

Comparative Performance of Artificial Tear Drops Assessed with Objective Non-Invasive Imaging

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Purpose: To perform a comparative analysis of 13 over the counter artificial tear formulations and perflourohexyloctane assessing performance using objective, non-invasive imaging. The data provides a rationale to make better informed therapeutic decisions regarding their use.

Patients and Methods: Prospective, sequential study of 13 drop formulations in participants over 18 years of age. Tear meniscus height, non-invasive keratographic break up time, and central lipid layer thickness were measured before and 5 and 15 minutes after drop administration. Outcomes were compared using linear mixed models. Predictors included group (between-subjects), time (within-subjects), and the group by time interaction.

Results: One hundred and thirty-seven participants, mean age 67 years (54.3% female), were evaluated. Most drops showed increased tear meniscus height at 5 and 15 minutes compared to baseline. Changes in non-invasive keratographic break up time and lipid layer thickness were more variable. A few artificial tears demonstrated better performance with regards to tear meniscus height, non-invasive keratographic break up time or lipid layer thickness; but no single drop outperformed others across all three measured endpoints. Perflourohexyloctane did not show better performance in any test parameter.

Conclusion: The performance of various over-the-counter artificial tears can be determined with non-invasive imaging technologies. Certain drops can outperform others with regard to individual test parameters suggesting that personalization or optimization of therapy may be possible. Both active and inactive ingredients contribute to the efficacy of artificial tears. Further work is needed to determine if differences observed here translate into meaningful clinical differences for dry eye disease treatment. This report highlights the complexity of dry eye disease and the need for ongoing work to find optimal ways to treat the ocular surface.

Keywords: dry eye disease, perflourohexyloctane, tear meniscus height, lipid layer thickness, non-invasive keratographic break up time, LipiView II, Oculus Keratograph 5M

Introduction

Dry Eye Disease (DED) is one of the most common disorders encountered in eye clinics with an estimated 4.91 million affected Americans and tens of millions more with subclinical manifestations.^{1,2} In one study, DED ranked as the sixth most common eye condition.³ The mainstay of DED therapy is over-the-counter (OTC) artificial tears (AT).⁴ Despite being available without a prescription, AT supplements remain a costly therapy. The market size for AT estimated at 3.5 billion dollars in 2024 is expected to grow from 3.73 billion in 2025 to 6.57 billion in 2034,⁵ and is approximately 2-fold greater than the combined sales of Restasis (sales of 1.2 billion in 2020) and Xiidra (sales of 487 million in 2022).^{5,6} AT contribute to the financial burden of DED treatment which has an average yearly cost of over eleven thousand dollars per patient.⁷

AT are complex formulations comprised of multiple ingredients including astringents, demulcents, emollients, and hypertonicity agents. The composition of AT is guided by a monograph that outlines what can be included in ophthalmic over-the-counter preparations.⁸ By varying the allowable ingredients (both active and inactive), the various AT substitutes acquire different properties that can provide a substitute for a lack of natural tears, replace poor quality tears on the ocular surface, and/or break the inflammatory cycle incited by tear film instability and decrease ocular surface inflammation.⁹ Many AT claim that they target different severities of DED or that they may perform better for various subtypes of DED such as disease due to contact lenses wear or extended work on video display terminals.

Despite being the most common DED therapy and claims that certain AT may perform better for certain types of disease,¹⁰ scant information is available to guide eye care professionals or patients about how to optimize their AT choices. The American Academy of Ophthalmology Preferred Practice Pattern currently does not provide any specific guidance regarding AT supplementation.¹¹ One meta-analysis indicated that hyaluronic-acid-based formulations may have utility in the treatment of DED over non-hyaluronic acid based formulations and saline.¹² Another study compared carboxymethylcellulose-hyaluronic acid and carboxymethylcellulose preparations.¹³ Frequent limitation of such studies is that they utilize non-comparable measurements as endpoints.¹⁴

One explanation for the paucity of data is the limited number of methods previously available to objectively assess AT performance. Unfortunately, DED lacks a gold standard for measurement of disease status.¹⁵ Conventional clinical measures of tear film function and architecture such as Schirmer's tear test, tear osmolarity, and fluorescein tear break up time all involve manipulation of the ocular surface and eyelids or the application of eye drops or dyes which stimulate reflex tearing; all confound attempts to measure the effects of AT.¹⁶ Recently introduced imaging technologies that have gained clinical acceptance (reviewed in¹⁷⁻¹⁹) make it possible to measure tear film architecture and function in an objective, non-invasive manner techniques. Two devices commonly used in clinical practice that allow such measurements are the Oculus Keratograph 5M[®] (OK5M) (OCULUS Inc., Arlington, WA 98223, USA) and the LipiView[®] II Ocular Surface Interferometer (LV2) (TearScience, Johnson & Johnson company).

The OK5M is an advanced keratograph that uses modified optics and a curved keratograph head to provide consistent and uniform illumination across the visible ocular surface (conjunctiva and cornea).²⁰ This device provides noninvasive measurement of tear meniscus height (TMH) (measured from anterior segment images using digital calipers). TMH is the most direct assessment of tear film volume, which when low, may be a key pathogenic mechanism and a diagnostic sign for DED independent of the DED type.¹⁵ Noninvasive TMH measurements were reproducible and reliable in one study,²¹ correlated with OSDI score in a Hispanic population,²² and distinguished DED from normal patients in a third.²³

Additional capabilities of the OK5M include the ability to measure non-invasive keratographic break up time (NIKBUT) via automated detection and mapping of tear breakup locations over time. As previously described,^{14,24} NIKBUT measured in seconds and automatically detected by the device, represents the time between the last complete blink and the first perturbation of placido disc rings projected onto the surface of the cornea. The OK5M generates two measures for NIKBUT: the time at the first breakup of tear film (NIKBUT-first) and the average time of all breakup incidents (NIKBUT-average). Measurement of NIKBUT may be preferable to traditional fluorescein breakup time.¹⁶ Measurements of TMH and NIKBUT obtained with the OK5M have been shown to be reliable with good repeatability and reproducibility in patients with and without DED.²⁵ Additionally, we have observed that OK5M measurements of TMH and NIKBUT can be used to follow the evolution of dry eye disease in laboratory models of aqueous deficient DED.²⁶

The tear film's outermost layer (lipid layer), a barrier to evaporation of the underlying aqueous and mucin layers, can be assessed with the LV2. The LV2 projects monochromatic light onto the cornea and records a 20 second video that analyzes the light reflection and interference pattern from the tear film using interferometry to measure the lipid layer thickness (LLT). Data is displayed in interferometric color units (ICU), where 1 ICU reflects approximately 1 nm of LLT. Low LLT values < 69 nm often indicate more severe lipid deficiency and evaporative dry eye.²⁷

Herein, we present a comparative analysis of 13 over the counter AT formulations and perflourohexyloctane (Miebo[®]), a recently approved medication that stabilizes the tear film by preventing evaporation. We assess performance using the OK5M and LV2 devices to measure the changes that occur in TMH, NIKBUT and LLT values after eye drop instillation. This report expands upon currently available data in the literature comparing AT performance and may provide a rationale for practitioners and patients to make better informed therapeutic decisions.

Materials and Methods

Patients

This study was approved by the Stony Brook Institutional Review Board and complied with the Declaration of Helsinki. Subjects over 18 years of age were recruited from multi-specialty clinics at an outpatient tertiary eye care center during regular clinic visits. Participants represented a broad spectrum of patients that would be expected in a comprehensive eye clinic. All participants had normal anterior segment exams without recent surgery or acute ophthalmology pathology requiring medical or surgical treatment. For the purpose of this study, participants were not classified according to their baseline DED symptoms or status. In order to minimize known environmental influences on the ocular surface and measurements taken with the devices, all participants were recruited during the summer months (June–August) and all were measured in a temperature (70 ± 5 °F) and humidity (40 ± 5 rH) controlled environment. Participants were enrolled after their eye exam confirmed the absence of active eye pathology. Up to two different eye drop brands were tested on a given day. Each participant received only one of the 2 eye drop brands tested on a given day. Both eyes of each participant were tested using the same study eye drop (when both eyes could be studied).

Measurements

TMH, NIKBUT, and central LLT were measured at baseline and at 5- and 15-minutes following administration of one drop of the study agent dispensed from its commercial bottle. Measurements were taken in both left and right eye for each participant and evaluated independently. The OK5M was used to obtain measures of TMH and NIKBUT as per manufacturer instructions. Briefly, TMH was measured along the lower lid under the center of the pupil with built-in software calipers from a single high-resolution image taken using infrared illumination. For NIKBUT, three successive measurements were taken and the mean of three Average NIKBUT values was used for statistical comparisons. A single measurement of central LLT was obtained using the LV2 as per manufacture guidelines.

Thirteen over the counter (OTC) AT preparations were analyzed. The active and inactive ingredients for each drop are shown in Table 1. Balanced salt saline (BSS), approximately 300 mOsm/Kg, was used as a control. Perfluorohexyloctane (Miebo[®]) was also studied due to its immediate action on tear film stability.

Table 1 List of Active and Inactive Ingredients of Utilized Eye Drops

Name	Active Ingredient	Inactive Ingredient	Preservative
Similasan [®]	Belladonna 6X (6 in 10 mL) (containing 0.000002% alkaloids) Euphrasia officinalis (Eyebright) 6X Mercurius sublimatus 15x	Boric acid Purified water Silver sulfate Sodium nitrate	Silver sulfate
Up&Up [®] (high performance lubricant eye drops)	Polyethylene glycol 400 0.4% Propylene glycol 0.3%	Boric acid Calcium chloride Disodium edetate Hypromellose Magnesium chloride Potassium chloride Purified water Sodium chloride Zinc chloride Sodium borate Sorbitol Hydrochloric acid and/or Sodium hydroxide to adjust pH	Purite

(Continued)

Table 1 (Continued).

Name	Active Ingredient	Inactive Ingredient	Preservative
Visine® (Dry eye relief all day comfort)	Polyethylene glycol 400 1%	Ascorbic acid Boric acid Dextrose Glycerin Glycine Hypromellose Magnesium chloride Potassium chloride Purified water Sodium borate Sodium chloride Sodium citrate Sodium lactate Sodium phosphate dibasic anhydrous	polyquaternium-42
Systane Complete PF®	Propylene glycol	Boric acid Dimyristoyl-phosphatidylglycerol Guaraprollose (3500 Mpa.S at 1%) Mineral oil Polyoxyl 40 stearate Sorbitan tristearate Sorbitol Water Hydrochloric acid Sodium hydroxide	None
Gentle Tears®	Dextran 70 0.1% Glycerin 0.2% Hypromellose 0.3%	Boric acid Calcium chloride Glycine Hydrochloric acid Sodium hydroxide Magnesium chloride Polysorbate 80 Potassium chloride Purified water Sodium chloride Zinc chloride	Polyquad
Gentle Gel®	Mineral Oil 3% White Petrolatum 94%	Lanolin	None
Ivizia®	Povidone 0.5%	Hydrochloric acid Purified water Sodium chloride Sodium hyaluronate Trehalose Tromethamine	None

(Continued)

Table 1 (Continued).

Name	Active Ingredient	Inactive Ingredient	Preservative
Refresh Optive Mega 3® Preservative Free	Carboxymethylcellulose sodium 0.5% Glycerin 1% Polysorbate 80 0.5%	Boric acid Butylated hydroxyl toluene Castor oil Erythritol Flaxseed oil Levocarnitine Pemulen TR-2 Polyoxyl 40 stearate Purified water Trehalose Sodium hydroxide Hydrochloric acid	None
Soothe XP®	Light mineral oil 1.0% Mineral oil 4.5%	Boric acid Edetate Disodium Octoxynol – 40 Polysorbate 80 Water Sodium borate Hydrochloric acid Sodium hydroxide	Edetate Disodium Polyquad
Refresh Relieva®	Carboxymethylcellulose Sodium 0.5% Glycerin 0.9%	Boric acid Calcium chloride Erythritol Magnesium chloride Potassium chloride Water Sodium chloride Sodium borate Trisodium citrate dihydrate Hyaluronate sodium Hydrochloric acid Sodium hydroxide	Purite
Systane Ultra®	Polyethylene glycol 400 0.4% Propylene glycol 0.3%	Aminomethylpropanol Boric acid Hydroxypropyl guar Potassium chloride Purified water Sodium chloride Sorbitol Hydrochloric acid Sodium hydroxide	Polyquad
Hylo-Tear®	Sodium hyaluronate 0.1%	Citric acid anhydrous Sodium citrate Sorbitol Water	None
Miebo®	Perfluorohexyloctane		None

(Continued)

Table 1 (Continued).

Name	Active Ingredient	Inactive Ingredient	Preservative
Balanced salt saline (BSS)		Sodium chloride 0.64% Potassium chloride 0.075% Calcium chloride dihydrate 0.048% Magnesium chloride hexahydrate 0.03% Sodium acetate trihydrate 0.39% Sodium citrate dihydrate 0.17% Sodium hydroxide Hydrochloric acid Water	None

Statistics

Outcomes were compared between groups using linear mixed models (LMM). Predictors included group (between-subjects), time (within-subjects), and the group by time interaction. The correlation between observations measured repeatedly within each subject (ie, multiple eyes and multiple time points) was modeled using random subject effects and structured variance-covariance matrices. The best-fitting model was selected according to information criteria. Least-square (LS) means and standard error were estimated, plotted, and compared post-hoc to determine the nature of significant effects. All analyses were performed using SAS, version 9.4 (Cary, NC).

Results

A total of 137 patients participated in the study. Mean age was 67.01 years and 54.3% were female. Baseline characteristics of the measured tear film parameters for the entire group and each of the tested tear drops are given in Table 2. No significant differences were seen in mean tear meniscus height between any of the tested drops and baseline for the entire group. With the exception of Hylo-Tear and Up&Up which both had a slightly lower average NIKBUT at baseline, all other tested drops were statistically equivalent to the entire group at baseline. For LLT most eye drops were

Table 2 Baseline Characteristics of Measured Tear Film Parameters for Each Tested Drop

Drop	N	Mean TMH	T Test	Mean Average NIKBUT	T Test	Mean LLT	T Test
All Eyes	20	0.34±0.19	–	14.0±4.9	–	72.5±24.0	–
Systane Complete	16	0.26±0.11	NS	14.9±5.1	NS	73.8±26.1	NS
Refresh Relieva	18	0.40±0.16	NS	14.3±3.4	NS	84.3±18.1	NS
Gentle Gel	16	0.30±0.13	NS	13.6±5.4	NS	69.2±20.4	NS
Systane Ultra	16	0.44±0.29	NS	15.2±4.4	NS	85.5±15.9	0.04
Refresh Optive Mega 3	16	0.34±0.19	NS	14.2±4.2	NS	75.4±23.8	NS
Soothe XP	16	0.36±0.29	NS	15.2±4.5	NS	54.1±18.9	0.00
Saline	12	0.24±0.12	NS	15.3±5.4	NS	86.7±17.1	NS
Gentle Tears	20	0.31±0.11	NS	14.1±4.8	NS	76.9±20.1	NS
Ivizia	27	0.32±0.14	NS	14.1±5.1	NS	70.6±23.6	NS
Hylo-Tear	20	0.37±0.12	NS	11.3±4.4	0.02	81.6±18.7	NS

(Continued)

Table 2 (Continued).

Drop	N	Mean TMH	T Test	Mean Average NIKBUT	T Test	Mean LLT	T Test
Visine	22	0.30±0.19	NS	12.3±6.2	NS	61.2±25.1	0.05
Up&Up	20	0.31±0.17	NS	11.3±6.3	0.03	63.8±24.1	NS
Similasan	20	0.37±0.29	NS	15.0±3.3	NS	71.7±26.5	NS
Miebo	28	0.41±0.20	NS	15.4±4.1	NS	71.5±33.3	NS

Note: All T tests are compared to the baseline for the entire cohort for all eyes for each tested parameter.

Abbreviation: NS, not significant.

equivalent to the entire group at baseline, with the exception of Systane Ultra which was slightly higher at baseline, and Soothe XP and Visine which were lower at baseline compared to the entire group.

As seen in Figure 1, almost all drops showed increased TMH at 5 minutes compared to baseline levels. TMH was slightly higher at 15 minutes for most eye drops as well. However, statistical improvement was only reached for Genteal Gel®, Refresh Optive Mega 3®, and Hylo-Tear® at 5 minutes.

Changes in NIKBUT (Figure 2) were more varied than those of TMH with about half of the drops showing some improvement at 5 minutes, and the other half showing no change or a small decline. Only Refresh Relieva® and BSS showed significant improvement at 5 minutes, while Visine®, Up&Up®, and Meibo® showed significant decreases in NIKBUT at 5 minutes.

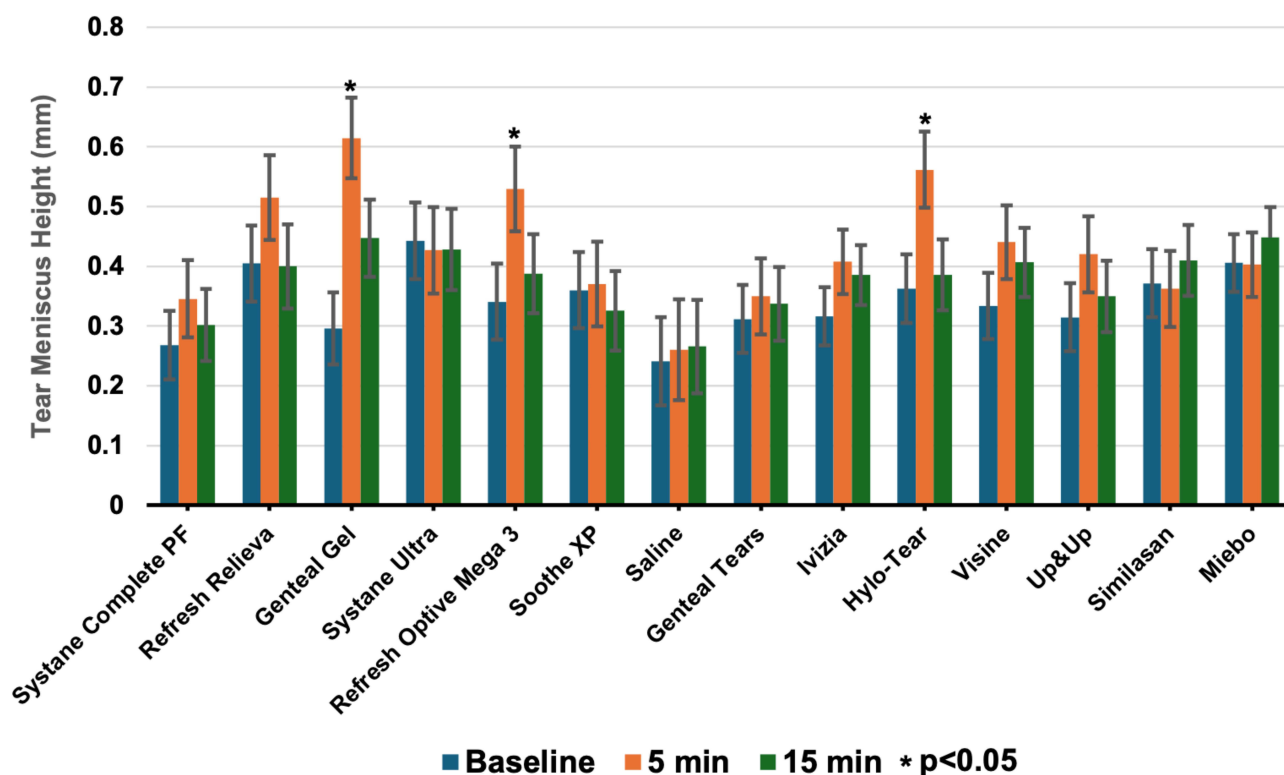


Figure 1 Bar graph showing tear meniscus height (TMH) at baseline, 5 minutes, and 15 minutes following drop administration. Asterisks (*) indicate significant change ($p < 0.05$) compared to baseline. Genteal Gel, Refresh Optive Mega 3, and Hylo-Tear outperformed other drops at 5 minutes. By 15 minutes no drops showed statistically significant change from baseline readings.

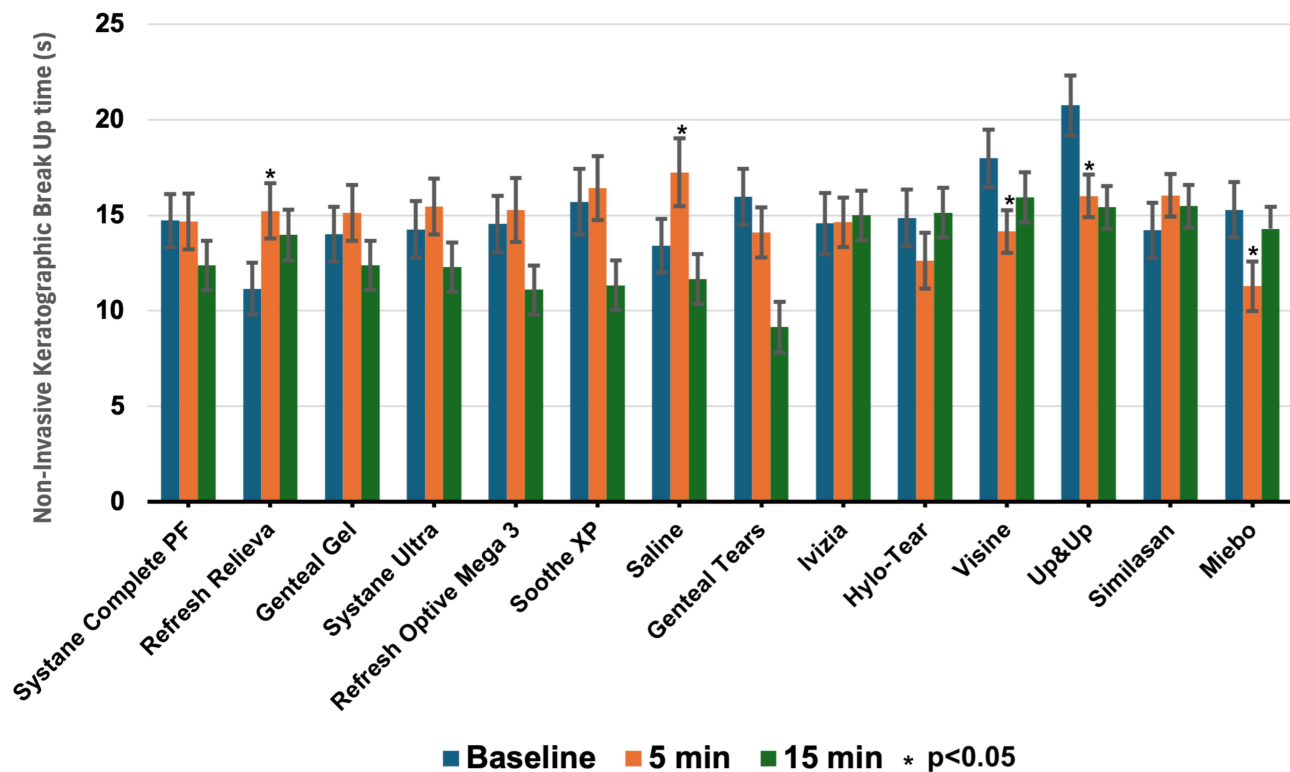


Figure 2 Bar graph showing non-invasive keratographic break up time (NIKBT) at baseline, 5 minutes, and 15 minutes following drop administration. Asterisks (*) indicate significant change ($p < 0.05$) compared to baseline. Refresh Relieva, and Saline (BSS) demonstrated significant improvement at 5 minutes while Visine, Up&Up, and Miebo demonstrated significant detrimental effects at 5 minutes. No drop showed statistically significant improvement at 15 minutes.

Measured changes in LLT (Figure 3) were also varied with about half showing an increase and the remainder a small decrease at 5 minutes. Although Genteal Gel®, Refresh Optive Mega 3®, BSS, and Miebo® showed an increase in LLT compared to baseline at 5 minutes, none reached statistical significance. Additionally, AT that demonstrated a statistical decrease in LLT at 5 minutes included Refresh Relieva®, Hylo Tear®, Visine®, and Up&Up®.

The changes in TMH, NIKBUT and LLT for each drop ranked by percent change at 5 minutes are given in Table 3. At 5 minutes an increase greater than or equal to 10% in magnitude was seen in 10/14 drops for TMH, 5/14 drops for NIKBUT, and 2/14 drops for LLT.

The comparative performance of various drops analyzed using a LMM approach that compensated for baseline values of each parameter as well as time are given for TMH, NIKBUT and LLT in Tables 4–6, respectively.

As seen in Table 4, most tested drops show similar performance statistically with regard to TMH. The one exception is Genteal Gel which outperformed all drops other than Hylo-Tears and Refresh Optive Mega 3. Hylo-Tear also performed well, showing better performance than 3 other eye drops tested here.

Fewer drops demonstrated increases in NIKBUT (Table 5). LMM analysis showed Systane Ultra outperformed all other commercially available eye drops tested for NIKBUT and was better but statistically equivalent to BSS drops. Among commercially available drops, Ivizia had the second best performance for NIKBUT, but only outperformed 3/14 drops tested. Up&Up and Visine underperformed relative to most other eye drop supplements.

Few drops showed large changes in LLT in this study (Table 6). Only 2/14 drops tested showed LLT increases >10% at 5 minutes. LMM analysis indicated that only one drop, SootheXP, excelled, outperforming all other drops except Hylo-Tears which performed statistically the same. Hylo-Tear also excelled, outperforming 5 other eye drops.

Discussion

Although the most commonly utilized therapy for patients with DED is AT, no clear guidance is available for use of these therapies, unlike prescription medications. Little comparative information is available to help practitioners or patients

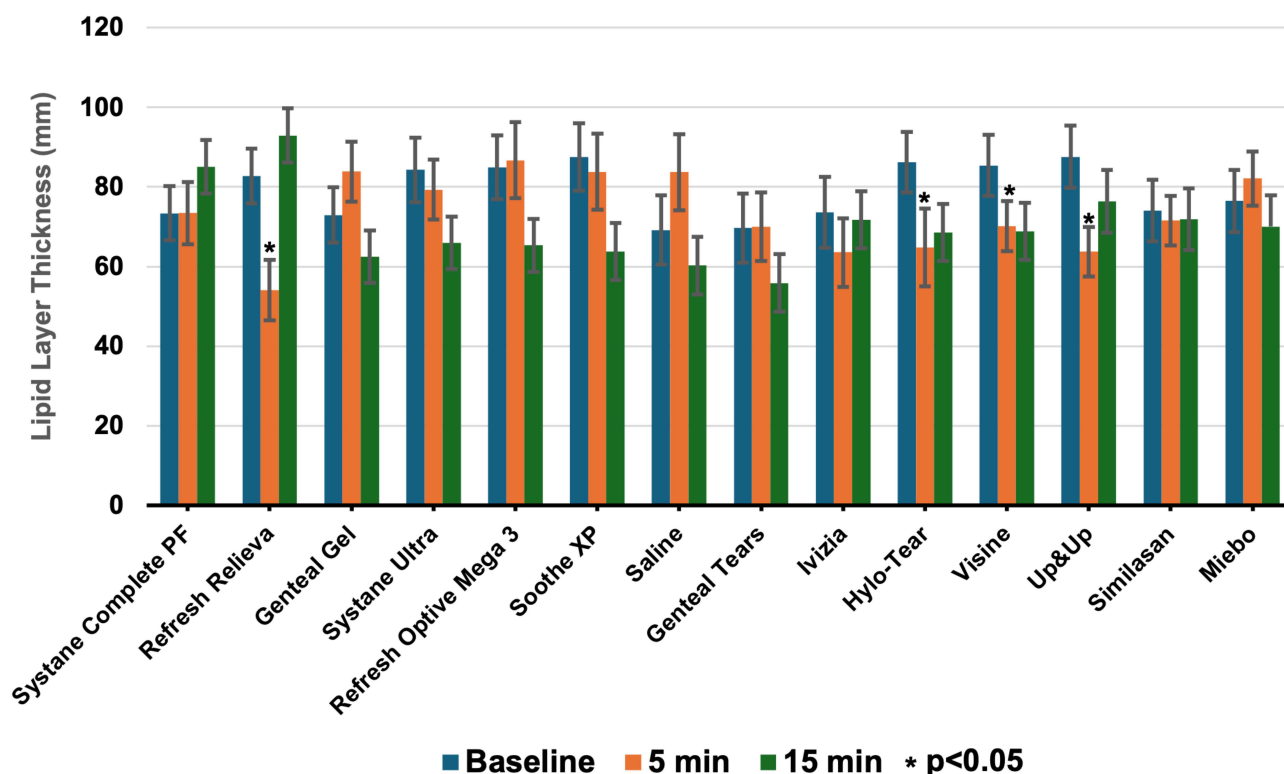


Figure 3 Bar graph showing lipid layer thickness (LLT) at baseline, 5 minutes, and 15 minutes following drop administration. Asterisks (*) indicate significant change ($p < 0.05$) compared to baseline. No drop demonstrated significant improvement from baseline at 5 or 15 minutes. Refresh Relieva, Hylo-Tear, Visine, and Up&Up showed deleterious effects at 5 minutes.

make informed decisions about which eye drop might provide better results. This report provides objective data about relative AT performance and may help practitioners make informed decisions about their use.

Herein we provide comparative performance data for a number of common AT supplements, as well as one recently available prescription medication perfluorohexyloctane (Miebo®). Although this study did not evaluate all available OTC AT supplements, the broad selection tested here represents the major categories of active ingredients while inclusion of perfluorohexyloctane provides comparative performance to an approved prescription medication whose mechanism of action is through stabilization of the tear film. Given perfluorohexyloctane's immediate action, comparisons to AT preparations are reasonable unlike lifitegrast and cyclosporin, which take much longer for their effects to occur.

Table 3 Percent Change in Eye Drop Performance at 5 and 15 Minutes Compared to Baseline

Eye Drop Performance Ranked by Percent Change								
TMH			NIK BUT			LLT		
	5 min	15 min		5 min	15 min		5 min	15 min
Genteal Gel	110	48	Systane Ultra	21	40	Soothe XP	55	47
Refresh Optive Mega 3	72	32	Genteal Gel	18	8	Systane Complete PF	11	-2
Hylo-Tear	55	6	Ivizia	18	16	Visine	8	8
Visine	46	35	Refresh Optive Mega 3	12	2	Hylo-Tear	5	14
Up&Up	34	11	Hylo-Tear	10	23	Refresh Optive Mega 3	3	-7

(Continued)

Table 3 (Continued).

Eye Drop Performance Ranked by Percent Change								
TMH			NIK BUT			LLT		
	5 min	15 min		5 min	15 min		5 min	15 min
Refresh Relieva	27	8	Saline	8	14	Refresh Relieva	1	-1
Systane Complete PF	25	7	Genteal Tears	5	-18	Genteal Gel	1	-2
Ivizia	24	21	Up&Up	3	-18	Miebo	0	-6
Genteal Tears	11	11	Refresh Relieva	2	13	Systane Ultra	-1	6
Saline	11	-11	Similasan	1	6	Ivizia	-3	11
Soothe XP	3	-10	Miebo	1	-7	Saline	-3	-3
Miebo	-1	6	Soothe XP	-1	1	Similasan	-4	-4
Similasan	-3	10	Visine	-1	-10	Up&Up	-12	-18
Systane Ultra	-4	-5	Systane Complete PF	-24	-3	Genteal Gel	-15	4

Abbreviations: TMH, Tear meniscus height; NIK BUT, Non-invasive keratographic break up time; LLT, lipid layer thickness.

We assess the ability of these eye drops to acutely change metrics of TMH, NIK BUT and LLT obtained with non-invasive imaging methods following their administration. As these metrics are used to commonly assess the tear film in clinical practice, we believe they should also serve as reasonable measures to assess how well AT supplements applied to the ocular surface mimic the naturally produced tears. Given the volume of each AT drop added to the ocular surface greatly exceeds the volume of the native tear film,²⁸ it is likely that the measurements taken represent the characteristics of the added AT and not the patient's own native tears.

As measured here, TMH may only reflect the residence time of the added AT drop on the ocular surface rather than tear production or the patient's natural tear volume. Similarly, as measured here LLT and NIK BUT likely represent how well the various AT supplements mimic the natural tear film and are unlikely to represent actual physiologic responses or changes in a patient's native tear film. However, if used very frequently, these measurements might indicate which AT products can replicate normal tear functions.

Our data suggests that the various OTC AT do not perform the same with regard to the parameters measured here. No single AT drop outperformed all others with regard to TMH, NIK BUT, and LLT. However, some trends were apparent. For TMH, GenTeal Gel[®] performed best; for NIK BUT, Systane Ultra[®] outperformed most other drops; and for LLT, Soothe XP[®] had the best performance. Of note, this study was limited to changes over 15 minutes and it is possible that different conclusions might be made with a different time endpoint. In addition, drop size of the AT was not controlled for; instead we simply applied a drop from the commercial dispenser, representing the real world clinical experience when using them. We also did not control patients for their underlying DED status, as all drops applied were in excess of the natural tear volume present. Despite these confounding factors, it is clear that the different OTC AT have different properties and may thus allow personalization of therapy.

Our study demonstrates the positive effect of AT on multiple DED parameters which is also consistent with a conclusion from the study by Maity et al.²⁹ Although the study by Maity et al did not show a significant difference between efficacy of any of the tested AT supplements used, this is most likely due to the specific AT drops tested which were different than those studied here. In addition, experimental differences including the patient population studied may also contribute to this discrepancy. Although both studies show beneficial effects of AT, the differences between eye drop performance only highlights the need for further work in this area to determine best practices for patients.

Our results also indicate that OTC AT cannot be compared based solely on the composition of their *active* ingredients. This is evident from the comparison of NIK BUT between Systane Ultra[®] and Up&Up[®]. Both of these drops have polyethylene glycol 400 0.4% and propylene glycol 0.3% as active ingredients. Despite the same active ingredient

Table 4 Comparative Tear Meniscus Height Performance for Various Eye Drops

Drop Comparisons	Systane Complete PF	Refresh Relieva	Genteal Gel	Systane Ultra	Refresh Optive Mega 3	Soothe XP	Balanced Salt Saline	Genteal Tears	Ivizia	Hylo-Tear	Visine	Up&Up	Similasan	Miebo
Systane Complete PF®	●	●	-	●	●	●	●	●	●	●	●	●	●	●
Refresh Relieva®	●	●	-	●	●	●	●	●	●	●	●	●	●	●
Genteal Gel®	+	+	●	+	●	+	+	+	+	●	+	+	+	+
Systane Ultra®	●	●	-	●	●	●	●	●	●	-	●	●	●	●
Refresh Optive Mega 3®	●	●	●	●	●	+	●	●	●	●	●	●	●	●
Soothe XP®	●	●	-	●	-	●	●	●	●	-	●	●	●	●
Balanced salt saline	●	●	-	●	●	●	●	●	●	-	●	●	●	●
Genteal Tears®	●	●	-	●	●	●	●	●	●	●	●	●	●	●
Ivizia®	●	●	-	●	●	●	●	●	●	●	●	●	●	●
Hylo-Tear®	●	●	●	+	●	+	+	●	●	●	●	●	●	●
Visine®	●	●	-	●	●	●	●	●	●	●	●	●	●	●
Up&Up®	●	●	-	●	●	●	●	●	●	●	●	●	●	●
Similasan®	●	●	-	●	●	●	●	●	●	●	●	●	●	●
Miebo®	●	●	-	●	●	●	●	●	●	●	●	●	●	●

Notes: + denotes significantly better performance, - denotes significantly worse performance, and ● denotes no difference in the performance of the item in given row compared to performance in given column.

Table 5 Comparative Non-Invasive Keratographic Break up Time Performance for Various Eye Drops

	Systane Complete PF	Refresh Relieva	Genteal Gel	Systane Ultra	Refresh Optive Mega 3	Soothe XP	Balanced Salt Saline	Genteal Tears	Ivizia	Hylo-Tear	Visine	Up&Up	Similasan	Miebo
Systane Complete PF®	●	●	●	-	●	●	-	●	-	●	●	●	●	●
Refresh Relieva®	●	●	●	-	●	●	●	●	●	●	●	+	●	●
Genteal Gel®	●	●	●	-	●	●	●	●	●	●	+	+	●	●
Systane Ultra®	+	+	+	●	+	+	●	+	+	+	+	+	+	+
Refresh Optive Mega 3®	●	●	●	-	●	●	●	●	●	●	●	+	●	●
Soothe XP®	●	●	●	-	●	●	●	●	●	●	+	+	●	●
Balanced salt saline	+	●	●	●	●	●	●	●	●	●	+	+	●	●
Genteal Tears®	●	●	●	-	●	●	●	●	●	●	●	●	●	●
Ivizia®	+	●	●	-	●	●	●	●	●	●	+	+	●	●
Hylo-Tear®	●	●	●	-	●	●	●	●	●	●	●	●	●	●
Visine®	●	●	-	-	●	-	-	●	-	●	●	●	-	●
Up&Up®	●	-	-	-	-	-	-	●	-	●	●	●	-	-
Similasan®	●	●	●	-	●	●	●	●	●	●	+	+	●	●
Miebo®	●	●	●	-	●	●	●	●	●	●	●	+	●	●

Notes: + denotes significantly better performance, - denotes significantly worse performance, and ● denotes no difference in the performance of the item in given row compared to performance in given column.

Table 6 Comparative Lipid Layer Thickness Performance for Various Eye Drops

Drop Comparisons	Systane Complete PF	Refresh Relieva	Genteal Gel	Systane Ultra	Refresh Optive Mega 3	Soothe XP	Balanced Salt Saline	Genteal Tears	Ivizia	Hylo-Tear	Visine	Up&Up	Similasan	Miebo
Systane Complete PF®	●	●	●	●	●	-	●	●	●	●	●	+	●	●
Refresh Relieva®	●	●	●	●	●	-	●	●	●	●	●	+	●	●
Genteal Gel®	●	●	●	●	●	-	●	●	●	●	●	●	●	●
Systane Ultra®	●	●	●	●	●	-	●	●	●	●	●	+	●	●
Refresh Optive Mega 3®	●	●	●	●	●	-	●	●	●	●	●	●	●	●
Soothe XP®	+	+	+	+	+	●	+	+	+	●	+	+	+	+
Balanced salt saline	●	●	●	●	●	-	●	●	●	●	●	●	●	●
Genteal Tears®	●	●	●	●	●	-	●	●	●	●	●	●	●	●
Ivizia®	●	●	●	●	●	-	●	●	●	-	●	●	●	●
Hylo-Tear®	●	●	●	●	●	●	●	●	+	●	+	+	+	+
Visine®	●	●	●	●	●	-	●	●	●	-	●	●	●	●
Up&Up®	-	-	●	-	●	-	●	●	●	-	●	●	●	●
Similasan®	●	●	●	●	●	-	●	●	●	-	●	●	●	●
Miebo®	●	●	●	●	●	-	●	●	●	-	●	●	●	●

Notes: + denotes significantly better performance, - denotes significantly worse performance, and ● denotes no difference in the performance of the item in given row compared to performance in given column.

Table 7 Comparison of Active and Inactive Ingredients for Best and Worst Performing Eye Drops for Various Dry Eye Parameters

Top Comparative Performer (Outperforms This Number of Competitors)	Test Parameter	Active Ingredients	Inactive Ingredients
GenTeal Gel® (11)	TMH	Mineral Oil 3% White Petrolatum 94%	Lanolin
Systane Ultra® (12)	NIK BUT	Polyethylene glycol 400 0.4% Propylene glycol 0.3%	Hydroxypropyl guar Aminomethyl propanol Sorbitol Boric acid Polyquarternium-I 0.001% Potassium chloride Sodium chloride Hydrochloric acid / sodium hydroxide
Soothe XP® (12)	LLT	Light mineral oil 1.0% Mineral oil 4.5%	Octoxynol – 40 Polysorbate 80 Boric acid Disodium edetate Sodium borate Hydrochloric acid /sodium hydroxide
Notable Mention			
HyloTears®	Well in TMH (3)/ LLT (5)	Sodium hyaluronate 0.1%	Sorbitol Citric acid anhydrous Sodium citrate
Lowest Comparative Performers	Test Parameter	Active Ingredients	Inactive Ingredients
No clear underperformers	TMH		
Up&Up® (9)	NIK BUT	Polyethylene glycol 400 0.4% Propylene glycol 0.3%	Hypromellose Stabilized oxychloro complex Sorbitol Boric acid Calcium chloride Disodium edetate Magnesium chloride Potassium chloride Sodium chloride Zinc chloride Sodium borate Hydrochloric acid Sodium hydroxide

(Continued)

Table 7 (Continued).

Visine® (6)	NIK BUT	Polyethylene glycol 400 1% (10 mg in 1 mL)	Ascorbic acid Boric acid Dextrose Glycerin Glycine Hypromellose Magnesium chloride Polyquaternium-42 Potassium chloride Purified water Sodium borate Sodium chloride Sodium citrate Sodium lactate Sodium phosphate dibasic anhydrous
Up&Up® (5)	LLT	Polyethylene glycol 400 0.4% Propylene glycol 0.3%	Hypromellose Stabilized oxychloro complex Sorbitol Boric acid Calcium chloride Disodium edetate Magnesium chloride Potassium chloride Sodium chloride Zinc chloride Sodium borate Hydrochloric acid Sodium hydroxide

Notes: For Top Performers, the drops perform statistically better than 75% of other drops tested. For Lowest performers, at least 40% of other drops tested performed statistically better than given drop. (at least 6 negatives). Water was removed as Inactive ingredient when listed.

Abbreviations: TMH, tear meniscus height; NIK BUT, non-invasive keratographic break up time; LLT, lipid layer thickness.

composition, the drops behave differently in NIK BUT testing, suggesting that the *inactive* ingredient, hydroxypropyl guar in the case of Systane Ultra®, also has an important impact on drop performance. For this reason, it is probably preferable to refer to them by their brand names, rather than to define them by their generic components.

Comparisons of OTC AT to perfluorohexyloctane did not show any significant changes with regard to TMH, NIK BUT or as might be expected, to LLT. This may be due to the short duration of this study, as perfluorohexyloctane has been shown to improve DED upon prolonged use.^{30,31} It is also possible that the LV2 interferometry based method to measure LLT of natural tears cannot measure or detect the presence of perfluorohexyloctane.

Conclusion

The performance of various OTC AT can be determined with non-invasive imaging technologies. The study performed here measures how well these AT supplements can acutely mimic the characteristics of the natural tear film. Although no single drop outperforms all others, certain drops can outperform others with regard to individual test parameters suggesting that some personalization of therapy or optimization of therapy may be possible (Table 7). Given that drops with the same active ingredient composition can perform differently (presumably due to the inactive ingredients), further work needs to be done to examine more of the commercially available formulations. In addition, further work needs to be done to determine if the differences in eye drop performance measured here with imaging translate into meaningful clinical differences in DED

symptoms and physical findings such as corneal staining with more extended use of these drops. This report highlights the complexity of DED and the need for ongoing work to find optimal ways to treat the ocular surface.

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Disclosure

Dr Basil Rigas reports equity positions from Apis Therapeutics LLC, JCARE Pharmaceuticals, LLC and Medicon Pharmaceuticals, Inc., outside the submitted work. In addition, Dr Basil Rigas has a patent “Treatment of dry eye disease” issued to Apis Therapeutics LLC. The authors report no other conflicts of interest in this work.

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