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REVIEW

Artificial tears potpourri: a literature review

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Abstract: Numerous brands and types of artificial tears are available on the market for the treatment of dysfunctional tear syndrome. Past literature has focused on comparing the components of these products on patient's clinical improvement. The wide array of products on the market presents challenges to both clinicians and patients when trying to choose between available tear replacement therapies. Different formulations affect patients based on etiology and severity of disease. In order to provide an unbiased comparison between available tear replacement therapies, we conducted a literature review of existing studies and National Institutes of Health clinical trials on commercially available, brand name artificial tears. Outcomes evaluated in each study, as well as the percent of patients showing clinical and symptomatic improvement, were analyzed. Fifty-one studies evaluating different brands of artificial tears, and their efficacy were identified. Out of the 51 studies, 18 were comparison studies testing brand name artificial tears directly against each other. Nearly all formulations of artificial tears provided significant benefit to patients with dysfunctional tear syndrome, but some proved superior to others. From the study data, a recommended treatment flowchart was derived.

Keywords: dry eye, tear film, dysfunctional tear syndrome, ophthalmic lubricant, artificial tears, lipid layer, tear osmolarity, TBUT, Systane®, Refresh®, Blink®, GenTeal®, Soothe®, Lacrisert®, ocular surface inflammatory disease, Sjogren's Syndrome, HPMC, CMC, polyvinyl alcohol, liquid polyols

Introduction

Dysfunctional tear syndrome (DTS), commonly known as dry eye syndrome, describes the multifactorial condition where the ocular system fails to produce good quality tears or a sufficient amount of tears to keep the eye moisturized.[1] Human tears, composed of electrolytes, water, proteins (eg, antibodies, lysozymes), and lipids, function to moisturize the ocular surface and minimize damage to the corneal epithelium. These components come together to form three distinct layers: 1) the outermost lipid layer, 2) a middle aqueous layer, and 3) the epithelium-covering mucoid layer. Dysfunction in any of these layers can yield tear film instability and hyperosmolarity.[2,3] External causes of such dysfunction are widespread including environmental factors, systemic diseases, and medications.[4–12]

DTS is among the most commonly encountered ocular morbidities, affecting as many as 15%–25% of individuals over the age of 65 and up to 6% of adults over the age of 40.[12–15] Inadequate lubrication results in ocular surface damage and discomfort. In addition to increasing the risk of ocular infection, DTS can cause irreversible scarring and fibrosis due to unprotected corneal epithelial exposure.[16–19] Many clinicians have begun to treat the condition with increased vigilance.[14] Furthermore, prompt intervention can offer substantial benefits with regards to quality of life and comfort.[20]

Artificial tears are currently the mainstay of therapy of DTS. They account for at least $540 million in annual sales globally and are the preferred first-line therapy due to their noninvasive nature and low side effect profile.[14,21,22] However, a dizzying array of brands and marketing strategies have made it a challenge for patients and clinicians alike to identify the product that best suits individual patients.

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Previous review articles have studied and compared the active ingredients within the artificial tears, but none have compared the full formulations available on the market.[23] With a focus on artificial tear brands, this study aims to provide a useful literature-based comparison between available tear replacement therapies for clinicians and patients considering starting therapy to manage DTS. The following is a detailed overview of the commercial agents available (summarized in Tables S1–S5) for treating dry eye, with a particular emphasis placed upon those agents and practices that are most effective in mitigating symptoms of DTS.

Materials and methods

Literature search

This study involved a review of the literature analyzing artificial tear treatments of DTS. The resources utilized were the electronic databases Medline (PubMed; http://www.ncbi.nlm.nih.gov), National Institutes of Health (NIH) clinical trials (http://clinicaltrials.gov), Google Scholar, and the Cochrane Library. Keywords used in the search included dry eye, dysfunctional tear syndrome, Actimist, Advance Eye Relief, Akorn, Akwa, Blink, Clarymist, Clear Eyes, Freshkote, GenTeal, Hylogel, Isopto, Just Tears, Lacril, Lacrisert, Liposic, Lubrifresh, Murine Tears, Natural Balance, Nature's Tears, Nutratear, Oasis Tears, Paralube, Refresh, Rohto Hydra, Systane, Soothe, Tearisol, Tears Again, Tears Natural, Thera Tears, Ultra Tears, Visco Tears, and Vizulize Dry Eye Mist. Both published articles and data from clinical trials (including multicenter, blinded studies as well as open label, industry-funded studies) were included in this study. Studies were excluded if the brand and specific type of artificial tear could not be identified. Data from unpublished clinical trials and articles from artificial tears that are no longer being produced were excluded. No other exclusion criteria were applied.

The etiology of dry eye syndrome in the studies reviewed included the following conditions: environmental (humidity, pollution, etc), situational (reading/prolonged focus), contact lens wear, LASIK surgery, autoimmune syndromes, nutritional deficiencies, vitamin A, Stevens–Johnson syndrome, and irritant exposure. The patient subgroups were not excluded but were also not specifically identified in many of the studies during analysis of the treatment of DTS, and thus we cannot readily distinguish between these patient populations. In future studies, this is an issue which will need to be clearly addressed.

Data compilation

Data from all studies were compiled into one group. Each study had its own means of data collection and definition for successful treatment with artificial tears. Methods for collecting the subjective data were mainly through questionnaires including McMonnies Dry Eye Symptom survey,[24] Ocular Surface Disease Index (ODSI) questionnaire,[18] impact of dry eye on everyday life (IDEEL) questionnaire,[25] Visual Analogue Scale, Salisbury Eye Evaluation (SEE) questionnaire,[26] Ocular Discomfort Severity questionnaire, direct brand comparison with drop preference selection, quality of life through the Measure Yourself Medical Outcome Profile-2 (MYMOP-2),[27] and Dry Eye Disease Comfort Assessment Score. Several studies also utilized custom questionnaires.[28–31] Objective data took the form of ocular surface staining using various dyes, usually fluorescein and rose bengal. Additionally, comparative data was collected through analysis of a variety of other parameters including Schirmer's test, tear break-up time, post-therapy corneal topography, tear meniscus volume, mucinous layer analysis with rose bengal staining, tear osmolarity, lipid layer thickness (LLT), improvement of visual acuity, conjunctival hyperemia, Ocular Protection Index (OPI) (examining the tear break-up time divided by the interblink interval), number of eyelid parallel conjunctival folds, blinking time analysis through the OPI 2.0 system, Global Staining Score, the TearLab Osmolarity System, and tear film normalization test (measurement of lines of improvement in visual acuity after administration of artificial tears).[28,29,32–36]

Commercially available tear film substitutes

To provide maximum utility for the patient and clinician, commercially available artificial tears were identified and categorized based on active ingredient (Tables S1–S5). Other over-the-counter treatments for DTS including gels, ointments, and sprays/mists were included in the compilation (Table S4). Active ingredients and preservatives were verified via package inserts for each product. Artificial tears were divided into groups based on active ingredients including hydroxypropyl methylcellulose (HPMC), carboxy methylcellulose (CMC), polyvinyl alcohol, homeopathic remedies, and the liquid polyols. A final group was made for other delivery methods including gel/ointments, spray/mist over-the-counter treatments, and the prescribed ophthalmic insert, Lacrisert® (Valeant, Bridgewater, NJ, USA). Lacrisert was included in the study because its composition and active ingredient mimic those of some artificial tears.

Results

A total of 18 articles comparing subjective and objective outcomes of artificial tear brands were identified in our

literature search. All articles were written in English or translated to English from other languages, including German, Spanish, and Chinese. The outcomes from these studies are summarized in Table 1. Many of these studies utilized different parameters to determine treatment efficacy.

Refresh versus Systane

The first study compared Systane® (Alcon Laboratories, Inc., Fort Worth, TX, USA) to Refresh Tears® (Allergan, Irvine, CA, USA) in 87 patients with dry eyes over a 6-week period.[37] Both investigators and patients were blinded to the artificial tear being used. The study evaluated the conjunctival/corneal staining and a custom symptom questionnaire at days 7, 14, 28, and 42. At days 14 and 28, patients using Systane® showed significantly improved conjunctival staining compared to patients using Refresh Tears®. At days 14 and 42, patients using Systane also had significantly decreased temporal corneal staining compared to patients using Refresh. Furthermore, subjective symptomatic improvement was significantly increased in patients using Systane when compared to those using Refresh.

Another study comparing Systane versus Refresh products utilized a three-way cross-over study design comparing Systane®, Refresh Tears®, and Refresh Endura® (now called Refresh Optive®; Allergan).[38] Including only patients with a history of dry eye signs or symptoms, 50 patients were evaluated using tear film breakup time (TBUT) and the OPI over three separate clinical visits. TBUT measurements were taken at 5, 10, 15, 20, 30, 45, and 60 minutes after tear application. Systane® significantly increased TBUT compared to both Refresh Tears® and Refresh Endura® at 5, 10, 15, 20, and 60 minutes after artificial tear application.

A third study analyzing Refresh and Systane products compared the effects of Refresh Liquigel® and Systane® on corneal staining and symptomatic improvement in 60 patients.[30] A reduced sum score of corneal staining and a reduction of corneal staining from baseline were only observed in the Refresh Liquigel® group (P=0.008 and P=0.019, respectively). Patient's tear preference and comfort were also analyzed in this study; however, patients were not blinded to the artificial tear assigned. Using one eye for each artificial tear, patient preference was recorded 5 minutes after application with 36% of patients preferring Refresh and 24% preferring Systane. Limited value may be drawn from the subjective component of this study since unilateral symptoms may have been present in the study participants.

The largest of the studies comparing artificial tears was completed in Germany.[39] The study was a multicenter, observational study involving patients from 835 ophthalmologists. Data from 5,277 patients who required a change in their artificial tear formulation or were naive to artificial tear treatment were analyzed after 2–4 weeks of treatment with Refresh Optive®. Patients had previously been using either Systane®, Hylo-Comod®, or Lacophtal® (Ursapharm Arzneimittel GmbH, Saarbrücken, Germany). Nearly 85% of patients reported improvement in ocular comfort with Refresh Optive®, and nearly 75% experienced an improvement in their symptoms after changing artificial tear treatment regimens. TBUT also significantly increased in patients using Refresh Optive® from a mean of 7.7 seconds to 10.0 seconds ($P<0.001$).

In an industry-sponsored, Alcon, head-to-head clinical trial, visual acuity was measured after application of Systane® Ultra and Refresh Optive®.[36] The study population included 48 patients with a history of dry eye. Each patient underwent visual acuity evaluation while completing a computer task at 15, 45, and 90 minutes postapplication. The amount of time the patients maintained their best-corrected visual acuity was the measured end point. At 90 minutes, the mean time best-corrected visual acuity was maintained for 9.17 seconds with Systane versus 6.84 seconds with Refresh. These data were not statistically analyzed.

Alcon sponsored another clinical trial comparing Systane® Ultra and Refresh Optive® with an emphasis on TBUT, corneal staining, and conjunctival staining after 0, 7, 14, 28, and 42 days of artificial tear use.[40] A total of 109 patients with a diagnosis of dry eye were enrolled in the clinical trial with 53 in the Systane® Ultra group and 56 in the Refresh Optive® group. Mean TBUT after 42 days was 4.5 seconds with Systane® Ultra and 4.2 seconds with Refresh Optive®. The study also compared corneal and conjunctival staining using a 0–10 scale, with 0 equaling no staining present. At day 14 and 42, Systane® Ultra-treated eyes had a mean corneal staining score of 2.9 on both visits while Refresh Optive®-treated eyes had a mean score of 4.5 and 4.2 for the respective visits.

Refresh versus Refresh

Allergan funded a project studying the efficacy of Refresh Tears®, Refresh Ultra®, and Refresh Optive® in relieving the signs and symptoms of dry eye.[43] A total of 37 participants completed the study; 18 with a history of dry eye and 19 controls without a history of dry eye. In this three-way cross-over study, each patient used each artificial tear formulation for 2 weeks while TBUT, tear evaporation, osmolarity, tear structure, and patient symptoms were evaluated.

Table 1 Summary of published papers and clinical trials comparing artificial tears

Comparison data between various brands of artificial tears			
Drops examined	**ST/SS**	**Trial results**	***P*-value**
Systane® versus Refresh Tears®,[37]	Double blinded RCT/87	After 14 days of daily therapy, Systane-treated patients exhibited decreased conjunctival staining and diminished temporal corneal staining compared to patients treated with Refresh Tears	Conjunctival stain: 0.025 Temporal stain: 0.024
Systane® versus Refresh Tears® versus\ Refresh Endura®,[38]	Double blinded, three-way cross-over, RCT/50	At 5, 10, 15, 20, and 60 minutes after application, Systane significantly prolonged tear break-up time compared to either Refresh therapies	5, 10, 15, 20, 60 minutes <0.05
Systane® versus Refresh Liquigel®,[30]	Open-label, RCT/60	Clinical trial revealed patient preference for Refresh Liquigel (36%) compared with Systane (24%). Mean corneal inferior staining was only significantly reduced in patients treated with Refresh Liquigel	Patient preference *P* not provided Corneal staining <0.001
Blink® Intensive versus Systane® versus\ Refresh Celluvisc®,[44]	Investigator masked RCT/60	At treatment day 30, the mean decrease in osmolarity 5 minutes postapplication was significantly greater with Blink Tears compared to Systane and Refresh	Osmolarity decrease <0.001
Blink® Tears versus Systane® Ultra[45]	Investigator masked, cross-over, RCT/40	After 1 month of therapy, TBUT was significantly increased by 2.4 seconds with Blink Tears while Systane Ultra showed no statistically significant increase in tear film	TBUT increase 0.003
Blink® Tears versus Refresh Optive®,[31]	Investigator masked, cross-over, RCT/50	After 16 days of therapy with either Blink Tears or Refresh Optive, patients reported similar improvement on the Dry Eye Disease Comfort Assessment questionnaire	*P* not provided
Refresh Liquigel® versus Refresh Tears®,[41]	Double blinded, cross-over, RCT/39	Refresh Liquigel (1.0% CMC) increased TBUT for a longer time when compared with Refresh Tears (0.5% CMC)	<0.05
Refresh Liquigel® versus Refresh Tears®,[24]	Subject masked, parallel-group, RCT/99	Corneal staining reduced greater from baseline with Refresh Liquigel than Refresh Tears, but more adverse events occurred with the Liquigel	Corneal staining 0.011 Adverse events 0.006
Refresh Plus® versus Refresh Liquigel® versus Refresh Celluvisc®,[42]	Subject masked, controlled trial/20	Both Refresh Liquigel and Refresh Celluvisc significantly decreased contrast sensitivity	Decreased contrast sensitivity <0.001
Refresh Optive® versus Systane® versus Hylo-Comod®,[39]	Open-label, observational study/5277	Questionnaire revealed 68.9% of Hylo-Comod users and 78.5% of Systane users had improvement of symptoms by switching to Refresh Optive. TBUT also improved with Refresh	Symptom improvement *P* not provided TBUT improvement <0.001
Refresh Tears® versus Refresh Ultra® versus Refresh Optive®,[43]	Double-blinded, cross-over, RCT/38	Refresh Optive and Refresh Ultra improved patient symptoms greater than Refresh Tears	Optive 0.013 Ultra 0.011
Systane® Ultra versus Refresh Optive®,[36]	Double-blinded, cross-over RCT/48	At 90 minutes after application, Systane Ultra users maintained BCVA for 9.17±0.0365 seconds compared to 6.84±0.0365 seconds of maintained BCVA in Refresh Optive users	*P* not provided
Systane® Ultra versus Refresh Optive®,[40]	Double-blinded, parallel, RCT/109	On a unit scale of 0–15, with 0 being no staining and 15 the most staining, corneal staining after 42 days of treatment with Systane Ultra showed 2.9±1.8 units of corneal staining compared to 4.2± 2.8 units of corneal staining in those treated with Refresh Optive	*P* not provided

Systane® Ultra versus Refresh Optive® versus GenTeal® versus Blink® Tears[46]	Double-blinded, cross-over, RCT/20	Posttherapeutic subjective comfort results revealed Systane Ultra outperformed Refresh Optive, GenTeal, and Blink Tears	*P* not provided
Soothe® versus Refresh Optive®[47]	Double-blinded, cross-over, RCT/41	The mean lipid layer thickness increase was significantly greater in eyes treated with Soothe (60.0 nm) compared to eyes treated with Refresh (23.6 nm)	Refresh <0.0001 Soothe <0.0001 Comparison <0.0001
Soothe® versus Systane®[48]	Double-blinded, cross-over, RCT/40	The lipid layer thickness increase was significantly greater in eyes treated with Soothe compared to eyes treated with Systane	Systane <0.0001 Soothe <0.0001 Comparison <0.0001
GenTeal® Tears versus Naturale-Free®[50]	Open-label, cross-over, RCT/37	Results showed adequate improvement of Shirmer Test and TBUT, but only GenTeal showed reduction of erosions that affected >25% of the corneal surface	0.027
Tears Again® versus Liposic®[49]	Investigator masked, cross-over, RCT/74	The tear break-up time in patients treated with Tears Again was increased greater than that of those treated with Liposic at 6 weeks	Both group improvement <0.001 Group difference 0.055

Notes: Manufacturers are as follows: Refresh®, Allergan, Irvine, CA, USA; Systane®, Alcon Laboratories, Inc., Fort Worth, TX, USA; Blink®, Abbott Laboratories Inc., Abbott Park, IL, USA; Hylo-Comod®, URSAPHARM, Saarbrücken, Germany; GenTeal®, Novartis Pharmaceuticals, East Hanover, NJ, USA; Soothe®, Bausch & Lomb Incorporated, Bridgewater, NJ, USA; Liposic®, Bausch & Lomb Incorporated; Naturale-Free®, Alcon Laboratories, Inc.; Tears Again®, OcuSoft, Rosenberg, TX, USA.
Abbreviations: BCVA, best-corrected visual acuity; CMC, carboxy methylcellulose; RCT, randomized controlled trial; SS, sample size; ST, study type; TBUT, tear film breakup time.

All patients with a history of dry eye experienced improvement in both their signs and symptoms of dry eye with all formulations ($P<0.05$). In the control group, Refresh Optive® and Refresh Ultra® treatment resulted in a decreased rate of evaporation, significantly greater than Refresh Tears® on cross-group comparison. Refresh Tears® was the only formulation observed to decrease tear osmolarity in the control group ($P<0.05$). No other statistical difference appeared on cross-group analysis.

A combination of three separate, independent studies aimed to find the differences in corneal staining and OPI in patients treated with either Refresh Tears® or Refresh Liquigel®, an artificial tear product with a thicker consistency than most drops.[29] A total of 607 patients were evaluated after 1 month of using either Refresh Tears® or Refresh Liquigel®. With regard to change in OPI, Refresh Liquigel®-treated patients showed greater improvements than those treated with Refresh Tears® ($P<0.05$). Additionally, after 1 week and 1 month of use, patients treated with Refresh Liquigel® showed significantly reduced corneal staining compared to those treated with Refresh Tears® ($P<0.001$ and $P=0.011$, respectively). Although study subjects did report increased blurring after application with Refresh Liquigel®, both artificial tears had statistically equivalent acceptability. Over a 1-month period, patients also reported using the Refresh Liquigel® less frequently compared to Refresh Tears® ($P=0.05$).

To assess the effects on blurring, distortion, and contrast sensitivity, Allergan funded a study to quantify changes in visual acuity after administration of Refresh Liquigel® and Refresh Celluvisc®, two products of thicker consistency than most artificial tears.[42] In 20 normal subjects without a history of dry eye disease, artificial tears were applied at different time points followed by testing of contrast sensitivity via a computer controlled stimulus. Both artificial tears significantly reduced contrast sensitivity immediately after application ($P<0.001$); however, Refresh Celluvisc® did so to a greater degree ($P<0.001$).

Further research compared the effect of Refresh Liquigel® and Refresh Tears® on TBUT in 39 patients.[42] For each patient, either Refresh Liquigel® or Refresh Tears® was initially applied, and TBUT was measured at 5, 10, 15, 20, 30, 45, and 60 minutes. This was repeated 1 week later with the other artificial tear formulation. Order of administration was randomly assigned. At 5 minutes, both drops increased TBUT; however, only Refresh Liquigel® significantly increased TBUT beyond 5 minutes. This effect was notable for up to 20 minutes postapplication.

Blink versus Refresh versus Systane

In a study of 60 participants, Blink® Intensive (Abbott Laboratories, Abbott Park, IL, USA), Systane®, and Refresh Celluvisc® were compared at baseline and after 30 days of product use.[44] Tear osmolarity measurement, Schirmer tear test, TBUT, fluorescein staining, corneal wavefront aberrometry, and visual acuity were all measured. All three treatment groups demonstrated improvement in all measured endpoints. However, cross–group comparison found Blink to better reduce the tear osmolarity compared to both Systane® and Refresh Celluvisc® ($P<0.001$). No other statistical differences were found between the groups.

One unpublished, Abbot-funded NIH clinical trial with 80 patients compared Blink® Tears to Systane® Ultra with regard to TBUT and visual acuity 1 month after treatment.[45] Blink® Tears proved superior to Systane® Ultra in both TBUT ($P=0.003$) and improvement in visual acuity ($P<0.001$).[46]

Blink® Tears was also compared to Refresh Optive® in a trial of 51 patients with a history of dry eye.[31] The primary goal of this Allergan-sponsored study was to improve subjective symptoms on the Dry Eye Disease Comfort Assessment questionnaire score over a 16-day period. No statistical analysis was performed on these data, but changes between the two groups appeared similar with a mean decrease on the questionnaire score of 1.41 with Refresh Optive® and 1.47 with Blink® Tears.

In an Alcon-sponsored clinical trial, Systane® Ultra, Refresh Optive®, GenTeal Moderate® (Novartis Pharmaceuticals, East Hanover, NJ, USA), and Blink® Tears were compared with regard to postapplication comfort.[46] Drop comfort grading was measured using a 0–9 scale, with 0 representing the highest level of comfort. The design was a randomized, double-masked, cross-over study with 20 patient participants. After drop administration, the comfort scores were 0.7±1.26 for Systane® Ultra, 1.05±1.10 for Refresh Optive®, 1.84±2.19 for Blink® Tears, and 1.1±1.21 for GenTeal®. No statistical analysis was performed.

Soothe versus Refresh or Systane

Soothe® (Bausch & Lomb Incorporated, Bridgewater, NJ, USA) is a lipid-based artificial tear. A pair of separate studies aimed to elucidate its effects on the LLT within the tear film. The first study evaluated the effectiveness of Soothe® versus Refresh Optive®. Enrollment included 41 patients with a LLT under 70 nm in both eyes and baseline visual acuity greater than 20/70. Each patient received a drop of Soothe® in one eye and Refresh Optive® in the contralateral eye. A custom-designed lipid layer interferometer quantified the LLT at 1, 5, and 15 minutes after application. Both artificial tears increased the LLT from a baseline of 61.5±1.6 nm ($P<0.001$), with a mean LLT of 83.2±3.6 nm for Refresh Optive® and 121.5±3.8 nm for Soothe® ($P<0.001$).[47]

A second study utilized the same inclusion criteria and study design but compared Soothe® to Systane®.[48] A total of 40 patients were included in this study. Results showed a mean LLT of 124.4±4.9 nm for Soothe® and a mean LLT of 71.3±2.6 nm for Systane®. This represents an increase from baseline of 107% for Soothe and only 16% for Systane. Both studies were industry sponsored by Ocular Research (Boston, MA, USA) and Alimera Sciences (Alpharetta, GA, USA), which have partial ownership of Soothe.

Other comparative studies

Another randomized controlled study analyzing lipid-based tear substitutes looked at their effect on TBUT, Schirmer's test, tear meniscus, and subjective symptoms.[49] This cross-over study compared Tears Again® (OcuSoft, Rosenberg, TX, USA) to Liposic® (Bausch & Lomb) in 74 patients with a history of dry eye over two separate 6-week periods. In both the initial treatment and after cross-over, Tears Again® improved all the aforementioned subjective and objective endpoints ($P<0.05$); 62.5% of patients preferred Tears Again®, 25% preferred Liposic®, and 12.5% found the preparations to be equal.

GenTeal Tears® with preservative, GenAqua®, and preservative-free Tears Naturale® (Alcon Laboratories, Inc.) were compared in an open-label, two-treatment, two-period study.[50] After 4 weeks of treatment, patients were evaluated with TBUT, Schirmer's test, and corneal staining as well as via a symptom questionnaire. A total of 37 patients completed the study. Both TBUT and Schirmer testing improved in the GenTeal group but not in the Tears Naturale® group ($P=0.27$). Both artificial tears were rated as excellent for tolerability and convenience. Subjective symptoms were not different between the two treatments.

Clinical improvement

Table 2 summarizes the clinical improvement of dry eye subjects based on objective and subjective criteria used on each study included in this review. Due to the heterogeneity of criteria used on these studies, a percent of improvement was calculated for each of the artificial tears evaluated. The percent of improvement was calculated based on the amount of subjects with symptomatic and clinical improvement with respect to the total subjects treated.

Table 2 Clinical data for performance of artificial tears and their corresponding percent improvement based upon respective subjective and objective criteria

Brand name	Pts treated (n)	Trials (n)	Improvement (%)
Thera Tears®,[80]	2	1	100
Refresh Tears®,[68,37,41,54,47,70,30]	739	7	100
Refresh Plus®,[69,71,72,32,82,35]	301	6	92.7
Refresh Celluvisc®,[80]	11	1	100
Refresh Liquigel®,[41,29,30,74]	778	4	100
GenTeal® Moderate to Severe[50]	37	1	100
Lacril®,[81]	55	1	100
Isopto® Alkaline[80]	2	1	100
Isopto® Plain[80]	9	1	100
Blink® Tears[45]	20	1	100
Blink® Intensive Tears[75,44,90]	60	3	100
Systane® Balance[83,84,33]	92	3	71.0
Systane®,[68,37,28,85,57,34,44,86,88,89]	502	10	87.3
Systane® Ultra[54,79,36,40]	130	4	100
Systane®, preservative-free[87]	27	1	100
Soothe®,[47]	30	1	100
GenTeal® Gel[55,56]	206	2	96.0
Viscotears®,[73,80]	456	2	100
Liposic®,[49]	74	1	100
Refresh Lacrilube®,[80]	239	1	100
Tears Again® (Actimist in the UK)[77,78,49]	287	3	93.0
Refresh Optive®,[42,36,40,31]	5,430	4	75.8
Refresh Optive® Sensitive[82]	114	1	100
Tears Naturale® II[80]	68	1	100
Tears Naturale Free®,[68]	22	1	100
Tears Naturale® Forte[71,76]	129	2	63.0

Notes: Improvement in DTS was defined in each study with the following subjective/objective criteria: subjective data: McMonnies Dry Eye Symptom survey, ODSI questionnaire, IDEEL questionnaire, SEE questionnaire, Ocular Discomfort Severity questionnaire, Direct Brand Comparison with drop preference selection, quality of life through the Measure Yourself Medical Outcome Profile-2 (MYMOP-2), Dry Eye Disease Comfort Assessment Score, and various custom questionnaires in addition to these. Objective data: McMonnies Dry Eye Symptom survey, ODSI questionnaire, IDEEL questionnaire, SEE Questionnaire, Ocular Discomfort Severity questionnaire, Direct Brand Comparison with drop preference selection, quality of life through the MYMOP-2, Dry Eye Disease Comfort Assessment Score, and various custom questionnaires in addition to these.[23–31] Manufacturers are as follows: Thera Tears®, Advanced Vision Research, Ann Arbor, MI, USA; Refresh®, Allergan, Irvine, CA, USA; GenTeal®, Novartis Pharmaceuticals, East Hanover, NJ, USA; Lacril®, Allergan; Isopto®, Alcon Laboratories, Inc., Fort Worth, TX, USA; Blink®, Abbott Laboratories Inc., Abbott Park, IL, USA; Systane®, Alcon Laboratories, Inc.; Soothe®, Bausch & Lomb Incorporated, Bridgewater, NJ, USA; Viscotears®, Novartis Pharmaceuticals; Liposic®, Bausch & Lomb Incorporated; Tears Again®, OcuSoft, Rosenberg, TX, USA; Tears Naturale®, Alcon Laboratories, Inc.

Abbreviations: DTS, dysfunctional tear syndrome; IDEEL, impact of dry eye on everyday life; ODSI, Ocular Surface Disease Index; pts, patients.

Discussion

In all 18 head-to-head studies, patients with dry eyes had clinical improvement both immediately after application and over the long term when using tear replacements. This occurred in both preserved and preservative-free artificial tear formulations. With head-to-head comparisons, the results varied greatly and often depended on the funding source. To no surprise, each study that was industry sponsored found the respective company's artificial tear to be most effective. Further, the newer artificial tears, Refresh Optive® and Systane® Ultra, definitively outperformed the older Refresh Tears® and Systane® in both subjective and objective tests. Interestingly, Soothe® dramatically increased the lipid layer of the tear film compared to its Systane and Refresh counterparts. A lipid layer under 60 nm indicates a higher likelihood of having dry eye symptoms. Conversely, having a LLT greater than 75 nm decreases symptoms, and generally, a thicker lipid layer directly correlates with decreased symptoms.[50] This is an important finding since studies have shown that a deficient lipid layer is the most common cause of DTS.[52] After reviewing all the studies, we elaborated a set of recommendations that may help both the physician and the patient in decision making when a tear replacement therapy is needed. Due to the lack of standardization and bias from industry-funded studies, these recommendations are not intended to be conclusive and final, but a good resource based on the comparative data we gathered on the discussed head-to-head studies.

Recommendations

Our recommendations for suggested drop brands in each of the respective categories is based upon both the number of studies completed on these brands as well as the trials that compared their efficacy against other brand name artificial tears (see Tables 1 and 2). Due to the heterogeneous data

available and lack of standardization between studies, the recommendations made are not intended to be definite and should be individualized based on disease severity and patient's expectations. This is a step approach, initiating therapy with the most studied artificial tears. Treatment recommendations (summarized in Figure 1) are as follows:

Step 1

The treatment algorithm allows for initial therapies to be divided into three categories of drops based on the active ingredient: CMC-based, HPMC-based, and hyaluronic acid-based. In a recent comprehensive review of the active ingredients contained in artificial tears, the above listed ingredients have been shown to be the most beneficial in improving patient comfort levels.[53] For each of these categories, the most studied brands of artificial tears were recommended. Additionally, Systane® and Refresh Tears® have been well studied and have been beneficial in the treatment of mild dry eye syndrome (see Tables 1 and 2).

Step 2

Systane® Ultra and Soothe® have both been shown in clinical research to out-perform the CMC/HPMC/hyaluronic acid-based formulations listed in Step 1 (see Tables 1 and S1). In the instance that initial therapy fails to adequately control the symptoms of DTS, either of these two drops should be considered as the next therapy.

Steps 3 and 4

In the event that standard artificial tears fail to adequately abate the patient's symptoms and/or in the case of severe DTS, lid malposition, or exposure keratopathy, the implementation of additional therapies such as gels, ointments, liposomal sprays, is indicated.[37,54–61] These therapies may need to be implemented earlier based on severity of disease.

Frequency/duration

Based on the duration and frequency of artificial tear use reported in all the studies referenced in Tables 1 and 2, a mean of 3.47 doses/day over a period 60.1 days was established. Thus, our recommendation would be to use the artificial tears three to four times per day over a period of 2 months before transitioning to the next step. If artificial tear use extends beyond four to six times per day, then a preservative-free formulation should be used.[62]

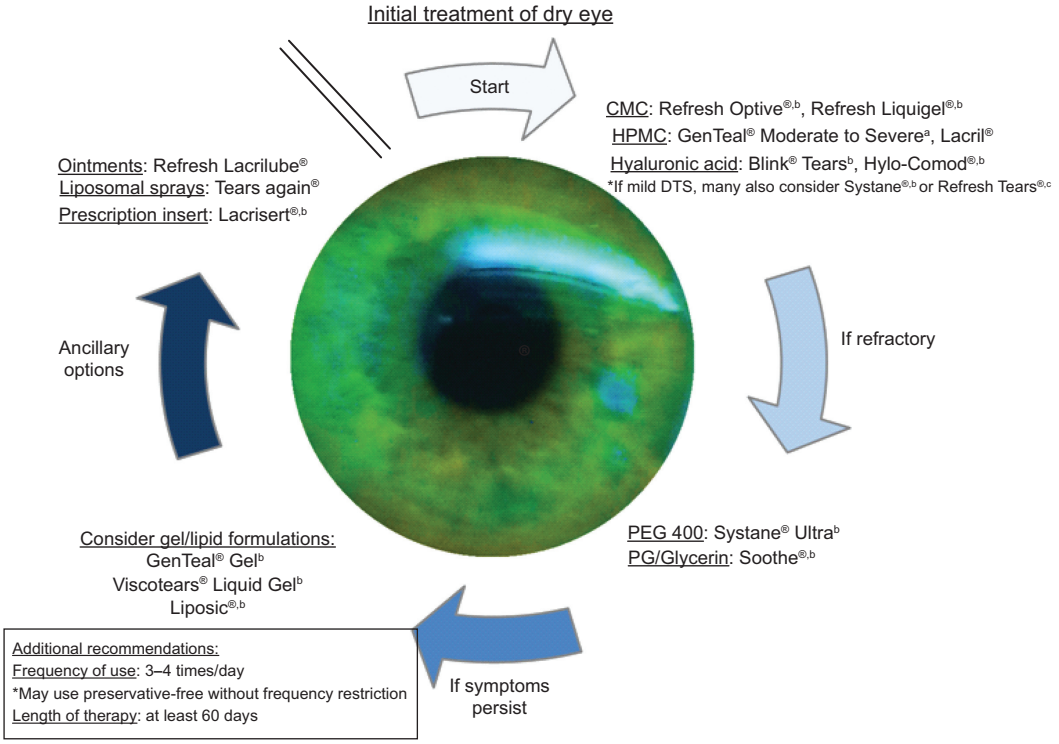

Figure 1 Treatment flowchart.

Notes: [a]Contains 0.3% HPMC and 0.25% CMC; [b]Preservative-free option available; [c]Preservative-free option: Refresh Plus®. Manufacturers are as follows: Refresh®, Allergan, Irvine, CA, USA; GenTeal®, Novartis Pharmaceuticals, East Hanover, NJ, USA; Lacril®, Allergan; Blink®, Abbott Laboratories Inc., Abbott Park, IL, USA; Systane®, Alcon Laboratories, Inc.; Soothe®, Bausch & Lomb Incorporated, Bridgewater, NJ, USA; Viscotears®, Novartis Pharmaceuticals; Liposic®, Bausch & Lomb Incorporated; Tears Again®, OcuSoft, Rosenberg, TX, USA.

Abbreviations: CMC, carboxy methylcellulose; DTS, dysfunctional tear syndrome; HPMC, hydroxypropyl methylcellulose; PEG, polyethylene glycol; PG, propylene glycol.

Preserved versus preservative-free

As seen in Tables S1–S5, many different tear replacement formulations include preservatives, but not all preservatives have the same effects. The most commonly used preservative was benzalkonium chloride (BAK). BAK has more antimicrobial activity than any other preservative in both animal and human subjects. However, BAK has been shown to damage the corneal epithelium and disrupt the tear film immediately after administration, which directly contradicts the goal of artificial tears.[63,64] Some of the newer preservative compounds appear to have a better safety profile than BAK but do not entirely prevent corneal epithelium damage.[65] These preservatives include Purite® (Bio-Cide International Inc., Norman, OK, USA), Polyquad® (Alcon Laboratories, Inc.), GenAqua® (Novartis Ophthalmics, East Hanover, NJ, USA), OcuPure® (Abbott Laboratories Inc.), Dissipate® (OCuSOFT, Rosenberg, TX, USA).[50,63,66] Since most of the corneal changes occur when the preservatives reach high concentrations, if one chooses to use a tear replacement with preservatives, daily use should be limited to four to six times.[62] Due to the risk of contamination, if a preservative-free artificial teardrop is chosen, single dose vials are recommended over multidose administration bottles.[67] Increased cost represents another downside to preservative-free artificial tears compared to those with preservatives. All things considered, a choice between preservative-free and preserved artificial tears should be discussed on an individual basis between physician and patient.

Limitations

The US is currently the epicenter of clinical research on DTS as it has been previously documented to conduct 70.8% of the registered clinical trials around the world which focused on dry eye.[23] The data presented in this paper may not be applicable in a global setting, as the American diet, and cultural and daily activities may play a role in the development of DTS and its corresponding treatment. With growing research in other countries, such as Japan, Australia, UK, and the Netherlands, treatment of DTS with artificial tears will progressively be refined on a global scale.[68] Furthermore, the research that has been presented in this article is based on a nonregulated health product, and the US permits distribution of artificial tears without any data revealing positive efficacy.[68,37] Any research investments made into this field may be affected by financial interests of the investigators and call into question the integrity of the outcomes, which may have influenced our recommendations. A recent meta-analysis of the comprehensive research on dry eye disease revealed that the pharmaceutical industry sponsored 78% of 185 clinical trials on this topic in the US.[68] For this reason, care should be taken when analyzing and applying data from industry-funded studies. Independent, unbiased research must increase on a worldwide level in order to more objectively and accurately elucidate the management of DTS.

In addition, this review article addressed a myriad of subjective and objective data with a multitude of data collection methods and varying result parameters, including dosing and length of treatment phase. For these reasons, further statistical analyses of improvements were not completed in this paper, but our study does suffer from lack of statistical backing. Furthermore, many of the individual papers which contributed to our information pool validated their data prior to their release. In future clinical trials, standardization of measurement instruments as well as dosage and time of treatment could enrich the generalizability of the outcomes and lead to a more consistent review of resultant data.

Finally, our study provides recommendations based on comparative studies previously published in the literature. Most of the artificial tears available in the market, as seen in Tables 2 and S1–S5, were not included in the recommendations since they have not been included in comparative studies. We recognize that the recommendations made are still a good guide for clinicians and patients when initiating DTS therapy based on the data available.

Conclusion

With the expansive amount of commercially available artificial tear options, specific recommendations are needed to help guide both the clinician and patient. Although limited by the lack of congruent methodology throughout the included studies and heterogeneous population, this paper aimed to provide unbiased recommendations based on the available data and should be a step towards the standardization of future studies regarding artificial tears. Utilizing both direct comparison and patient improvement following artificial tear use, a treatment flowchart was created (Figure 1). Ultimately, artificial tear selection should be individualized to the patient's specific needs. In the future, a standardized method to evaluate dry eye, as well as efficacy of artificial tear treatment, will allow for improved recommendations to be formed.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Methylcellulose-based artificial tears commercially available

Name	Active ingredients	Preservatives
GenTeal® Mild	0.2% HPMC	GenAqua® (sodium perborate)
GenTeal® Moderate to Severe	0.3% HPMC	GenAqua® (sodium perborate)
	0.25% CMC	
Ultra Tears®	0.3% HPMC	BAK
Tearisol®	0.3% HPMC	BAK
Lacril®	0.5% HPMC	Chlorobutonal
Isopto® Alkaline	1.0% HPMC	BAK
Isopto® Plain	0.5% HPMC	BAK
Isopto® Tears	0.5% HPMC	BAK
Nature's Tears®	0.4% HPMC	BAK
Natural Balance Tears	0.4% HPMC	BAK
Rohto® Hydra	0.3% HPMC	Polyaminopropyl biguanide
Thera Tears®	0.25% CMC	Preserved-form[a]
		Dequest (sodium perborate and phosphoric acid)
Refresh Tears®	0.5% CMC	Purite (stabilized oxychloro complex)
Refresh Plus®	0.5% CMC	None
Refresh Celluvisc®	1.0% CMC	Preserved-form[a]
		Purite (stabilized oxychloro complex)
Refresh Liquigel®	1.0% CMC	Preserved-form[a]
		Purite (stabilized oxychloro complex)
Just Tears	0.5% CMC	Purite (stabilized oxychloro complex)

Notes: [a]Both preserved and preservative-free formulations commercially available. Manufacturers are as follows: GenTeal®, Novartis Pharmaceuticals, East Hanover, NJ, USA; Ultra Tears®, Alcon Laboratories, Inc., Fort Worth, TX, USA; Tearisol®, Novartis Pharmaceuticals; Lacril®, Allergan, Irvine, CA, USA; Isopto®, Alcon Laboratories, Inc.; Nature's Tears®, Bio-Logic Aqua Technologies, Grants Pass, OR, USA; Natural Balance Tears, Major Pharmaceuticals, Livonia, MI, USA; Rohto® Hydra, Rohto Laboratories Indonesia, Padalarang, Indonesia; Thera Tears®, Advanced Vision Research, Ann Arbor, MI, USA; Refresh®, Allergan; GenAqua®, Novartis Ophthalmics, East Hanover, NJ, USA; Just Tears, Blairex, Columbus, IN, USA.
Abbreviations: BAK, benzalkonium chloride; CMC, carboxy methylcellulose; HPMC, hydroxypropyl methylcellulose.

Table S2 Polyvinyl alcohol-based artificial tears commercially available

Name	Active ingredients	Preservatives
Nutratear®	0.4% PVA	Polexitonium
Murine Tears®	0.5% PVA	BAK
	0.6% povidone	
Akorn® Artificial Tears	1.4% PVA	BAK
MiniDrops®	1.4% PVA	None
	0.6% providone	
Refresh Classic®	1.4% PVA	None
	0.4% povidone	
Clear Eyes® Artificial Tears	0.5% PVA	BAK
	0.6% povidone	
Freshkote®	2.7% PVA	Polixetonium
	2.0% povidone	

Notes: Manufacturers are as follows: Nutratear®, Medco Lab, Inc, Sioux City, IA, USA; Murine Tears®, Prestige Brands Holdings, Inc., Tarrytown, NY, USA; Akorn®, Akorn, Incorporated, Lake Forest, IL, USA; MiniDrops®, Optics Laboratory, Inc., El Monte, CA, USA; Refresh®, Allergan, Irvine, CA, USA; Clear Eyes®, Prestige Brands Holdings, Inc., Tarrytown, NY, USA; Freshkote®, FOCUS Laboratories, Inc., North Little Rock, AR, USA.
Abbreviations: BAK, benzalkonium chloride; PVA, polyvinyl alcohol.

Table S3 Liquid polyol-based artificial tears available on the market

Name	Active ingredients	Preservatives
Oasis® Tears	0.2% glycerin (15%)	No
Oasis® Tears Plus	0.2% glycerin (30%)	No
Advanced Eye Relief™ "Environmental"	1.0% glycerin	BAK
Advanced Eye Relief™ "Rejuvenation"	0.3% glycerin	BAK
	1.0% propylene glycol	
Blink® Tears	0.25% polyethylene glycol 400	Preserved-form[a]
	Hyaluronic acid	OcuPure® (stabilized oxychloro complex)
Blink® Gel Tears	0.25% polyethylene glycol 400	OcuPure® (stabilized oxychloro complex)
	Hyaluronic acid	
Systane® Balance	0.6% propylene glycol	Polyquad® (polyquaternium-1)
Systane® Gel Drops	0.4% polyethylene glycol 400	Polyquad® (polyquaternium-1)
	0.3% propylene glycol	
Systane®	0.4% polyethylene glycol 400	Preserved-form[a]
	0.3% propylene glycol	Polyquad® (polyquaternium-1)
Systane® Ultra	0.4% polyethylene glycol 400	Preserved-form[a]
	0.3% propylene glycol	Polyquad® (polyquaternium-1)
Soothe®	0.6% glycerin	No
	0.6% propylene glycol	
Viva Drops®	1.0% polysorbate 80	No

Notes: [a]Both preserved and preservative-free formulations commercially available. Manufacturers are as follows: Oasis®, Oasis Medical, Inc., Glendora, CA, USA; Advanced Eye Relief™, Bausch & Lomb Incorporated, Bridgewater, NJ, USA; Blink®, Abbott Laboratories Inc., Abbott Park, Illinois, USA; Systane®, Alcon Laboratories, Inc., Fort Worth, TX, USA; Soothe®, Bausch & Lomb Incorporated; Viva Drops®, Dakota Laboratories, LLC, Mitchell, SD, USA; Polyquad®, Alcon Laboratories, Inc.; OcuPure®, Abbott Laboratories Inc.
Abbreviation: BAK, benzalkonium chloride.

Table S4 Gels, ointments, sprays, and an ophthalmic insert for dysfunctional tear syndrome

Name	Active ingredients	Delivery	Preservatives
GenTeal® Gel	0.3% HPMC	Gel	Preserved-form[a]
	Carbopol 980		GenAqua®
Tears Again® Night & Day Gel	1.5% CMC	Gel	Dissipate (stabilized oxyborate complex)
Hylo®-Gel	0.2% hyaluronic acid	Gel	None
ViscoTears® Liquid Gel	0.2% carbomer 980	Gel	None
Liquivisc™	0.25% carbomer 974P	Gel	BAK
Liposic®	0.2% carbomer 980	Gel	None
Soothe® Lubricant Eye Ointment	20% mineral oil	Ointment	None
	80% white petrolatum		
Akwa® Tears Ointment	15% mineral oil	Ointment	None
	83% white petrolatum		
Rugby® Artifical Tear Ointment	15% mineral oil	Ointment	None
	83% white petrolatum		
Puralube® Ointment	15% mineral oil	Ointment	None
	85% white petrolatum		
Lubrifresh™ PM	15% mineral oil	Ointment	None
	83% white petrolatum		
Refresh PM® Ointment	42.5% mineral oil	Ointment	None
	57.3% white petrolatum		
Tears Naturale® PM	56.8% white petrolatum	Ointment	None
	42.5% mineral oil		
Refresh Lacrilube®	42.5% mineral oil	Ointment	Chlorobutanol
	56.8% white petrolatum		
Systane® Nighttime Ointment	3% mineral oil	Ointment	None
	94% white petrolatum		
Clarymist™	1.0% woy lecithin	Spray	Phenoxyethanol
Actimist™	1% woy Lecithin	Spray	Phenoxyethanol

(*Continued*)

Table S4 (Continued)

Name	Active ingredients	Delivery	Preservatives
Tears Again®	1.4% PVA	Spray	Dissipate (stabilized oxyborate complex)
Nature's Tears®	Bio-Logic Aqua® tissue-culture grade water	Spray	None
Vizulize Dry Eyes Eye Mist	0.10% hyaluronate	Spray	N-IG
Lacrisert®,[b]	5 mg HPMC	Insert	None

Notes: [a]Both preserved and preservative-free formulations commercially available; [b]Prescription-only ophthalmic insert. Manufacturers are as follows: GenTeal®, Novartis Pharmaceuticals, East Hanover, NJ, USA; Tears Again®, OcuSoft, Rosenberg, TX, USA; Hylo®-Gel, URSAPHARM, Saarbrücken, Germany; Viscotears®, Novartis Pharmaceuticals; Liquivisc™, URSAPHARM; Liposic®, Bausch & Lomb Incorporated, Bridgewater, NJ, USA; Soothe®, Bausch & Lomb Incorporated; Akwa®, Akorn, Incorporated, Lake Forest, IL, USA; Rugby®, Rugby Laboratories, Livonia, MI, USA; Puralube®, Fougera Pharmaceuticals Inc., Melville, NY, USA; Lubrifresh™, Major Pharmaceuticals, Livonia, MI, USA; Refresh®, Allergan, Irvine, CA, USA; Systane®, Alcon Laboratories, Inc., Fort Worth, TX, USA; Clarymist™, Savant Distribution, Leeds, UK; Actimist™, Reckitt Benckiser plc, Berkshire, UK; Nature's Tears®, Bio-Logic Aqua Technologies, Grants Pass, OR, USA; Lacrisert®, Valeant Pharmaceuticals North America LLC, Bridgewater, NJ, USA; GenAqua®, Novartis Ophthalmics, East Hanover, NJ, USA; Tears Again®, OcuSoft; Vizulize Dry Eyes Eye Mist, Butterflies Healthcare, Banbury, OX, UK; Bio-Logic Aqua®, Bio-Logic Aqua Technologies.
Abbreviations: BAK, benzalkonium chloride; CMC, carboxy methylcellulose; HPMC, hydroxypropyl methylcellulose; N-IG, N-hydroxymethylglycinate; PVA, polyvinyl alcohol.

Table S5 Artificial tears with combinations of active ingredients

Name	Active ingredients	Preservatives
Refresh Optive® Advanced	0.5% CMC 1.0% glycerine 0.5% polysorbate 80	Preserved-form[a] Purite® (stabilized oxychloro complex)
Refresh Optive®	0.5% CMC 0.9% glycerine	Preserved-form[a] Purite® (stabilized oxychloro complex)
Refresh Optive® Sensitive	0.5% CMC 0.9% glycerine	None
Tears Naturale® II	0.3% HPMC 0.1% dextran 70	Polyquad® (polyquaternium-1)
Tears Naturale® Free	0.3% HPMC 0.1% dextran 70	None
Tears Naturale® Forte	0.3% HPMC 0.1% dextran 70 0.2% glycerin	Polyquad® (polyquaternium-1)
Tears Naturale® – Bion Tears	0.3% HPMC 0.1% dextran 70 Zinc + bicarbonate	None
Tears Renewed®	0.3% HPMC 0.1% dextran 70	BAK
Hypotears®	1.0% PVA 1.0% polyethylene glycol	BAK
Soothe® XP	1% light mineral oil 4.5% mineral oil	Polyhexamethylene biguanide
Hylo®-Fresh	0.03% hyaluronic acid	None
Hylo-Comod®	0.1% hyaluronic acid	None
Similasan® Dry Eye Relief	Belladonna Euphrasia Mercurius sublimatus	Silver sulfate
Similasan® Irritated Eye Relief	Belladonna Euphrasia Hepar sulfuris	Silver sulfate

Notes: [a]Both preserved and preservative-free formulations commercially available. Manufacturers are as follows: Refresh®, Allergan, Irvine, CA, USA; Tears Naturale®, Alcon Laboratories, Inc., Fort Worth, TX, USA; Tears Renewed®, Akorn, Incorporated, Lake Forest, IL, USA; Hypotears®, Novartis Pharmaceuticals, East Hanover, NJ, USA; Soothe®, Bausch & Lomb Incorporated, Bridgewater, NJ, USA; Hylo®-Fresh and Hylo-Comod®, URSAPHARM, Saarbrücken, Germany; Similasan®, Similasan Corporation, Highlands Ranch, CO, USA; Polyquad®, Alcon Laboratories, Inc.; Purite®, Bio-Cide International Inc., Norman, OK, USA.
Abbreviations: BAK, benzalkonium chloride; CMC, carboxy methylcellulose; HPMC, hydroxypropyl methylcellulose; PVA, polyvinyl alcohol.