therapeutic landscape for DED, it is imperative to understand the breadth of management options and the evidence base of formulations to inform treatment decisions and treatment guidelines.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. 2017;15:334–365.
2. Farrand KF, Fridman M, Stillman IO, et al. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. *Am J Ophthalmol*. 2017;182:90–98. doi:10.1016/j.ajo.2017.06.033
3. Mohamed HB, Abd El-Hamid BN, Fathalla D, et al. Current trends in pharmaceutical treatment of dry eye disease: a review. *Eur J Pharm Sci*. 2022;175:106206. doi:10.1016/j.ejps.2022.106206
4. Semp DA, Beeson D, Sheppard AL, et al. Artificial tears: a systematic review. *Clin Optom (Auckl)*. 2023;15:9–27. doi:10.2147/OPTO.S350185
5. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15(3):575–628. doi:10.1016/j.jtos.2017.05.006
6. Buckley RJ. Assessment and management of dry eye disease. *Eye (Lond)*. 2018;32(2):200–203. doi:10.1038/eye.2017.289
7. Hynnekleiv L, Magno M, Vernhardsdottir RR, et al. Hyaluronic acid in the treatment of dry eye disease. *Acta Ophthalmol*. 2022;100:844–860. doi:10.1111/aos.15159
8. Stapleton F, Velez FG, Lau C, et al. Dry eye disease in the young: a narrative review. *Ocul Surf*. 2024;31:11–20. doi:10.1016/j.jtos.2023.12.001
9. Al-Mohtaseb Z, Schachter S, Shen Lee B, et al. The relationship between dry eye disease and digital screen use. *Clin Ophthalmol*. 2021;15:3811–3820. doi:10.2147/OPTH.S321591
10. Aggarwal S, Galor A. What's new in dry eye disease diagnosis? Current advances and challenges. *F1000Res*. 2018;7:7. doi:10.12688/f1000research.16468.1.
11. Statista Research Department. Usage of eye drops and eye wash in the U.S. 2011-2024. 2024.
12. Simon L, Murillo BA, Sabater AL. A comprehensive update on over the counter artificial tears. *Curr Opin Ophthalmol*. 2025;36(1):76–82. doi:10.1097/ICU.0000000000001109
13. El Fekih L, Khairallah M, Ben Amor H, et al. Successful management of dry eye disease with a new eye drop formulation combining hyaluronic acid, trehalose, and N-acetyl-aspartyl-glutamic acid (NAAGA). *J Fr Ophtalmol*. 2024;47:104169.
14. Matossian C, McDonald M, Donaldson KE, et al. Dry eye disease: consideration for women's health. *J Womens Health (Larchmt)*. 2019;28(4):502–514. doi:10.1089/jwh.2018.7041
15. Constable PA, Al-Dasooqi D, Bruce R, et al. A review of ocular complications associated with medications used for anxiety, depression, and stress. *Clin Optom (Auckl)*. 2022;14:13–25. doi:10.2147/OPTO.S355091
16. Chaudhary S, Ghimire D, Basu S, et al. Contact lenses in dry eye disease and associated ocular surface disorders. *Indian J Ophthalmol*. 2023;71:1142–1153.
17. Naderi K, Gormley J, O'Brart D. Cataract surgery and dry eye disease: a review. *Eur J Ophthalmol*. 2020;30(5):840–855. doi:10.1177/1120672120929958
18. Gupta PK, Stevens MN, Kashyap N, et al. Prevalence of meibomian gland atrophy in a pediatric population. *Cornea*. 2018;37(4):426–430. doi:10.1097/ICO.0000000000001476

19. Mehra D, Galor A. Digital screen use and dry eye: a review. *Asia Pac J Ophthalmol (Phila)*. 2020;9(6):491–497. doi:10.1097/APO.0000000000000328
20. Yeu E, Koetting C, Calvelli H. Prevalence of meibomian gland atrophy in patients undergoing cataract surgery. *Cornea*. 2023;42(11):1355–1359. doi:10.1097/ICO.0000000000003234
21. Kamoy B, Magno M, Noland ST, et al. Video display terminal use and dry eye: preventive measures and future perspectives. *Acta Ophthalmol*. 2022;100(7):723–739. doi:10.1111/aos.15105
22. Cardona G, Garcia C, Seres C, et al. Blink rate, blink amplitude, and tear film integrity during dynamic visual display terminal tasks. *Curr Eye Res*. 2011;36(3):190–197. doi:10.3109/02713683.2010.544442
23. Casemore RK, Wolffsohn JS, Utheim TP, et al. A prospective, longitudinal study to assess progression of ocular surface signs, tear cytokines and protein profiles in young adults. *Ocul Surf*. 2025;37:57–67. doi:10.1016/j.jtos.2025.02.011
24. Naseer S, Hasan S, Bhuiyan J, et al. Current public trends in the discussion of dry eyes: a cross-sectional analysis of popular content on TikTok. *Cureus*. 2022;14(2):e22702. doi:10.7759/cureus.22702
25. Lemp MA, Foulks GN. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf*. 2007;5(2):75–92. doi:10.1016/S1542-0124(12)70081-2
26. Phadatare SP, Momin M, Nighojkar P, et al. A comprehensive review on dry eye disease: diagnosis, medical management, recent developments, and future challenges. *Advances in Pharmaceutics*. 2015;2015:1–12. doi:10.1155/2015/704946
27. Uchino M, Schaumberg DA. Dry eye disease: impact on quality of life and vision. *Curr Ophthalmol Rep*. 2013;1(2):51–57. doi:10.1007/s40135-013-0009-1
28. Morthen MK, Magno MS, Utheim TP, et al. The physical and mental burden of dry eye disease: a large population-based study investigating the relationship with health-related quality of life and its determinants. *Ocul Surf*. 2021;21:107–117. doi:10.1016/j.jtos.2021.05.006
29. Morthen MK, Magno MS, Utheim TP, et al. The work-related burden of dry eye. *Ocul Surf*. 2023;28:30–36. doi:10.1016/j.jtos.2023.01.006
30. Schiffman RM, Walt JG, Jacobsen G, et al. Utility assessment among patients with dry eye disease. *Ophthalmology*. 2003;110(7):1412–1419. doi:10.1016/S0161-6420(03)00462-7
31. Buchholz P, Steeds CS, Stern LS, et al. Utility assessment to measure the impact of dry eye disease. *Ocul Surf*. 2006;4(3):155–161. doi:10.1016/S1542-0124(12)70043-5
32. Chan C, Ziai S, Myageri V, et al. Economic burden and loss of quality of life from dry eye disease in Canada. *BMJ Open Ophthalmol*. 2021;6(1):e000709. doi:10.1136/bmjophth-2021-000709
33. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. *Cornea*. 2011;30(4):379–387. doi:10.1097/ICO.0b013e3181f7f363
34. McDonald M, Patel DA, Keith MS, et al. Economic and humanistic burden of dry eye disease in Europe, North America, and Asia: a systematic literature review. *Ocul Surf*. 2016;14(2):144–167. doi:10.1016/j.jtos.2015.11.002
35. Kathuria A, Shamloo K, Jhanji V, et al. Categorization of marketed artificial tear formulations based on their ingredients: a rational approach for their use. *J Clin Med*. 2021;10(6):1289. doi:10.3390/jcm10061289
36. Labetoulle M, Benitez-Del-Castillo JM, Barabino S, et al. Artificial tears: biological role of their ingredients in the management of dry eye disease. *Int J Mol Sci*. 2022;23(5):2434. doi:10.3390/ijms23052434
37. Srinivasan S, Garofalo R, Williams R. Safe and effective management of dry eye symptoms with hydroxypropyl guar and hyaluronic acid dual-polymer lubricating eye drops: a review of preclinical and clinical studies. *Clin Ophthalmol*. 2023;17:3883–3898. doi:10.2147/OPTH.S428725
38. Weng J, Fink MK, Sharma A. A critical appraisal of the physicochemical properties and biological effects of artificial tear ingredients and formulations. *Int J Mol Sci*. 2023;24(3):2758. doi:10.3390/ijms24032758
39. Electronic Code of Federal Regulations. 21 CFR part 349—ophthalmic drug products for over-the-counter human use.
40. Che Arif F, Hilmi MR, Kamal K, et al. Evaluation of 18 artificial tears based on viscosity and pH. *Malaysian Journal of Ophthalmology*. 2020;2(2):96–111. doi:10.35119/myjo.v2i2.109
41. Che Arif F, Hilmi MR, Kamal K, et al. Comparison of immediate effects on usage of dual polymer artificial tears on changes in tear film characteristics. *Mal J Med Health Sci*. 2021;17(3):252–258.
42. Tong L, Petznick A, Lee S, et al. Choice of artificial tear formulation for patients with dry eye: where do we start? *Cornea*. 2012;31(Suppl 1):S32–S36.
43. Kahook MY, Rapuano CJ, Messmer EM, et al. Preservatives and ocular surface disease: a review. *Ocul Surf*. 2024;34:213–224. doi:10.1016/j.jtos.2024.08.001
44. Gomes JAP, Azar DT, Baudouin C, et al. TFOS DEWS II iatrogenic report. *Ocul Surf*. 2017;15(3):511–538. doi:10.1016/j.jtos.2017.05.004
45. Walsh K, Jones L. The use of preservatives in dry eye drops. *Clin Ophthalmol*. 2019;13:1409–1425. doi:10.2147/OPTH.S211611
46. Goldstein MH, Silva FQ, Blender N, et al. Ocular benzalkonium chloride exposure: problems and solutions. *Eye (Lond)*. 2022;36(2):361–368. doi:10.1038/s41433-021-01668-x
47. Agarwal P, Craig JP, Rupenthal ID. Formulation considerations for the management of dry eye disease. *Pharmaceutics*. 2021;13(2):207. doi:10.3390/pharmaceutics13020207
48. Nasser L, Rozycka M, Gomez Rendon G, et al. Real-life results of switching from preserved to preservative-free artificial tears containing hyaluronate in patients with dry eye disease. *Clin Ophthalmol*. 2018;12:1519–1525. doi:10.2147/OPTH.S160053
49. U.S. Food and Drug Administration. Final administrative order OTC000023: ophthalmic drug products for over-the-counter human use (monograph M018). 2022.
50. Hynnekleiv L, Magno M, Moschowits E, et al. A comparison between hyaluronic acid and other single ingredient eye drops for dry eye, a review. *Acta Ophthalmol*. 2024;102(1):25–37. doi:10.1111/aos.15675
51. Nelson JD. Cellulose acetate impressions of the ocular surface. Dry eye states. *Arch Ophthalmol*. 1983;101(12):1869–1872. doi:10.1001/archopht.1983.01040020871007
52. Ang BCH, Sng JJ, Wang PXH, et al. Sodium hyaluronate in the treatment of dry eye syndrome: a systematic review and meta-analysis. *Sci Rep*. 2017;7(1):9013. doi:10.1038/s41598-017-08534-5
53. van Setten GB. Impact of attrition, intercellular shear in dry eye disease: when cells are challenged and neurons are triggered. *Int J Mol Sci*. 2020;21(12):4333. doi:10.3390/ijms21124333

54. Stern ME, Beuerman RW, Fox RI, et al. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. *Cornea*. 1998;17(6):584–589. doi:10.1097/00003226-199811000-00002
55. Aragona P, Papa V, Micali A, et al. Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. *Br J Ophthalmol*. 2002;86(2):181–184. doi:10.1136/bjo.86.2.181
56. Rah MJ. A review of hyaluronan and its ophthalmic applications. *Optometry*. 2011;82(1):38–43. doi:10.1016/j.optm.2010.08.003
57. You IC, Li Y, Jin R, et al. Comparison of 0.1%, 0.18%, and 0.3% hyaluronic acid eye drops in the treatment of experimental dry eye. *J Ocul Pharmacol Ther*. 2018;34(8):557–564. doi:10.1089/jop.2018.0032
58. Kojima T, Nagata T, Kudo H, et al. The effects of high molecular weight hyaluronic acid eye drop application in environmental dry eye stress model mice. *Int J Mol Sci*. 2020;21(10):3516 doi:10.3390/ijms21103516.
59. Paschier A, Manuelli A, Chauchat L, et al. Overview of 37 tear substitutes in Europe based on various physicochemical parameters. *Ophthalmol Ther*. 2024;13(10):2799–2812. doi:10.1007/s40123-024-01023-9
60. Jiang D, Liang J, Noble PW. Hyaluronan as an immune regulator in human diseases. *Physiol Rev*. 2011;91(1):221–264. doi:10.1152/physrev.00052.2009
61. Tavianatou AG, Caon I, Franchi M, et al. Hyaluronan: molecular size-dependent signaling and biological functions in inflammation and cancer. *FEBS J*. 2019;286(15):2883–2908. doi:10.1111/febs.14777
62. Salwowska NM, Bebenek KA, Zadlo DA, et al. Physiochemical properties and application of hyaluronic acid: a systematic review. *J Cosmet Dermatol*. 2016;15(4):520–526. doi:10.1111/jocd.12237
63. Yang Y-J, Lee W-Y, Kim Y-J, et al. A meta-analysis of the efficacy of hyaluronic acid eye drops for the treatment of dry eye syndrome. *Int J Environ Res Public Health*. 2021;18(5):2383. doi:10.3390/ijerph18052383
64. Maity M, Allay MB, Ali MH, et al. Effect of different artificial tears on tear film parameters in dry eye disease. *Optom Vis Sci*. 2025;102(1):37–43. doi:10.1097/OPX.0000000000002206
65. Ouyang X-W, Fang S, Yi Y-M, et al. Different concentrations of hyaluronic acid eye drops for dry eye syndrome: a systematic review and meta-analysis. *Int J Ophthalmol*. 2024;17(6):1110–1119. doi:10.18240/ijo.2024.06.17
66. Laihia J, Kaarniranta K. Trehalose for ocular surface health. *Biomolecules*. 2020;10(5):10. doi:10.3390/biom10050809
67. Ballesteros-Sánchez A, Martinez-Perez C, Alvarez-Peregrina C, et al. Trehalose and dry eye disease: a comprehensive systematic review of randomized controlled trials. *J Clin Med*. 2023;13(1):12. doi:10.3390/jcm13010012
68. Teramoto N, Sachinvala ND, Shibata M. Trehalose and trehalose-based polymers for environmentally benign, biocompatible and bioactive materials. *Molecules*. 2008;12(23):7301. doi:10.3390/jcm12237301
69. Chen A, Gibney PA. Dietary trehalose as a bioactive nutrient. *Nutrients*. 2023;15(6):1393. doi:10.3390/nu15061393
70. Kuczyńska-Wiśnik D, Stojowska-Swędrzyńska K, Laskowska E. Intracellular protective functions and therapeutical potential of trehalose. *Molecules*. 2024;29(9):2088. doi:10.3390/molecules29092088
71. Crowe JH. Trehalose and anhydrobiosis: the early work of J.S. Clegg. *J Exp Biol*. 2008;211(18):2899–2900. doi:10.1242/jeb.012476
72. Scott P. Resurrection plants and the secrets of eternal leaf. *Ann Bot*. 2000;85(2):159–166. doi:10.1006/anbo.1999.1006
73. Jain NK, Roy I. Effect of trehalose on protein structure. *Protein Sci*. 2009;18(1):24–36. doi:10.1002/pro.3
74. Yancey PH. Organic osmolytes as compatible, metabolic and counteracting cytoprotectants in high osmolarity and other stresses. *J Exp Biol*. 2005;208(15):2819–2830. doi:10.1242/jeb.01730
75. Matsuo T. Trehalose protects corneal epithelial cells from death by drying. *Br J Ophthalmol*. 2001;85(5):610–612. doi:10.1136/bjo.85.5.610
76. Chen W, Zhang X, Liu M, et al. Trehalose protects against ocular surface disorders in experimental murine dry eye through suppression of apoptosis. *Exp Eye Res*. 2009;89(3):311–318. doi:10.1016/j.exer.2009.03.015
77. Li J, Roubeix C, Wang Y, et al. Therapeutic efficacy of trehalose eye drops for treatment of murine dry eye induced by an intelligently controlled environmental system. *Mol Vis*. 2012;18:317–329.
78. Matsuo T, Tsuchida Y, Morimoto N. Trehalose eye drops in the treatment of dry eye syndrome. *Ophthalmology*. 2002;109(11):2024–2029. doi:10.1016/S0161-6420(02)01219-8
79. Matsuo T. Trehalose versus hyaluronan or cellulose in eyedrops for the treatment of dry eye. *Jpn J Ophthalmol*. 2004;48(4):321–327. doi:10.1007/s10384-004-0085-8
80. Kim M, Lee Y, Mehra D, et al. Dry eye: why artificial tears are not always the answer. *BMJ Open Ophthalmol*. 2021;6(1):e000697. doi:10.1136/bmjophth-2020-000697
81. Uchino M, Yokoi N, Shimazaki J, et al. Adherence to eye drops usage in dry eye patients and reasons for non-compliance: a web-based survey. *J Clin Med*. 2022;11(2):367. doi:10.3390/jcm11020367
82. Puertas-Bartolome M, Gutierrez-Urrutia I, Teruel-Enrico LL, et al. Self-lubricating, living contact lenses. *Adv Mater*. 2024;36(27):e2313848. doi:10.1002/adma.202313848
83. Jeyabalan N, Pillai AM, Khamar P, et al. Autophagy in dry eye disease: therapeutic implications of autophagy modulators on the ocular surface. *Indian J Ophthalmol*. 2023;71(4):1285–1291. doi:10.4103/IJO.IJO_2912_22
84. Astolfi G, Lorenzini L, Gobbo F, et al. Comparison of trehalose/hyaluronic acid (HA) vs. 0.001% hydrocortisone/HA eyedrops on signs and inflammatory markers in a desiccating model of dry eye disease (DED). *J Clin Med*. 2022;11(6):1518 doi:10.3390/jcm11061518.
85. Chiambaretta F, Doan S, Labetoulle M, et al. A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome. *Eur J Ophthalmol*. 2017;27(1):1–9. doi:10.5301/ejo.5000836
86. Pinto-Bonilla JC, Del Olmo-Jimeno A, Llovet-Osuna F, et al. A randomized crossover study comparing trehalose/hyaluronate eyedrops and standard treatment: patient satisfaction in the treatment of dry eye syndrome. *Ther Clin Risk Manag*. 2015;11:595–603. doi:10.2147/TCRM.S77091
87. Sánchez-González JM, Silva-Viguera C, Sánchez-González MC, et al. Tear film stabilization and symptom improvement in dry eye disease: the role of hyaluronic acid and trehalose eyedrops versus carmellose sodium. *J Clin Med*. 2023;12(20):6647 doi:10.3390/jcm12206647.
88. Mencucci R, Favuzza E, Decandia G, et al. Hyaluronic acid/trehalose ophthalmic solution in reducing post-cataract surgery dry eye signs and symptoms: a prospective, interventional, randomized, open-label study. *J Clin Med*. 2021;10(20):4699 doi:10.3390/jcm10204699.
89. Cagini C, Di Lascio G, Torroni G, et al. Dry eye and inflammation of the ocular surface after cataract surgery: effectiveness of a tear film substitute based on trehalose/hyaluronic acid vs hyaluronic acid to resolve signs and symptoms. *J Cataract Refract Surg*. 2021;47(11):1430–1435. doi:10.1097/j.jcrs.0000000000000652

90. Cagini C, Torroni G, Mariniello M, et al. Trehalose/sodium hyaluronate eye drops in post-cataract ocular surface disorders. *Int Ophthalmol*. 2021;41(9):3065–3071. doi:10.1007/s10792-021-01869-z
91. Morya AK, Solanki K, Prakash S, et al. Randomized controlled trial of trehalose: an efficient autophagic bioprotectant in the management of dry eye disease. *Taiwan J Ophthalmol*. 2021;11(2):161–167. doi:10.4103/tjo.tjo_58_20
92. Schmidl D, Schmetterer L, Witkowska KJ, et al. Tear film thickness after treatment with artificial tears in patients with moderate dry eye disease. *Cornea*. 2015;34(4):421–426. doi:10.1097/ICO.0000000000000358
93. Wozniak PA, Schmidl D, Bata AM, et al. Effect of different lubricant eye gels on tear film thickness as measured with ultrahigh-resolution optical coherence tomography. *Acta Ophthalmol*. 2017;95(4):e307–e13. doi:10.1111/aos.13342
94. Caretti L, La Gloria Valerio A, Piermarocchi R, et al. Efficacy of carbomer sodium hyaluronate trehalose vs hyaluronic acid to improve tear film instability and ocular surface discomfort after cataract surgery. *Clin Ophthalmol*. 2019;13:1157–1163. doi:10.2147/OPTH.S208256
95. Doan S, Bremond-Gignac D, Chiambaretta F. Comparison of the effect of a hyaluronate-trehalose solution to hyaluronate alone on Ocular Surface Disease Index in patients with moderate to severe dry eye disease. *Curr Med Res Opin*. 2018;34(8):1373–1376. doi:10.1080/03007995.2018.1434496
96. Karaca EE, Ozek D, Evren Kemer O. Comparison study of two different topical lubricants on tear meniscus and tear osmolarity in dry eye. *Cont Lens Anterior Eye*. 2020;43(4):373–377. doi:10.1016/j.clae.2019.10.001
97. Mateo-Orobia AJ, Farrant S, Del-Prado-Sanz E, et al. A preservative-free combination of sodium hyaluronate and trehalose improves dry eye signs and symptoms and increases patient satisfaction in real-life settings: the TEARS Study. *Ophthalmol Ther*. 2024;13(12):3123–3134. doi:10.1007/s40123-024-01044-4