Can the optimum artificial tear treatment for dry eye disease be predicted from presenting signs and symptoms?

Abstract

Purpose To assess dry eye treatment with four preservative-free dry eye artificial tear treatments to facilitate evidence-based prescribing.

Methods A randomised, single masked crossover trial of Clinitas Soothe, Hyabak, Tears Again and TheraTears artificial tears was conducted on 50 symptomatic dry eye patients, aged 60.8±14.2 years. At baseline and after trialling each treatment for 4 weeks, signs and symptoms were assessed using the Ocular Surface Disease Index (OSDI), non-invasive tear break-up time, fluorescein tear break-up time, tear meniscus height (TMH), Phenol Red test, lid-parallel conjunctival folds (LIPCOF), ocular surface staining, and lipid layer grading and osmolarity (baseline visit only).

Results The impact of each dry eye treatment on ocular signs and symptoms was similar, however OSDI (p=0.002), LIPCOF (p=0.014) and conjunctival staining (p<0.001) significantly improved from baseline. Clinitas Soothe and Hyabak were preferred by 34%/30% of participants, but only subjective comparison with the other drops influenced this choice. TheraTears was preferred (by 24%) by those with a lower baseline tear volume (p=0.01) and Tears Again (by 12%) by those with a thinner baseline lipid layer (p=0.04). The treatment that afforded the greatest improvement in clinical signs did not consistently match each individual's preferred treatment.

Conclusions If prescribed to a general dry eye population, the artificial tears performed similarly, improving symptoms and conjunctival signs. However, osmolarity balanced artificial tears were the preferred treatment in individuals with low baseline tear volume and lipisomal spray for individuals with a baseline lipid layer deficiency.

Key words

Dry eye; carboxymethylcellulose; liposomal spray; sodium hyaluronate; randomised control trial; artificial tears

Highlights

- In a general dry eye population, the artificial tears tested performed similarly
- Treatment effects still evident after 4 months of treatment
- Artificial tears provide more than transient relief to symptoms
- Artificial tears aid in breaking the vicious dry eye disease cycle
- Osmolarity balanced drops preferred by those with low baseline tear volume
- Lipisomal spray preferred treatment by those with baseline lipid layer deficiency

Introduction

Dry eye signs and symptoms are typically triggered by a dysfunction of the ocular tear film, which may arise due to deficiencies in the aqueous phase of the tear film (termed aqueous-deficient dry eye) and, more commonly, the lipid phase of the tear film (termed evaporative dry eye) [1]. The primary course of dry eye treatment is topical application of eye drops, gels and sprays to re-build and stabilise the tear film. Numerous compositions of dry eye treatments are commercially available, principally differing in which element of the tear film they primarily aim to replace. Sodium hyaluronate is a glycosaminoglycan with viscoelastic properties[2] that increases tear film stability [2-4] and increases epithelial cell migration [5-6]. Carboxymethylcellulose (CMC) is an anionic cellulose polymer with a carboxylic group, which exhibits a high affinity for bioadhesion [7], increases tear film stability[3] and increases epithelial cell migration [8]. Liposomal dry eye treatments consist of phospholipids, which enhance the lipid tear film layer [9] and also increase tear film stability [9-11]. Osmolarity is considered a key driver of ocular surface damage from dry eye [12] and an artificial tear has been formulated to overcome this but this has not been extensively tested clinically against other treatment options [13]. Approximately 78% of dry eye patients have been reported to have lipid layer deficiencies [1], therefore Lee and colleagues recommended liposomal sprays should be the first choice of treatment for all dry eye patients [14]. However previous studies tend to compare

the benefit of one 'class' of artificial tear, with perhaps saline as a control, some over short durations, rather than cross class to inform optimum prescribing decisions (Table 1).

Despite knowing that artificial treatment individually help to reduce symptoms compared to a saline placebo, evidence-based criteria indicating which composition of treatment is best suited to alleviate particular dry eye signs and symptoms are currently unavailable. The aim of the current study was to compare the performance of four commercially available preservative-free dry eye treatments compared to baseline dry eye assessment in a randomised controlled crossover trial, in order to facilitate evidence-based dry eye treatment prescribing.

Study	Drops Used	Tests compared	Design	Sample Size	Evaluation period	Conclusions
Brignole *et al. 2005 [15]*	• Sodium hyaluronate (0.18%) • CMC (1%)	• Flow cytometry • Subjective reports	Randomised, double-masked, non-crossover study	22 (100% documented history of moderate dry eye)	2 months (instilled 3 times daily)	• Sodium hyaluronate improvement of comfort & reduction in CD44 expression superior when compared with CMC • CMC caused blurred vision
Dausch *et al. 2006 [10]*	• Tears Again liposomal spray • Eye gel containing triglycerides	• LIPCOF • TBUT • Schirmer's • Eyelid health • Visual acuity • Subjective reports	Randomised controlled, multi-centre, crossover study	74 (100% lipid layer disturbances[14])	6 weeks (instilled 3 times daily)	• LIPCOF, TBUT, Schirmer's, eyelid health, visual acuity & comfort were superior after liposomal spray treatment
Johnson *et al. 2006 [2]*	• Sodium hyaluronate (0.1%) • Sodium hyaluronate (0.3%) • Saline (control)	• NITBUT • Subjective reports	Randomised controlled crossover study	13 (100% moderate dry eye)	6 hours	• NITBUT & comfort improvement was greater with sodium hyaluronate 0.3% than 0.1%
Craig *et al. 2010 [9]*	• Tears Again Liposomal spray • Saline (control)	• LLG • NITBUT • TMH • Subjective reports	Randomised, double-masked, contralateral eye study	22 (18% had borderline dry eye according to McMonnies Dry Eye Questionnaire[13])	135 minutes (single application)	• LLG, NITBUT & comfort improvement was superior after liposomal spray treatment • TMH did not change
Lee *et al. 2011 [3]*	• Sodium hyaluronate (0.1%) • CMC (0.5%)	• NaFl staining • TBUT • Subjective reports	Randomised, double-masked, non-crossover study	65 (100% mild to moderate dry eye according to unspecified criteria)	8 weeks (6 times daily)	• NaFl staining, TBUT & symptoms improvement was not significantly different between treatment types
Evangelista *et al. 2011 [17]*	• Carnidrop • Optive • Blu Sal	• TBUT • Ocular protection index	Randomised, double-masked, non-crossover study	27 (moderate – DEWS classification)	15 and 60 minutes	• Carnidrop outperformed comparators

Pult *et al. 2012 [11]*	• Optrex ActiMist • Dry Eyes Mist • Tear Mist	• OSDI • NITBUT	Randomised, multi-centred, double-masked, contralateral eye study	80 (26.9% had dry eye according to OSDI)	10 minutes (single application)	• Optrex ActiMist significantly improved OSDI & NITBUT • Tear Mist & Dry Eyes Mist reduced OSDI & NITBUT
Baeyens *et al. 2012 [18]*	• Hyaluronate sodium (0.18%) • Carbomer (0.3%) • Saline	• Symptoms • Fluorescein staining	Randomised, double-masked, non-crossover study	304	84 days (instilled 2-4 times daily)	• Sodium hyluronate outperformed other treatments
Barabino *et al. 2014 [19]*	• Hyaluronic acid and tamarind seed polysaccharide • Carmellose sodium	• OSDI • TBUT • Schirmer • Corneal & conjunctival staining	Randomised, double-masked, non-crossover study	49 (moderate dry eye)	3 months (instilled 4 times daily)	• Formulations equally effective in reducing symptoms and staining. No effect on tear volume.
Simmons *et al. 2015 [20]*	• Lipid-based tear formulations containing carboxymethylcellulose, glycerin, polysorbate 80, and emulsified lipid	• Subjective Evaluation of Symptom of Dryness • OSDI	Randomised, double-masked, non-crossover study	256 (reduced TBUT and staining)	3 months (instilled 1-2 times daily)	• Formulations non-inferior to existing lipid based product
Simmons *et al. 2015 [21]*	• Carmellose sodium • Hyaluronic acid at different concentrations and osmoprotectants • Standard carmellose sodium-containing formulation (Refresh Tears)	• OSDI	Randomised, double-masked, non-crossover study	305 (mild-to-moderate signs of dry eye, an OSDI score of 18–65, TBUT <10s & currently using artificial tears	3 months (instilled ≥2 times daily)	• Reduction in symptoms with all formulations, but differences between them in patients with pre-existing staining.
Perez-Balbuena *et al. 2016 [22]*	• Xanthan gum • Chondroitin sulfate preservative free	• Schirmer • TBUT • OSDI	Randomised, double-masked, non-crossover study	148	2, 7, 15, 30 and 60 days	• Xanthan gum/chondroitin sulfate preservative free showed similar clinical efficacy

Table 1: Summary of dry eye studies comparing artificial tears dry eye treatments on patients without Sjögren's syndrome. OSDI= Ocular Surface Disease Index; NITBUT= Non-Invasive Tear Break-Up Time; TBUT=fluorescein Tear Break-Up Time; LLG= Lipid Layer Grade; TMH= Tear Meniscus Height; LIPCOF= Lid Parallel Conjunctival Folds; CD44= hyaluronate receptor

Method

The study was approved by the Aston University Ethics Committee and was conducted in accordance with the tenets of the Declaration of Helsinki. It was registered as a clinical trial with www.clinicaltrials.gov (Identifier: NCT02420834). Symptomatic dry eye patients (Ocular Surface Disease Index (OSDI) questionnaire score ≥13) [23], were recruited from a community optometric practice in North West England and were screened to exclude those with history of previous ocular or intraocular surgery, evidence of acute or chronic infections or an inflammatory condition of the cornea and conjunctiva, a positive history of systemic disease, hay fever, contact lens wear, punctal plug occlusion, use of topical ocular medications, pregnancy or a history of intolerance or hypersensitivity to any component of the study medications. No other tear film stability, volume or ocular surface damage requirements were applied to avoid selection bias in the general prescribing guidance objective of the study [12]. Informed written consent was obtained from all the participants after an explanation of the nature and possible consequences of the study.

The study design was a single-masked randomised crossover trial, involving four commercially available dry eye treatments selected to represent viscosity increasing, lipid replacement and osmolarity balancing approach 'classes'. Fifty symptomatic dry eye patients (70% female) with a mean age of 60.8 ± 14.2 years (range 26 to 82 years) participated in the study. Prior to the initiation of treatment, baseline dry eye symptoms were quantified using the OSDI questionnaire [23], generating a severity score between 0 and 100. Dry eye diagnosis for inclusion was defined as an OSDI ≥50. Baseline anterior eye examination included non-invasive break-up time (NITBUT) using a Tearscope Plus (Keeler Ltd, Windsor, UK) averaging 3 readings, lipid layer thickness analysis using a Tearscope Plus, osmolarity (highest value from the two eyes) using a TearLab (TearLab Ltd, California, USA), tear meniscus height (TMH) measurement (25x magnification from a slit-lamp biomicroscope with graticule), lid parallel conjunctival folds (LIPCOF) counted and graded under 25x magnification [24], the Phenol Red Test (PRT), fluorescein tear break-up time (NaFl TBUT), corneal

fluorescein staining assessment (graded against an Efron grading scale) and conjunctival staining assessment using Lissamine green (graded against an Oxford grading scale).

Participants were prescribed preservative-free Clinitas Soothe (Farmigea SpA., Pisa Italy), Hyabak (Laboratories Théa, Clermont-Ferrand, France), Tears Again (Optima Pharmazeutische GmbH., Freising, Germany) and TheraTears (Advanced Vision Research Inc., Massachusetts, USA) in a randomised order each treatment to be used for four weeks as this is typical of artificial tear studies (Table 2) [25]. Each participant was also asked to keep a diary to document how many times a day the treatment was applied as often as required. The baseline tests described previously were repeated at the end of each treatment phase (except for osmolarity and lipid grade) and overall comfort, ease of insertion and visual clarity were graded on a visual analogue scale (out of 10), prior to a 4 day 'wash-out' period between treatments (no use of artificial tears or other dry eye management therapy). An appropriate wash-out period with artificial tears has not been established, but the randomised repeated measures design overcomes any bias of any improvements in the ocular surface beyond the wash-out period. A forced choice preference for one of the 4 artificial treatments was elicited at the end of the study.

Brand name	Ingredients	Form
Clinitas Soothe	**Sodium hyaluronate** (0.4%), monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride, water	20 re-sealable droppers, of 8-10 drops each
Hyabak	**Sodium hyaluronate** (0.15%), sodium chloride, trometamol, hydrochloric acid, water	10 ml bottle
TheraTears	**Sodium carboxymethylcellulose** (0.25%), borate buffers, calcium chloride, Dequest®, magnesium chloride, potassium chloride, purified water, sodium bicarbonate, sodium chloride, sodium perborate, sodium phosphate	32 single use containers
Tears Again	**Phospholipid liposomes**, soy lecithin, sodium chloride, ethanol, phenoxyethanol, vitamin A, vitamin E, aqua purificata	10ml bottle

Table 2: The ingredients of Clinitas Soothe, Hyabak, TheraTears and Tears Again and the form supplied to each participant. The bold ingredient depicts the key lubricant.

Statistical analysis

Assessment of normal distribution using one-Sample Kolmogorov-Smirnov Tests showed that only NITBUT of the metrics used in this study was normally distributed. Where data was normally distributed, repeated measure analysis of variance was conducted whereas all other measurements were assessed with related-samples Friedman's two-way analysis of variance by ranks. The data were analysed using SPSS 20 software (IBM Corporation, New York, USA). Due to the repeated measures design of the study (four artificial tears each tested on 50 subjects) more than the 15 degrees of freedom were achieved in the replicates to allow sufficient statistical power to detect differences in all the metric assessed [26].

Results

Usage

The artificial tears were used on average similarly across all the types (Clinitas Soothe 2.1 ± 1.2times/day; Hyabak 2.6 ± 1.8 times/day; Tears Again 2.3 ± 1.2 times/day; Theratears 2.5 ± 1.6 times/day; p = 0.121) according to the diaries of daily use.

Effectiveness of Treatments

Signs, symptoms and patient satisfaction were similar after treatment with each of the four artificial tear supplements (Table 3), but were significantly better than pre-treatment for OSDI symptoms (Figure 1) and signs of LiPCOF (Figure 2) and conjunctival staining (Figure 3).

	Artificial Tears (after 4 weeks)					Baseline	
	Clinitas Soothe	**Hyabak**	**Tears Again**	**Theratears**	**Significance between treatments**	**Value**	**Significance vs treatments**
OSDI	28.8 ± 21.2	23.6 ± 18.8	27.7 ± 20.9	28.9 ± 18.4	*p*=0.521	33.9 ± 20.0	***p*=0.002**
NITBUT (s)	13.3 ± 2.6	13.6 ± 2.4	13.2 ± 2.2	13.3 ± 2.4	F=1.315, *p*=0.272	13.2 ± 1.9	F=0.959, *p*=0.431
NaFl TBUT (s)	13.5 ± 2.7	13.7 ± 2.7	13.7 ± 2.4	13.8 ± 2.4	*p*=0.225	13.2 ± 2.4	*p*=0.588
TMH (mm)	0.11 ± 0.01	0.11 ± 0.02	0.11 ± 0.01	0.11 ± 0.01	*p*=0.443	0.11 ± 0.02	*p*=0.184
Phenol Red Test (mm)	14.1 ± 4.6	14.0 ± 4.4	14.0 ± 4.2	14.0 ± 4.5	*p*=0.724	14.1 ± 5.1	*p*=0.797
LIPCOF	1.4 ± 0.8	1.2 ± 0.9	1.3 ± 0.7	1.4 ± 0.7	*p*=0.688	1.6 ± 0.8	***p*=0.014**
Corneal staining	0.04 ± 0.30	0.08 ± 0.40	0.00 ± 0.00	0.12 ± 0.44	*p*=0.137	0.08 ± 0.27	*p*=0.218
Conjunctival staining	0.88 ± 1.00	0.92 ± 0.99	0.88 ± 0.98	1.02 ± 1.00	*p*=0.752	1.64 ± 0.75	***p*<0.001**
Overall comfort	5.6 ± 2.6	6.2 ± 2.6	5.9 ± 2.7	5.9 ± 2.8	*P=0.658*		
Ease of insertion	6.0 ± 2.5	6.9 ± 2.0	7.1 ± 2.1	6.5 ± 2.4	*P=0.081*		
Visual clarity	6.2 ± 2.5	6.9 ± 2.0	7.1 ± 1.8	6.5 ± 2.5	*P=0.534*		

Table 3: Average ± SD of dry eye signs, symptoms and patient ratings at baseline and after 4 weeks treatment with each of Clinitas Soothe, Hyabak, TheraTears and Tears Again. N=50. OSDI= Ocular Surface Disease Index; NITBUT= Non-Invasive Tear Break-Up Time; NaFl TBUT = fluorescein Tear Break-Up Time, TMH= Tear Meniscus Height; LIPCOF= Lid Parallel Conjunctival Folds. Bold *p* values denote statistical significance. N=50.

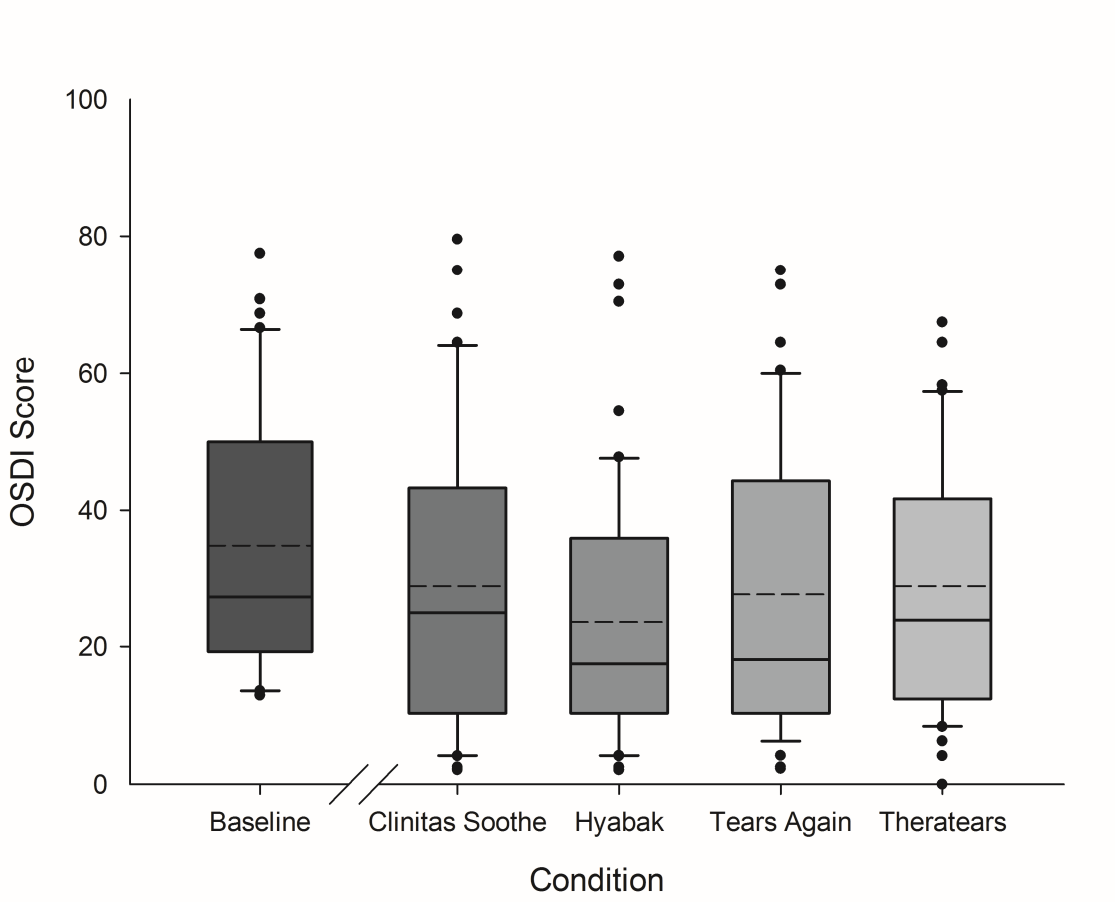

Figure 1: Ocular comfort as measured by the OSDI questionnaire box plot (the boundaries of the box indicates the 25th and 75th percentile, the solid line within the box marks the median and the dashed line the mean, the error bars indicate the 90th and 10th percentiles and the dots the outliers) with the four different artificial tears used. n=50.

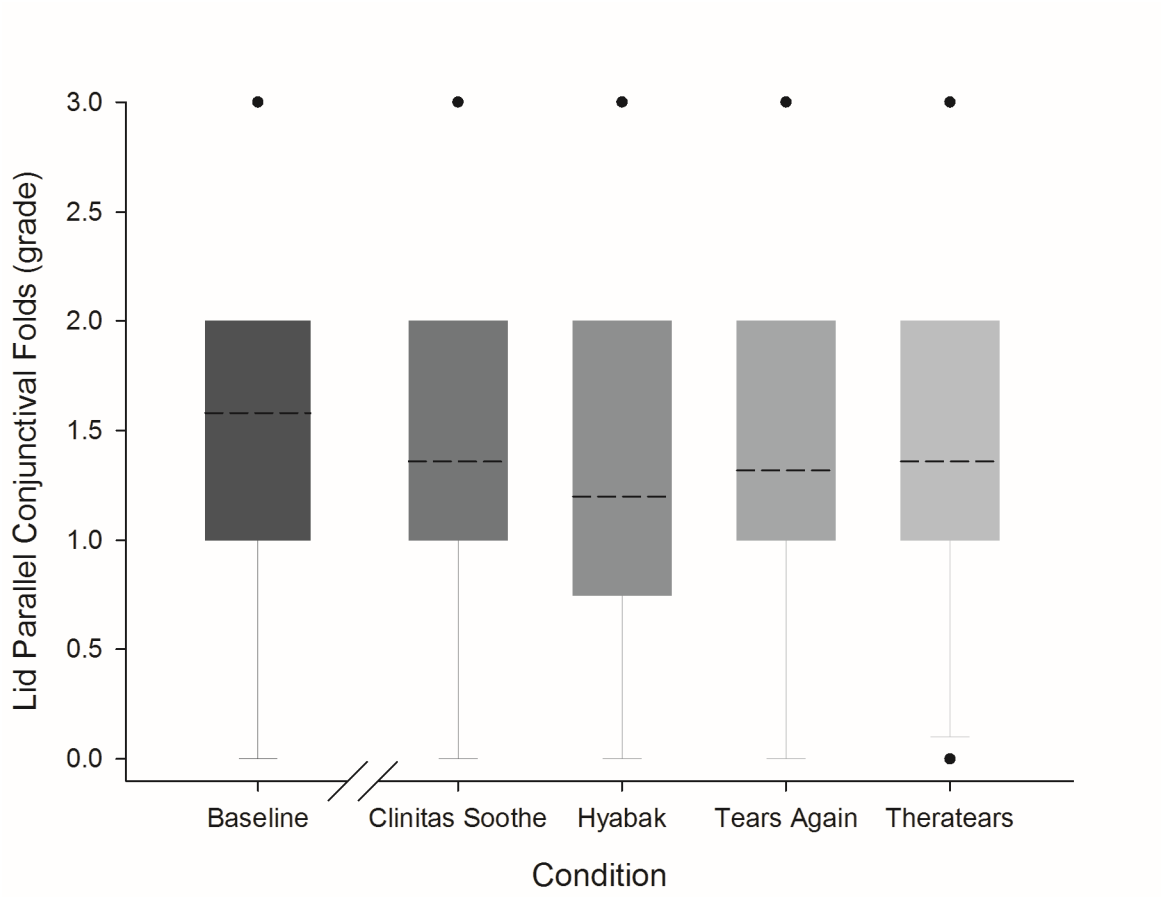

Figure 2: LIPCOF box plot (the boundaries of the box indicates the 25th and 75th percentile, the dashed line the mean, the error bars indicate the 90th and 10th percentiles and the dots the outliers) with the four different artificial tears used. Medians were all 2 except for 1 for Hyabak. n=50.

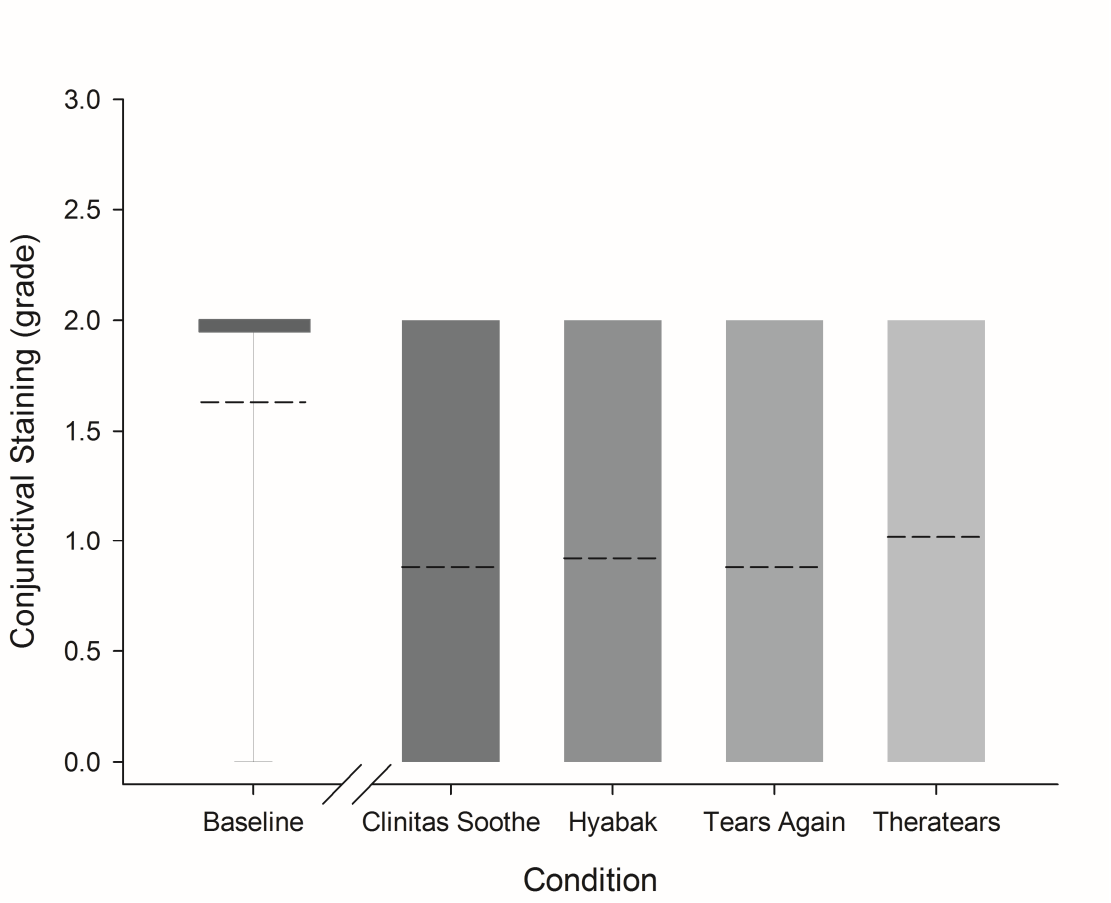

Figure 3: Conjunctival Staining (the boundaries of the box indicates the 25th and 75th percentile which coincide with the 90th and 10th percentiles and there were no outliers; the dashed line indicates the mean) with the four different artificial tears used. Medians were all 2 as were the baseline 25th and 75th percentiles. n=50.

Treatment effect with time

NITBUT, Nafl TBUT, Phenol Red test, TMH and corneal staining showed no treatment effect with time ($p>0.05$; Table 4). OSDI results showed a significant treatment effect with time between the first and last 2 months ($p>0.05$), whereas lid parallel conjunctival folds ($p=0.014$) and conjunctival staining ($p=0.002$) showed a significant treatment effect from the first to the fourth month of treatment only. Patient ratings of overall comfort (between first and last 2 months; $p<0.05$), and clarity of vision (between second and fourth month; $p=0.036$) after instilling the drops significantly

improved with time, whereas ease of insertion was similar over the 4 month treatment period (Table 4).

	Visit Month				
	1	**2**	**3**	**4**	**Significance**
OSDI	29.1 ± 20.1	30.4 ± 19.1	24.9 ± 19.4	24.8 ± 20.3	***p*=0.041**
NITBUT (s)	13.2 ± 2.4	13.3 ± 2.3	13.4 ± 2.5	13.6 ± 2.4	F=1.584, *p*=0.196
NaFl TBUT (s)	13.3 ± 2.7	13.6 ± 2.4	13.9 ± 2.5	13.9 ± 2.5	*p*=0.259
TMH (mm)	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	*p*=0.289
Phenol Red Test (mm)	14.3 ± 4.7	14.2 ± 4.2	14.2 ± 4.3	13.4 ± 4.2	*p*=0.221
LIPCOF	1.5 ± 0.8	1.3 ± 0.8	1.3 ± 0.7	1.1 ± 0.8	*p*=0.038
Corneal staining	0.06 ± 0.24	0.02 ± 0.14	0.04 ± 0.20	0.02 ± 0.14	*p*=0.629
Conjunctival staining	0.98 ± 0.94	0.80 ± 0.90	0.66 ± 0.80	0.52 ± 0.76	*p*=0.012
Overall comfort	5.2 ± 2.9	5.5 ± 2.8	6.3 ± 2.6	6.5 ± 2.2	***p*=0.003**
Ease of insertion	6.8 ± 2.4	6.4 ± 2.4	6.6 ± 2.2	6.8 ± 2.1	*p*=0.339
Visual clarity	6.3 ± 2.6	6.5 ± 2.3	6.9 ± 2.2	6.9 ± 1.9	***p*=0.036**

Table 4: Average ± SD of dry eye signs, symptoms and patient ratings after each 4 weeks of treatment with artificial tears. OSDI= Ocular Surface Disease Index; NITBUT= Non-Invasive Tear Break-Up Time; NaFl TBUT = fluorescein Tear Break-Up Time, TMH= Tear Meniscus Height; LIPCOF= Lid Parallel Conjunctival Folds. Bold *p* values denote statistical significance. N=50.

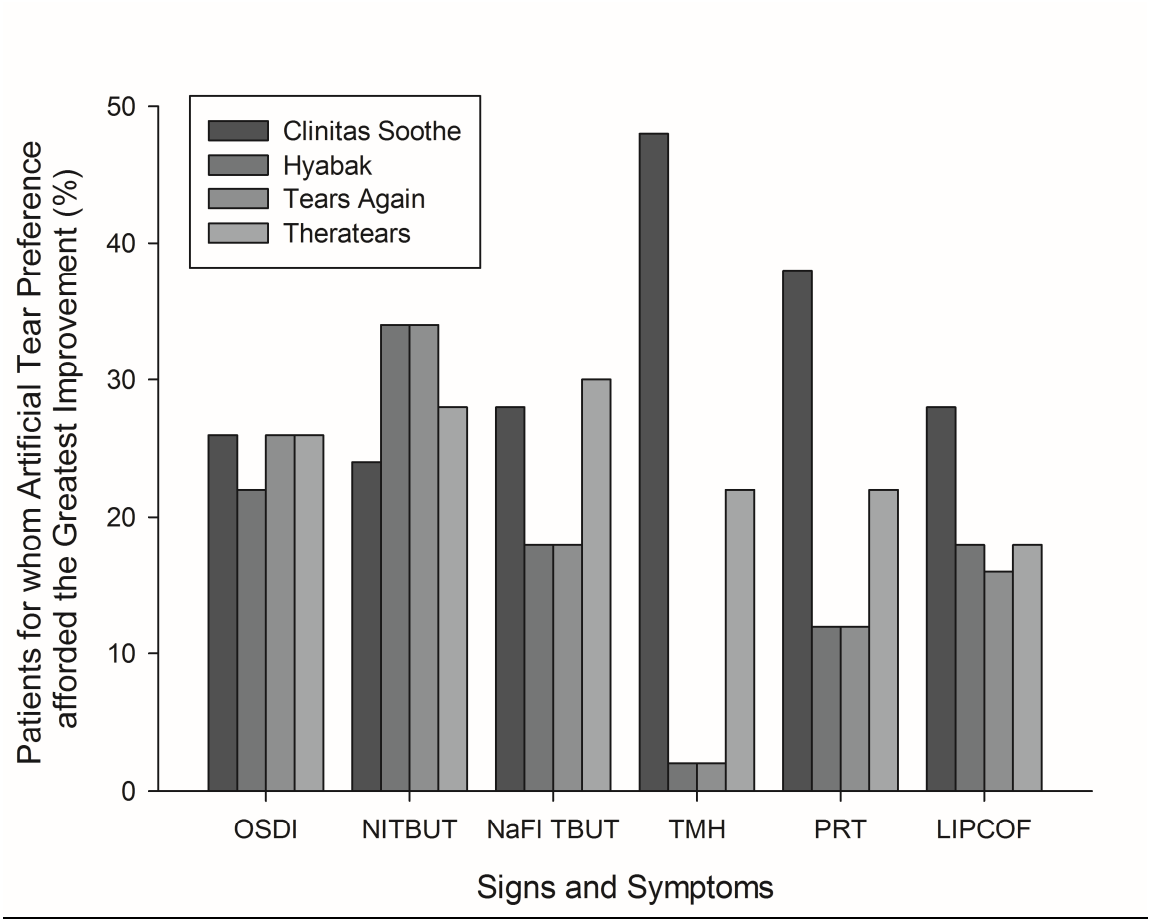

Figure 4: Percentage of participants whose treatment preference matched the treatment that gave the largest improvement in signs and symptoms. OSDI= Ocular Surface Disease Index; NITBUT= Non-Invasive Tear Break-Up Time; NaFl TBUT = fluorescein Tear Break-Up Time, TMH= Tear Meniscus Height; LIPCOF= Lid Parallel Conjunctival Folds. n=50.

Treatment preference

After trialling all four treatments, 17 (34%) participants preferred Clinitas Soothe, 15 (30%) preferred TheraTears, 12 (24%) preferred Tears Again and 6 (12%) preferred Hyabak. Grouping the participants according to their treatment preference, the rating of overall comfort (Hyabak: 8.6 ± 1.0; Tears Again: 8.3 ± 1.0; TheraTears: 8.2 ± 1.5; Clinitas Soothe: 8.3 ± 1.2; p=0.117), ease of insertion (Hyabak: 9.0 ± 1.3; Tears Again: 8.5 ± 1.1; TheraTears: 8.1 ± 1.7; Clinitas Soothe: 8.6 ± 1.1; p=0.233) and clarity of vision (Hyabak: 9.2 ± 1.2; Tears Again: 8.4 ± 1.1; TheraTears: 8.1 ± 1.7; Clinitas Soothe: 8.4 ± 1.5; p=0.091) by those that preferred each treatment after 4 weeks was not significantly different.

Can the drop preferred be predicted from baseline measures?

Considering the baseline parameters, TheraTears was preferred by those with a lower tear volume and Tears Again was preferred by those with a thinner (lower grade) lipid film layer (Table 5). Clinitas Soothe and Hyabak preference could not be predicted from baseline measures (Table 5).

	Age (yrs)	OSDI (%)	NITBUT (s)	NaFL TBUT (s)	TMH (mm)	PRT (mm)	LIPCOF (grade)	Osmolarity (mOsms/L)	Lipid Pattern (grade)
Clinitas Soothe									
Preferred Drop (n=17)	58.4 ± 17.1	31.1 ± 19.8	13.5 ± 2.0	13.3 ± 2.7	0.11 ± 0.02	16.4 ± 5.1	1.8 ± 0.6	307.5 ± 10.6	2.7 ± 0.8
Remaining Subjects (n=33)	62.0 ± 12.5	35.3 ± 20.3	13.1 ± 1.9	13.1 ± 2.3	0.11 ± 0.02	13.0 ± 4.7	1.5 ± 0.8	312.5 ± 20.2	2.5 ± 1.2
***p* value**	0.28	0.12	0.54	0.55	0.95	0.09	0.06	0.34	0.86
Hyabak									
Preferred Drop (n=6)	64.8 ± 11.0	38.8 ± 22.8	14.2 ± 1.8	14.1 ± 2.2	0.12 ± 0.02	14.8 ± 6.1	1.8 ± 0.8	315.5 ± 23.1	2.8 ± 0.8
Remaining Subjects (n=44)	60.2 ± 14.6	33.2 ± 19.8	13.1 ± 1.9	13.0 ± 2.4	0.11 ± 0.02	14.0 ± 5.0	1.5 ± 0.8	310.1 ± 16.9	2.5 ± 1.1
***p* value**	0.18	0.59	0.19	0.39	0.65	0.90	0.57	0.87	0.46
Tears Again									
Preferred Drop (n=12)	60.6 ± 14.0	33.6 ± 24.5	13.4 ± 1.5	12.9 ± 2.0	0.11 ± 0.02	14.1 ± 3.6	1.0 ± 0.9	318.1 ± 25.8	2.4 ± 0.8
Remaining Subjects (n=38)	60.8 ± 14.4	33.9 ± 18.8	13.1 ± 2.1	13.3 ± 2.5	0.11 ± 0.02	14.2 ± 5.5	1.8 ± 0.7	308.5 ± 13.7	2.7 ± 1.1
***p* value**	0.94	0.46	0.62	0.65	0.57	0.77	0.05	0.51	**0.04**
TheraTears									
Preferred Drop (n=15)	64.1 ± 9.5	35.2 ± 16.7	12.3 ± 2.0	12.8 ± 2.5	0.11 ± 0.03	11.3 ± 4.8	1.7 ± 0.7	306.8 ± 12.5	2.6 ± 1.4
Remaining Subjects (n=35)	59.4 ± 15.7	33.3 ± 21.5	13.6 ± 1.8	13.3 ± 2.4	0.11 ± 0.02	15.3 ± 4.8	1.5 ± 0.8	312.5 ± 19.3	2.5 ± 0.9
***p* value**	0.62	0.85	0.31	0.85	0.39	**0.01**	0.27	0.30	0.99

Table 5: Comparison of age and baseline signs and symptoms of the participants who preferred each treatment type, compared to the remaining cohort (average ± standard deviation). OSDI= Ocular Surface Disease Index; NITBUT= Non-Invasive Tear Break-Up Time; NaFl TBUT = fluorescein Tear Break-Up Time, TMH= Tear Meniscus Height; LIPCOF= Lid Parallel Conjunctival Folds. Bold *p* values denote statistical significance.

Did the preferred artificial tear give patients better signs or symptoms compared to the other drops trialled?

Intrasubject differences in OSDI, NITBUT, TMH, LIPCOF and NaFl TBUT results were not dependent on treatment type amongst the participants who preferred Clinitas Soothe, TheraTears, Tears Again or Hyabak (Table 6). However, participants who preferred Clinitas Soothe or TheraTears reported subjective overall comfort, ease of insertion and clarity of vision was superior after treatment with their preferred treatment when compared to the other treatment options (Table 6). Despite no differences in reported overall comfort, participants who preferred Tears Again found this treatment provided better clarity of vision and was easier to insert than the other treatment options. Whereas, participants who preferred Hyabak reported significantly better overall comfort with no significant difference in ease of insertion or clarity of vision after using Hyabak drops when compared to the other treatment options.

	OSDI (%)	NITBUT (s)	NaFL TBUT (s)	TMH (mm)	PRT (mm)	LIPCOF (grade)	Overall comfort	Ease of instillation	Clarity of vision
Clinitas Soothe (n=17)									
Preferred Drop	25.1 ± 18.4	13.7 +2.1	13.8 ± 2.4	0.11 ± 0.01	15.5 ± 4.6	1.4 ± 0.9	8.3 ± 1.2	8.6 ± 1.0	8.4 ± 1.5
Non-Preferred drops	25.2 ± 18.5	14.1 ± 2.1	14.2 ± 2.3	0.11 ± 0.01	15.6 ± 4.4	1.2 ± 0.8	6.1 ± 2.8	7.1 ± 2.4	7.2 ± 2.0
***p* value**	0.756	0.408	0.932	0.053	0.924	0.689	**0.048**	**0.014**	**0.041**
Hyabak (n=6)									
Preferred Drop	24.8 +26.8	15.1 +2.0	14.9 +1.5	0.11 +0.01	14.8 +3.5	1.0 +0.9	8.6 +1.0	9.0 +1.3	9.2 +1.2
Non-Preferred drops	30.7 +24.2	13.9 +1.7	14.5 +1.6	0.11 +0.01	14.7 +4.2	1.3 +0.6	6.2 +3.0	7.5 +2.1	7.6 +2.1
***p* value**	0.042	0.278	0.674	0.102	0.785	0.234	**0.042**	0.066	0.068
Tears Again (n=12)									
Preferred Drop	22.3 ± 18.2	13.3 +2.3	13.7 +2.3	0.11 +0.01	13.6 +4.1	1.3 +0.6	8.3 +1.0	8.5 +1.1	8.4 +1.1
Non-Preferred drops	27.7 ± 21.0	13.3 +2.4	13.8 +2.8	0.11 +0.01	13.3 +4.3	1.1 +0.7	5.8 +2.7	6.2 +2.2	5.9 +2.6
***p* value**	0.937	0.788	0.969	0.516	0.637	0.271	0.081	**0.036**	**0.036**
TheraTears (n=15)									
Preferred Drop	35.6 ± 19.1	12.4 ± 2.5	12.7 ± 2.6	0.11 ± 0.02	12.8 ± 4.5	1.7 ± 0.7	8.2 ± 1.5	8.1 ± 1.7	8.1 ± 1.7
Non-Preferred drops	28.1 ± 19.2	12.5 ± 2.7	12.8 ± 2.9	0.11 ± 0.02	12.4 ± 3.8	1.5 ± 0.8	5.5 ± 2.5	6.4 ± 2.1	6.4 ± 2.0
***p* value**	0.256	0.703	0.589	0.749	0.932	0.887	**0.002**	**0.022**	**0.013**

Table 6: Comparison of signs, symptoms and subjective ratings after treatment with each individual's preferred treatment and the results attained after the same participants used the other treatments available (average ± standard deviation). OSDI= Ocular Surface Disease Index; NITBUT= Non-Invasive Tear Break-Up Time; NaFl TBUT = fluorescein Tear Break-Up Time, TMH= Tear Meniscus Height; LIPCOF= Lid Parallel Conjunctival Folds. Bold p values denote statistical significance.

The preferred treatment preference afforded the greatest improvement in OSDI, NITBUT, NaFl TBUT, TMH, PRT and LIPCOF in less than 50% of participants (Figure 4).

Discussion

The current investigation is one of few randomised controlled crossover trial to examine the subjective and objective ocular surface impact of a range of commercially available dry eye treatments and the first to provide evidence-based criteria indicating which composition of treatment is best suited to alleviate particular dry eye signs and symptoms. Baseline measures confirm all the patients would be diagnosed with dry eye disease according to the new TFOS DEWS II criteria (symptoms and tear film instability, hyperosmolarity or ocular surface staining) [27]. Tear film stability was generally above the cut off required for diagnosis, whereas tear volume as indicated by the TMH was low, suggesting the general cohort of patients' dry eye was more aqueous deficient than evaporative in nature.

Whilst the impact of each dry eye treatment on OSDI, NITBUT, NaFl TBUT, TMH, PRT, LIPCOF, NaFl corneal staining and conjunctival staining results was similar, OSDI, LIPCOF and conjunctival staining measurements significantly improved from baseline following the completion of the study. The observed improvement in conjunctival tissue could feasibly be associated with an improvement in the mucus layer of the tear film, which would ameliorate the entire tear film; however a significant improvement in the quality and volume of the tear film was not observed during the course of the study. Nevertheless, it is possible a commensurate improvement in tear quality and volume may be observed after a longer duration of treatment or more sensitive tests such as Optical Coherence Tomography analysis of tear meniscus area. The improvement in the conjunctival tissue, but not corneal signs, in the duration of the study also suggests this could be a more sensitive tissue for assessing the efficacy of dry eye treatments.

Considering the treatment preference of each participant, Clinitas Soothe and Theratears were the most popular treatment options, followed by Tears Again and Hyabak. It is likely Clinitas Soothe was preferred by more participants than Hyabak due to the higher concentration of sodium hyaluronate contained in Clinitas Soothe (0.4%) when compared to Hyabak (0.15%), as found previously [2].

Beside the concentration of sodium hyaluronate the molecular weight forms of hyaluronan have distinct effects on CD44 clustering [28]. Sodium hyaluronate increases tear film stability by increasing tear film viscosity between blinks [2]. Clinical trials of sodium hyaluronate dry eye treatment have reported an increase in ocular comfort [1-4,15], a reduction in NaFl corneal staining [3], a reduction in Rose Bengal staining [28], an increase in NITBUT [2,4], an increase in Schirmer's score [29] and an improvement in impression cytology grading [16]. Sodium hyaluronate is a naturally occurring glycosaminoglycan of the extracellular matrix and a ligand for the hyaluronate receptor CD44 [30]. Activation of CD44 promotes the interaction with cytoskeletal proteins, facilitating cellular migration [5,6,31,32]. CD44 is over-expressed within conjunctival and corneal cells of patients with dry eye [13] and corneal inflammation [29]. Sodium hyaluronate has a high affinity for CD44 receptors and tri-daily application of sodium hyaluronate for 2 months has been shown to significantly reduce the expression of CD44 [15]. Therefore, it is likely sodium hyaluronate dry eye drops help to protect the ocular surface [33], promote faster wound healing [5,6] and reduce ocular surface inflammation [34], thus relying on measurements of tear stability at baseline may not indicate which patients may benefit from sodium hyaluronate dry eye treatment as found in this study.

Hyabak provided superior overall comfort when compared to the other treatments trialled by participants who preferred Hyabak. However, Hyabak gave the largest improvement in OSDI, NITBUT, TMH, PRT, LIPCOF and NaFl TBUT of all the treatments trialled in less than 35% of participants who preferred Hyabak, indicating a weak correlation between subjective dry eye symptoms and objective measurements, as reported previously [35]. Similar results were observed for participants who preferred Clinitas Soothe, however the proportion of participants attaining the largest improvement in TMH and PRT with Clinitas Soothe approached 50%. Future dry eye studies should consider measuring expression of CD44 to determine the utility of CD44 expression to select patients (when clinical tests become available) who are likely to respond positively to sodium hyaluronate treatment.

TheraTears was preferred by participants with a lower tear volume at baseline, as quantified by the Phenol Red Test, but this was not supported by TMH data, perhaps due to a lack of sensitivity in the latter test when assessed subjectively. The key lubricating ingredient in TheraTears is carboxymethylcellulose (CMC), which is a mucomimetic [36] that exhibits a high affinity for bioadhesion [7]. The mucus layer is essential for corneal wettability and adherence of the tear film [37]. In addition, CMC has been shown to stimulate corneal epithelial cell migration [8] and a significant improvement in goblet cell density has been observed after one month of CMC treatment [38], further enhancing the mucus layer of the tear film. A reduction in goblet cell density is likely to be associated with ocular surface inflammation and loss of vascularisation [39] and appears to be an early sign of an abnormality of epithelial differentiation (also examined using impression cytology) [40,41].

Brignole *et al.* [15] utilised flow cytology in impression cytology specimens to show the reduction in expression of CD44 was superior following treatment with sodium hyaluronate when compared to CMC eye drops, however CMC does not bind to CD44, and instead, is thought to bind to glucose receptor GluT-1 to stimulate cellular migration [8]. A significant improvement in comfort [3,41], TBUT [3], NaFl corneal staining [3] and Schirmer's test [40] has been reported following CMC dry eye treatment, which was similar to the improvement attained following sodium hyaluronate treatment, as found by the current study. Additionally, TheraTears also has a patented hypotonic electrolyte balance that reduces elevated tear osmolarity,[42] reversing the osmotic gradient and ensuring the tear film hydrates the ocular surface and prevents ocular tissue dessication. Hypotonic 0.4% sodium hyaluronate eye drops produced a greater improvement in Rose Bengal staining, fluorescein staining, TBUT and impression cytology grade than isotonic 0.4% sodium hyaluronate eye drops amongst individuals with Sjögren's syndomen [34]. However, participants who preferred TheraTears did not have significantly different tear osmolarity at baseline than the remaining cohort, therefore

it is likely the aforementioned benefits of CMC may have been primarily responsible for the subjective improvement in dry eye symptoms.

Similarly to Clinitas Soothe, TheraTears provided superior overall comfort, ease of instillation and clarity of vision to those patients that preferred it when compared to the other treatments trialled by those participants; however TheraTears gave the largest improvement in OSDI, NITBUT, TMH, PRT, LIPCOF and NaFl TBUT of all the treatments trialled in less than 30% of participants who preferred TheraTears. Perhaps futures dry eye studies should consider assessing the mucus phase of the tear film and the expression of CMC receptors in order to aid identification (when clinical tests become available) of patients who are likely to respond positively to treatment containing CMC.

As expected, Tears Again was preferred by participants with a thinner lipid tear film layer at baseline. Tears Again is a phospholipid (phosphatidylcholine) liposomal spray, which is applied to closed eyelids, allowing liposomes to leach into the tear film via the lid margins, integrating with the habitual lipid reservoir and spreading across the tear film during each blink [9-11]. The stability and evaporation rate of the tear film depends on the lipid layer [43,44]. The lipid layer of the tear film reduces aqueous evaporation by 90 to 95% and reduces the surface-tension of the tear film phase by approximately 25% [43]. Therefore, rebuilding and enhancing the lipid tear film layer aims to reduce aqueous evaporation [12] and increase tear film stability [9], although this was not evident in the timescale of this study. A significant improvement in comfort [9-11], lipid layer thickness [9], NITBUT [9-11], LIPCOF [10,12] and Schirmer's results [12] have been reported following treatment with liposomal sprays. However, Tears Again gave the largest improvement in OSDI, NITBUT, TMH, PRT, LIPCOF and NaFl TBUT of all the treatments trialled in less than 35% of participants who preferred Tears Again in the current study, indicating a weak correlation between subjective and objective measurements. It is feasible the relative ease of instillation of the spray compared to traditional eye droppers may have factored highly in a participant's judgement of overall treatment preference. Indeed, Lee *et al.* [12] stated 100% of 382 patients found application with a spray was favourable to

eye droppers. Participants from the current study who preferred Tears Again reported the ease of instillation and clarity of vision was significantly superior compared to the other treatment options, whereas the overall comfort of Tears Again was not statistically significantly better than the other treatments trialled by the participants preferring Tears Again.

In conclusion, one type of dry eye treatment was not capable of adequately treating the dry eye symptoms of all participants. Assessment of the tear film using a battery of tests is required in order to determine the type of dry eye and to aid selection of the optimum dry eye treatment. Initial treatment effects were first seen in conjunctival tests so these may be a more sensitive tissue to assess dry eye treatment efficacy. Treatment effects were evident still after 4 months following initial treatment and this should be communicated to patients so they don't reject prescribed treatments after short trials. It also suggests that artificial tears do provide more than transient relief to symptoms and aid in breaking the vicious dry eye disease cycle. The treatment that afforded the greatest improvement in clinical signs did not consistently match each individual's preferred treatment. However, in terms of subjective preference, an artificial tear focused on balancing ocular surface osmolarity (TheraTears) was the most appropriate treatment for individuals with a low tear volume at baseline and a liposomal spray (Tears Again) was the most appropriate treatment for individuals with a lipid layer deficiency at baseline. Owing to the promotion of epithelial cell migration, eye drops containing sodium hyaluronate and CMC are also suitable for the treatment of ocular surface disorders and post-operative healing following corneal surgery, but newer clinical tests such as meibography and inflammatory marker indicators are required to determine patients for whom this should be the first choice treatment [37].

Conflicts of Interest

None

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