Management of Dry Eye Disease: Expanding the Evidence-Base

David Adam Semp

Doctor of Philosophy

September 2024

Abstract

Aston University

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Dry eye disease (DED) is a common and highly symptomatic condition, affecting many millions of individuals around the world, therefore appropriate diagnosis and management is of high importance. Effective long-term management remains challenging, and frustrates clinicians and patients alike. A thorough review of the literature identified several research evidence gaps.

To identify the most suitable tests and equipment, a randomised trial was conducted, comparing a novel multi-functional device to established methods. The Oculus Keratograph 5M was shown to be more reliable for key DED metrics, especially non-invasive breakup time (NIBUT), and was therefore selected for data collection. A systematic review of artificial tears was undertaken, to reveal deficits in the literature. Newer artificial tears, containing combination formulations are more effective in treating DED, and further research into molecular weight is indicated. A randomised crossover trial was conducted, comparing the relative efficacy of drops containing different molecular weights of sodium hyaluronate. The drops performed similarly, however further research is warranted. Another study assessed the efficacy of a novel treatment for meibomian gland dysfunction (MGD), using a multi-modal device with heated reusable attachments. The MGrx device is as effective as traditional debridement and expression, but has time, space and cost-saving advantages. A global survey of clinical practice patterns was also conducted, revealing changes in DED management between regions and over time.

High quality research evidence is key to informing clinical practice. The work in this thesis fills knowledge gaps and adds to the evidence in artificial tears, the mainstay of DED management, and treatments for MGD, the leading cause of evaporative DED. The dissemination of its findings ensures that they can be translated into clinical care, resulting in a significant contribution to the field of evidence-based management of dry eye disease, for the benefit of clinicians and their patients.

Key words:

Dry eye disease, artificial tears, hyaluronic acid, sodium hyaluronate, meibomian gland dysfunction, debridement and expression, evidence-based management, therapy

Dedication

This thesis is dedicated to my parents, family and friends, with all my love.

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Contents

Terminology and Abbreviations

ADDE – Aquesous deficiant dry eye

ANOVA – Analysis of variance

AT – Artificial tears

BUT – Breakup time (method not defined)

CID – Clinically important difference

CLD – Contact lens discomfort

CLDEQ – Contact lens dry eye questionnaire

CLDEQ-8 – 8-item contact lens dry eye questionnaire

CLIQ – Contact lens impact on quality of life

CMC – Carboxymethyl cellulose

CoQ10 – Coenzyme Q_{10} / ubiquinone

DED – Dry eye disease

DEQ – Dry eye questionnaire

DEQ-5 – 5-item dry eye questionnaire

DEQS – Dry eye-related quality-of-life score

Dx – Diagnosis

EDE – Evaporative dry eye

EudraCT – European Union Drug Regulating Authorities Clinical Trials

FBUT – Fluorescein breakup time

GVHD – Graft versus host disease

GP – General practitioner

HA – Hyaluronic acid

HLA-DR – Human leukocyte antigen – DR isotype

HMWHA – High molecular weight hyaluronic acid

HP-guar – Hydroxypropyl-guar

HPMC – Hydroxypropyl methylcellulose / hypromellose

IDEEL – Impact of dry eye on everyday life

IL – Interleukin

IPL – Intense pulsed light

K5M – Keratograph 5M

LFA-1 – Lymphocyte function-associated antigen 1

LG – Lissamine green

LIPCOF – Lid-parallel conjunctival folds

LWE – Lid wiper epitheliopathy

Mg – Management

MGD – Meibomian gland dysfunction

MGE – Meibomian gland examination

MGX – Meibomian gland expression

MMP-9 – Matrix metalloproteinase-9

MQ – McMonnies' questionnaire

NaCl – Sodium chloride

NaFl – Sodium fluorescein

NEI-VFQ – National Eye Institute - visual function questionnaire

NIBUT – Non-invasive breakup time

NITBUT – Non-invasive tear breakup time

OCI – Ocular comfort index

OSDI – Ocular surface disease index

PEG – Polyethylene glycol

PG – Propylene glycol

PLL-g-PEG – Poly-L-Lysine graft polyethylene glycol

PVA – Polyvinyl alcohol

QoL – Quality of life

RCT – Randomised controlled trial

SANDE – Symptoms assessment in dry eye

SH – Sodium hyaluronate

SPEED – Standard patient evaluation of eye dryness

TBUT – Tear breakup time (method not defined)

TFOS DEWS II – Tear Film and Ocular Surface Society Dry Eye Workshop II

TMH – Tear meniscus height

UD – Unit-dose

VAS – Visual analogue scale

WMP – Wilcoxon matched pairs

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1. Dry eye disease and its management

1.1. Introduction

DED is a highly prevalent and symptomatic condition, which impacts quality of life for many millions of individuals worldwide. Its multifactorial and burdensome nature make appropriate diagnosis and management paramount. However, effective long-term management remains challenging and frustrates clinicians and patients alike. To aid understanding, a thorough review of the relevant literature was conducted, centred on clinical management and therapy. This chapter details the important knowledge gaps which were identified, leading to the planning and implementation of multiple studies and clinical trials.

1.2. Definition

Defining a disease is highly important, as it facilitates accurate diagnosis and treatment, provides consistency, for example in clinical research, and aids patient understanding. The definition of DED has evolved over the years, to reflect advances in research evidence. Dry eye was first defined by the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes (Lemp, 1995), which identified the importance of tear quality as well as quantity, but defined dry eye as a disorder, rather than a disease. This was addressed by the original 2007 TFOS DEWS definition, which stated that dry eye was a multifactorial *disease*, and introduced increased osmolarity and ocular surface inflammation, as well as symptoms of visual disturbance.

In 2017, with the culmination of around two and a half years of research, TFOS published the seminal DEWS II reports, encompassing the work of around one hundred and fifty ocular surface and other research experts from around the world. The Definition and Classification Subcommittee updated the 2007 DEWS definition of dry eye, to recognise some important developments and changes in emphasis over the intervening years. The, now well-known, definition was revised as follows:

> "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" (Craig et al., 2017a).

It is important to note that the definition includes ocular symptoms, therefore clinical signs without symptoms, or vice-versa, are not considered to be DED (Wolffsohn et al., 2021a), however may be indicative of other ocular pathology, or predisposition towards DED. TFOS DEWS II suggested a standardised system for the diagnosis of DED based on validated symptoms questionnaires and key clinical signs (Wolffsohn et al., 2017).

1.3. Prevalence

Estimates of the prevalence of DED vary considerably, due to the differing diagnostic criteria adopted by each research team, but generally range from 5-50% in studies involving symptoms and/or signs, and up to 75% when only signs have been considered (Stapleton et al., 2017). A recent cross-sectional study (Vidal-Rohr et al., 2023) involving 282 residents of Birmingham, UK, using the TFOS DEWS II and Women's Health Study diagnostic criteria, found prevalences of 32.1% and 29.5% respectively.

The high prevalence and symptomatic nature of DED results in considerable burden, both human and economic, due to loss of productivity, and healthcare costs to the individual and the taxpayer (Luo et al., 2021; McDonald et al., 2016; Morthen et al., 2021). In severe cases symptoms become debilitating and impinge on almost all daily activities, such that quality of life and health utility scores can be equivalent to chronic systemic conditions such as angina (Schiffman et al., 2003), and sufferers have an increased risk of anxiety and depression (Li et al., 2011).

1.4. Tear film

A stable preocular tear film is a key indicator of ocular health, as it forms the primary refracting surface for light entering the eye, as well as protecting and hydrating the cornea. The classical three-layered tear film model, which became widely adopted, was first introduced by Wolff (Wolff, 1946), however more modern theories suggest that the precorneal tear film operates as a unified, dynamic functional entity (Yokoi et al., 2014).

Studies using ultrahigh resolution ocular coherence tomography have determined the thickness of the precorneal tear film to be 2-5.5 μm, which agrees with data from interferometry studies (King-Smith et al., 2000, King-Smith et al., 2004, Chen et al., 2010). Water has a high surface tension, and to achieve an ultrathin film that does not collapse or form droplets, the ocular surface must have similar properties to water; however, the tear film must have a reduced surface tension at its air interface (Holly and Lemp, 1971, Holly, 1973).

The tear film contains antimicrobial peptides, proteins, and soluble immunoglobulins, which defend the ocular surface from infection, as well as providing oxygen, metabolites and electrolytes to the ocular surface. Advancements in proteomics have identified that over 1500 proteins are found in the human tear film (Zhou et al., 2012) and more than 200 peptides derived from several of these proteins (Azkargorta et al., 2015).

Sensitive lipid analyses reveal that tears possess a lipid profile resembling that of meibomian lipids, albeit with a higher proportion of phospholipids (Brown et al., 2013). This, as well as the observed movement of meibum into the tear film, suggests that the tear lipid layer is almost

entirely produced by the meibomian glands. Meibum, produced by meibocytes, consists of an array of long-chain lipids, primarily composed of neutral lipids, such as non-polar wax esters, cholesteryl esters, free cholesterol, and triacylglycerols, alongside a smaller proportion of polar lipids (Butovich et al., 2008).

The lacrimal gland is responsible for the majority of tear volume and flow (Mishima et al., 1966, Braun, 2012), with the conjunctiva also contributing (Dartt, 2002). Innervation of the main lachrymal glands is via the parasympathetic and sympathetic pathways and some sensory nerves (Botelho et al., 1966, Sibony et al., 1988). Stimulation of the ocular surface activates afferent sensory nerves of the cornea and conjunctiva, leading to secretion from acinar and tubular cells in the lacrimal gland, via efferent parasympathetic and sympathetic innervation (Botelho, 1964).

Tears can be divided into four types - basal (sometimes known as open-eye), reflex, emotional and closed-eye (Craig et al., 2013). The majority of basal, reflex and emotional tears emanate from the lacrimal glands, via the neural arc (Belmonte et al., 2017), but contain different concentrations of certain proteins (Craig et al., 2013). During sleep, secretion from the lacrimal gland significantly reduces, resulting in closed-eye tears exhibiting a distinct composition compared to the other three types. For example, in closed-eye conditions, there is an elevated concentration of serum-derived proteins, which leak from the conjunctival blood vessels (Craig et al., 2013).

With the eyes open, tears distribute themselves into three areas: the fornical compartment (which occupies the fornix and retrotarsal space), the inferior and superior tear menisci, and the preocular tear film (Willcox et al., 2017). The osmolarity of the tear film is commonly quoted as being around 302 mOsm/L, however this relates to samples obtained from the inferior tear meniscus, with no evidence that this is consistent across other regions of the ocular surface (Willcox et al., 2017).

Tear film thinning between blinks can be detected with various methods, and is predominantly due to evaporation (Willcox et al., 2017). There are several tests which measure tear production, turnover and volume, but they do not correlate well (Sullivan et al., 2014), and in TFOS DEWS II it was noted that there was a need for more non-invasive tests for DED (Wolffsohn et al., 2017). Tear meniscus height (TMH) can be estimated non-invasively at the slit-lamp, or measured accurately using electronic devices, and is linearly proportional to the lacrimal secretory rate (Mishima et al., 1966).

While tear breakup is normal when blinking is prevented, excessive tear instability is indicative of a disordered tear film, especially in dry eye conditions, therefore, assessment of tear film stability is a core diagnostic tool to investigate tear film homeostasis. Tear breakup time (TBUT) is the most common measure of tear film stability, and this can be achieved accurately and non-invasively (Best et al., 2012, Tian et al., 2016). Non-invasive tear breakup time should be measured three times per eye, with the median value being recorded, due to its variability; the lower of the two median values for the two eyes being taken as the final diagnostic value (Wolffsohn et al., 2017).

1.5. Pathophysiology

The overarching pathophysiology of DED involves evaporation-induced tear film hyperosmolarity, inflammation and tissue damage, which result in a self-perpetuating vicious cycle of ocular surface inflammation (Bron et al., 2017). There are multiple points of entry to this cycle, which can have numerous aetiologies. In aqueous deficient dry eye (ADDE), hyperosmolarity results from insufficient aqueous secretion in conditions of normal tear evaporation, whereas evaporative dry eye (EDE) occurs when tear evaporation is accelerated, in conditions of normal aqueous secretion. Hence, Bron et al. (2017) state that all forms of DED may be considered to be evaporative, as tear hyperosmolarity results from tear evaporation in both ADDE and EDE, therefore EDE should be considered to be a 'hyper-evaporative state'.

EDE results predominantly from meibomian gland dysfunction (MGD); a type of posterior marginal blepharitis. Changes in meibomian gland physiology result in a defective tear lipid layer, leading to insufficient surface protection and excessive evaporation of the aqueous phase of the tears (Craig et al., 2017a). Meibum secreted by healthy meibomian glands is clear, oily and fluid at body temperature, enabling a small quantity to be expressed with each blink (Knop et al., 2011). In MGD, the phase-transition temperature is higher and the consistency of the gland contents is more viscous at physiological temperatures, hence meibum becomes cloudy or inspissated, is harder to express and can cause gland blockage (Magno et al., 2022).

In ADDE, tear hyperosmolarity occurs due to reduced tear secretion, with a variety of aetiologies, and can be generalised as being lachrymal gland related (Craig et al., 2017a). Factors leading to reduced aqueous secretion may include impaired function, destruction, scarring or atrophy of lachrymal gland or conjunctival tissues (Conrady et al., 2016, Bron et al., 2017). ADDE is a prominent feature of Sjögren's syndrome, which is the second commonest autoimmune disease in America, after rheumatoid arthritis, and is also characterised by oral features such as dry mouth and major salivary gland swelling (Vivino et al., 2019).

Hyperosmolarity initiates a cascade of biochemical signals in surface epithelial cells, resulting in the release of inflammatory mediators and proteases (Bron et al., 2017). This, coupled with direct damage induced by high tear osmolarity, results in goblet and epithelial cell death, which damages the epithelial glycocalyx (Yeh et al., 2003). The resultant reduction of tear film stability, and further increase in tear osmolarity and surface damage serve to reinforce the vicious cycle of DED, as shown by Figure 1.1 (Bron et al., 2017). The aim of therapy is therefore to break the cycle, restore homeostasis to the ocular surface, and bring about symptomatic relief for the patient.

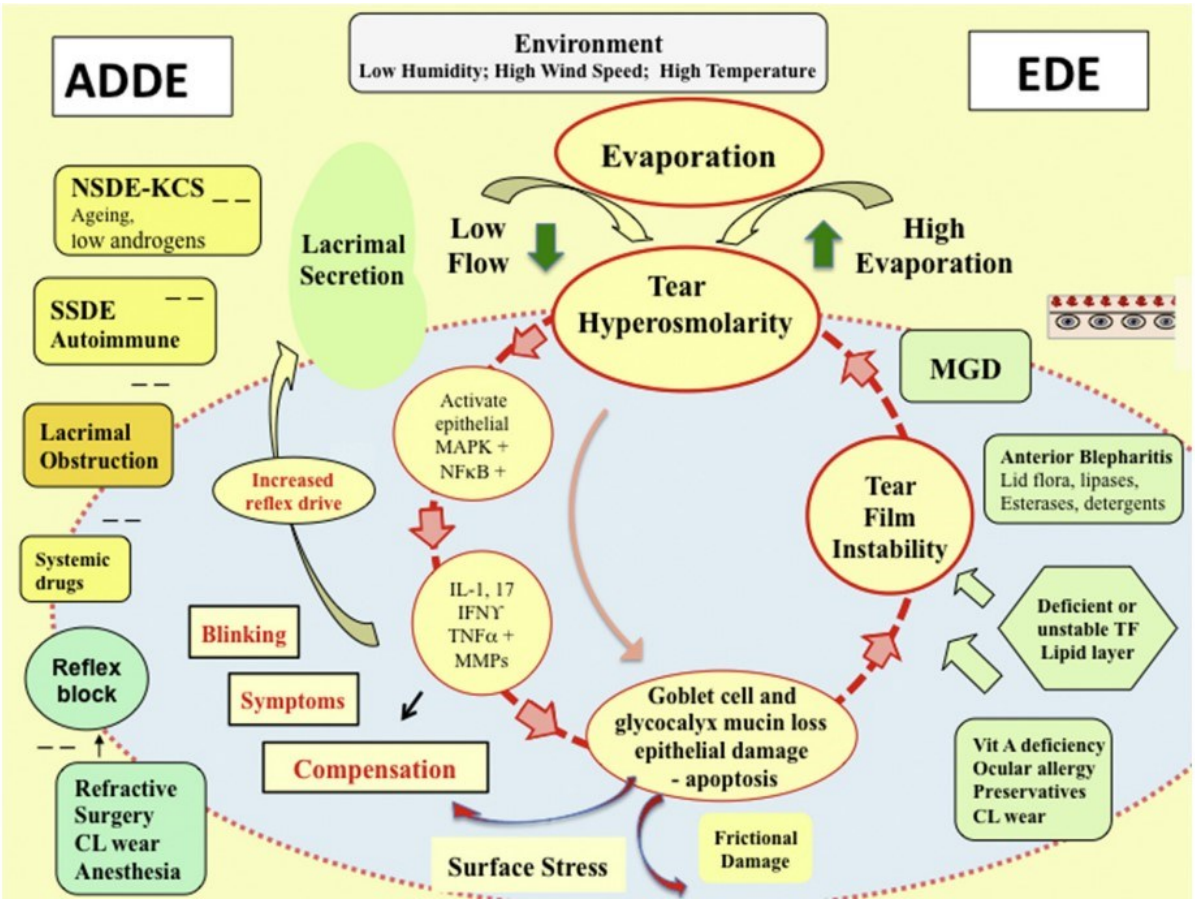


Figure 1.1. The vicious cycle of DED (Bron et al., 2017). Reprinted from The Ocular Surface 15(3) 438-510, Bron et al., TFOS DEWS II pathophysiology report, copyright 2017, with permission from Elsevier.

1.6. Diagnosis

1.6.1. Triaging questions

There are various differential diagnoses which must be borne in mind when faced with a patient complaining of ocular discomfort or presenting with signs such as redness, foreign body sensation and visual disturbance. For this reason, it is useful to use a series of triaging questions, which can help to steer the clinical examination (Wolffsohn et al., 2017). Figure 1.2 shows the suggested triaging questions, along with an explanation of each question, highlighting its importance.

How severe is the eye discomfort?	Unless severe, dry eye presents with signs of irritation such as dryness and grittiness rather than 'pain'. If pain is present, investigate for signs of trauma / infection / ulceration
Do you have any mouth dryness or enlarged glands?	Trigger for Sjogren syndrome investigation
How long have your symptoms lasted & was there any triggering event?	Dry eye is a chronic condition, present from morning to evening but generally worse at the end of the day, so if sudden onset or linked with an event, examine for trauma / infection / ulceration
Is your vision affected and does it clear on blinking?	Vision is generally impaired with prolonged staring, but should largely recover after a blink; a reduction in vision which does not improve with blinking, particularly with sudden onset, requires an urgent ophthalmic examination
Are the symptoms or any redness much worse in one eye than the other?	Dry eye is generally a bilateral condition, so if symptoms or redness are much greater in one eye than the other, detailed eye examination is required to exclude trauma & infection
Do the eyes itch, are they swollen, crusty or have they given off any discharge?	Itching is usually associated with allergies while a mucopurulent discharge is associated with ocular infection
Do you wear contact lenses?	Contact lenses can induce dry eye signs and symptoms and appropriate management strategies should be employed by the contact lens prescriber
Have you been diagnosed with any general health conditions (including recent respiratory infections) or are you taking any medications?	Patients should be advised to mention their symptoms to the health professionals managing their condition, as modified treatment may minimise or alleviate their dry eye

Figure 1.2. Triaging questions for the differential diagnosis of dry eye disease. Adapted from TFOS DEWS II Diagnostic Methodology report (Wolffsohn et al., 2017).

1.6.2. Risk factors

Once other disease entities are excluded, it is useful to examine risk factors, which may predispose towards DED. As some of these are modifiable, this may have a direct bearing on the appropriate management strategy. For example, a cross-sectional study by Wang et al. (2021) found that increased screen time was a modifiable risk factor. Interestingly, it was also found that caffeine intake was protective. Another cross-sectional study by Wolffsohn et al. (2021b) concluded that some risk factors applied to evaporative dry eye, but not aqueous deficient dry eye, whilst others applied to both. It was found that East and South Asian ethnicity, contact lens

wear and VDU use were risk factors for evaporative dry eye, whilst female sex and lack of sleep were risk factors for aqueous deficient dry eye. Other risk factors, such as aging, stress and perception of poor general health were common to both subtypes. Other studies have shown associations with dry eye and microvascular characteristics (Shokr et al., 2021) and systemic conditions, such as migraine headaches (Wolffsohn et al., 2020). Numerous other risk factors have been identified, with some having a high degree of certainty and others being less conclusive, as summarised in Table 1.1.

1.6.3. Symptom questionnaires

As mentioned above, a diagnosis of dry eye requires both signs and symptoms. The Ocular Surface Disease Index (OSDI) and 5-item Dry Eye Questionnaire (DEQ-5), when self-administered, have been validated for this purpose, with a score of 13 or more on OSDI, and/or 6 or more on DEQ-5 being consistent with DED (Schiffman et al., 2000, Chalmers et al., 2010). The OSDI questionnaire consists of 12 questions covering symptoms, impact on vision and triggering factors, whilst DEQ-5 has five questions relating to discomfort, dryness and watering. A shortened version of the standard OSDI has also been validated, with fewer questions and a simplified scoring system, with the aim of making it easier and quicker for patients and practitioners to use (Pult and Wolffsohn, 2019). A positive symptomology on OSDI or DEQ-5 should trigger clinical examination to investigate homeostatic markers of DED. Table 1.2 summarises the key features of common DED questionnaires, including their original and recent citations, and the types of validation documented in the referenced literature.

Table 1.1. Risk factors for dry eye disease. Adapted from TFOS DEWS II Epidemiology Report (Stapleton et al., 2017).

	Consistent[a]	**Probable**[b]	**Inconclusive**[c]
Non-modifiable	Aging	Diabetes	Hispanic ethnicity
	Female sex	Rosacea	Menopause
	Asian race	Viral infection	Acne
	Meibomian gland disfunction	Thyroid disease	Sarcoidosis
	Connective tissue diseases	Psychiatric conditions	
	Sjögren syndrome	Pterygium	
Modifiable	Androgen deficiency	Low fatty acids intake	Smoking
	Computer use	Refractive surgery	Alcohol
	Contact lens wear	Allergic conjunctivitis	Pregnancy
	Hormone replacement therapy		Demodex infestation
	Hematopoietic stem cell transplantation		Botulinum toxin injection
	Environment: pollution, low humidity, sick building syndrome		
	Medications: antihistamines, anti-depressants, anxiolytics, isotretinoin	Medications: anticholinergic, diuretics, betablockers	Medications: multivitamins, oral contraceptives

[a] Consistent evidence implies the existence of at least one adequately powered, and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data.

[b] Suggestive evidence implies the existence of either inconclusive information from peer-reviewed publications or inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal.

[c] Inconclusive evidence implies either directly conflicting information in peer-reviewed publications, or inconclusive information but with some basis for a biological rationale.

Table 1.2. Features of a range of dry eye questionnaires & supporting literature. Adapted from TFOS DEWS II Diagnostic Methodology report (Wolffsohn et al., 2017).

Name	Primary & Recent References	Dry Eye Screening Criteria	Type of Validation	Other Comments
Dry Eye Questionnaire (DEQ)	**Primary:** Begley et al. (2002)	-	Discriminant focus ADDE	Developed at Indiana University Symptom frequency & intensity
5-Item Dry Eye Questionnaire (DEQ-5)	**Primary:** Chalmers et al. (2010) **Recent:** Camp et al. (2015) Galor et al. (2015) Fernandez et al. (2013)	≥6 KCS ≥12 suspect SS	Discriminant focus ADDE Subgroup Glaucoma. Across posttraumatic stress disorder, depression.	Developed at Indiana University Symptom frequency & intensity
Dry Eye-Related Quality-of-Life Score (DEQS)	**Primary:** Sakane et al. (2013)	-	Content Face Psychometric Reproducibility	Symptom frequency & degree
Impact of Dry Eye on Everyday Life (IDEEL)	**Primary:** Abetz et al. (2011) **Recent:** Fairchild et al. (2008)	Mild 40 – 50 Moderate 51 – 63 Severe >64	Content Psychometric Discriminant focus ADDE Responsiveness CID = 8 Symptom bother	Developed by Alcon Research, Ltd., MAPI Values Symptom bother only
McMonnies' Questionnaire (MQ)	**Primary:** McMonnies & Ho (1987) **Recent:** Tang et al. (2016)	>14.5 Dry Eye	Chinese translation & validation	Symptom frequency only
Ocular Comfort Index (OCI and OCI-C)	**Primary:** Johnson & Murphy (2007) **Recent:** Chao et al. (2014) Golebiowski et al. (2017)	-	Rasch scaled items Item reduction Responsiveness CID = 3 Chinese translation & validation MGD female cross-section.	Symptom frequency & intensity
Ocular Surface Disease Index (OSDI)	**Primary:** Schiffman et al. (2000) **Recent:** Amparo et al. (2015)	Mild 13 – 22 Moderate 23 – 32 Severe ≥ 33	Concurrent with SANDE Concurrent with SPEED Severe ≥ 33	Developed by Allergan, Inc. Better for Research than SANDE

Name	Primary & Recent References	Dry Eye Screening Criteria	Type of Validation	Other Comments
	Asiedu et al. (2017) Baudouin et al. (2014) Finis et al., (2014) Galor et al. (2015) Miller et al. (2010) Ogawa et al. (2013)		Concurrent with SPEED Concurrent with DEQ-5 CID = 7.0 – 9.9 GVHD Subgroup	Better for ADDE than SPEED Symptom frequency & intensity
Symptom Assessment in Dry Eye (SANDE)	**Primary:** Schaumberg et al. (2007) **Recent:** Amparo et al. (2015) Saboo et al. (2015)	-	Concurrent with OSDI Concurrent with OSDI, NEI-VFQ	Symptom frequency & intensity Visual Analogue Scales Better for clinical than OSDI
Standard Patient Evaluation of Eye Dryness (SPEED)	**Primary:** Blackie et al. (2009) **Recent:** Asiedu et al. (2017) Finis et al. (2014)	-	Concurrent with OSDI Concurrent with OSDI	Symptom frequency & intensity Better for MGD dry eye
Developed for Use with Contact Lens Wearers				
Contact Lens Dry Eye Questionnaire (CLDEQ)	**Primary:** Begley et al. (2002) Nichols et al. (2002)	Screening		Symptom frequency & intensity
8-Item Contact Lens Dry Eye Questionnaire (CLDEQ-8)	**Primary:** Chalmers et al. (2012) **Recent:** Chalmers et al. (2016)	≥12 = CLD	Discriminant Concurrent with overall opinion of CLs CID = 3 Responsiveness Concurrent with Overall Opinion of CLs, Eye Dryness & Eye Sensitivity	Symptom frequency & intensity For soft contact lens wear
Contact Lens Impact on Quality of Life (CLIQ)	**Primary:** Pesudovs et al. (2006) **Recent:** Erdurmus et al. (2009)	QoL Keratoconus only	Rasch scaling Across CL types	Frequency of bundled symptoms More of a contact lens-related QoL questionnaire than a direct measure of symptoms

ADDE = Aqueous Deficient Dry Eye, CLD = Contact Lens Discomfort, MGD = Meibomian Gland Dysfunction, QoL = Quality of Life. CID = Clinically Important Difference, GVHD = Graft Versus Host Disease, NEI-VFQ = National Eye Institute - Visual Function Questionnaire.

1.6.4. Clinical signs

It is recommended that clinical tests for dry eye be conducted in a sequence which minimises errors due to their own invasiveness (Wolffsohn et al., 2017). Hence, the least invasive tests should be conducted first, followed by more invasive tests such as tear sampling and the instillation of diagnostic stains. The diagnosis and sub-classification of DED is summarised in Figure 1.3.

1.6.4.1. Tear breakup time

Tear breakup time should ideally be measured non-invasively, for example with the aid of automated video keratography software, which can analyse the breakup of the tear film over a wide corneal area simultaneously (Best et al., 2012). Where specialised systems are not available, other non-invasive methods include visualisation of keratometry mires, however this is intrinsically subjective. NIBUT should be measured three times per eye to account for its variability, and the lower of the two median values from both eyes taken as the final diagnostic value (Wolffsohn et al., 2017). A NIBUT of <10 s, in conjunction with a positive symptomology score, is diagnostic of DED. In practice, many clinicians use fluorescein breakup time (FBUT), however the instillation of fluorescein may affect the behaviour of the tear film through the change in chemical composition and increased volume from the dye solution, hence FBUT should be conducted only if non-invasive methods are unavailable (Lan et al., 2014).

1.6.4.2. Tear osmolarity

The use of tear osmolarity in diagnosing DED has been intensively studied (Potvin et al., 2015), but has traditionally been the preserve of the research community. However, the advent of lab-on-a-chip technology has brought its measurement within reach of optometric practice. The TearLab (Trukera Medical, Southlake, TX, USA), for example, samples a tiny quantity of tears and provides a rapid measurement of tear osmolarity (Eperjesi et al., 2012). The TearLab device is no longer manufactured, but has been replaced by the similar ScoutPro osmolarity system. Another handheld device, the I-PEN (I-MED Pharma Inc, Dollard-des-Ormeaux, Quebec, Canada) is also validated for this purpose (Chan et al., 2018). A reading of 308 mOsm/L or more (Lemp et al., 2011, Jacobi et al., 2011), or an inter-eye difference of more than 8 mOsm/L (Sullivan, 2013) is taken as the diagnostic threshold.

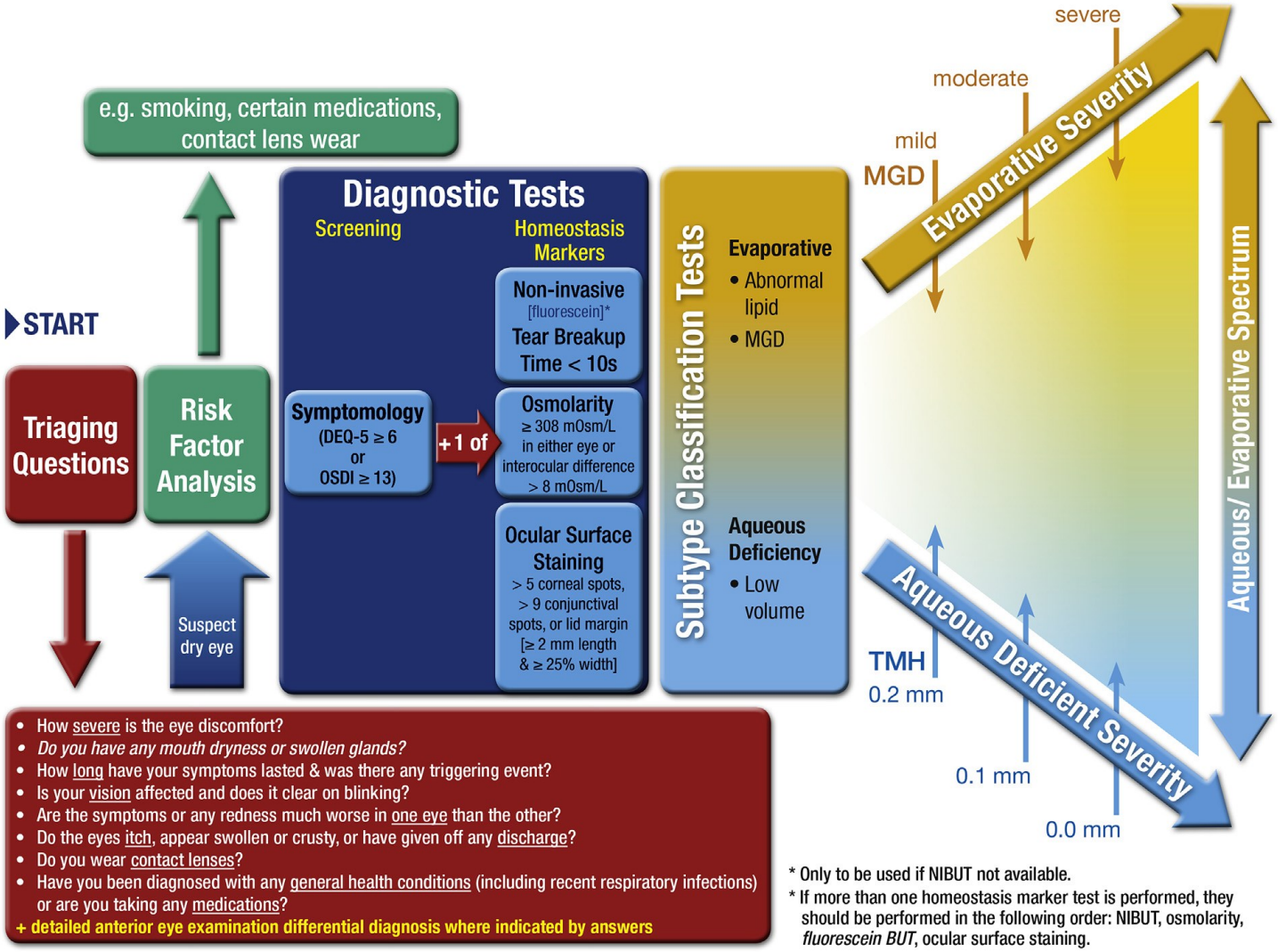


Figure 1.3. TFOS DEWS II diagnostic test battery (Wolffsohn et al., 2017). Reprinted from The Ocular Surface 15(3) 539-74, Wolffsohn et al., TFOS DEWS II Diagnostic Methodology report, copyright 2017, with permission from Elsevier.

1.6.4.3. Ocular staining

Lissamine green and sodium fluorescein can be used to visualise areas of ocular surface damage (Figure 1.4). Lissamine green stains devitalised cells in the conjunctiva and eyelid margin and is viewed under white light illumination. Sodium fluorescein fluoresces when excited by blue light, making it suitable for revealing ocular surface defects. It is best observed with a 495nm blue light, viewed through a 500nm cut-off yellow filter (Peterson et al., 2006). The threshold is a count of 10 or more conjunctival spots with lissamine green, or 6 or more corneal spots with fluorescein (Whitcher et al., 2010). Lid-wiper epitheliopathy can be seen with lissamine green or fluorescein and the diagnostic threshold is 2mm or more in length or 25% or more in sagittal eyelid width (Korb et al., 2005). Ocular staining is considered to be a relatively late-stage sign of DED (Craig et al., 2021).

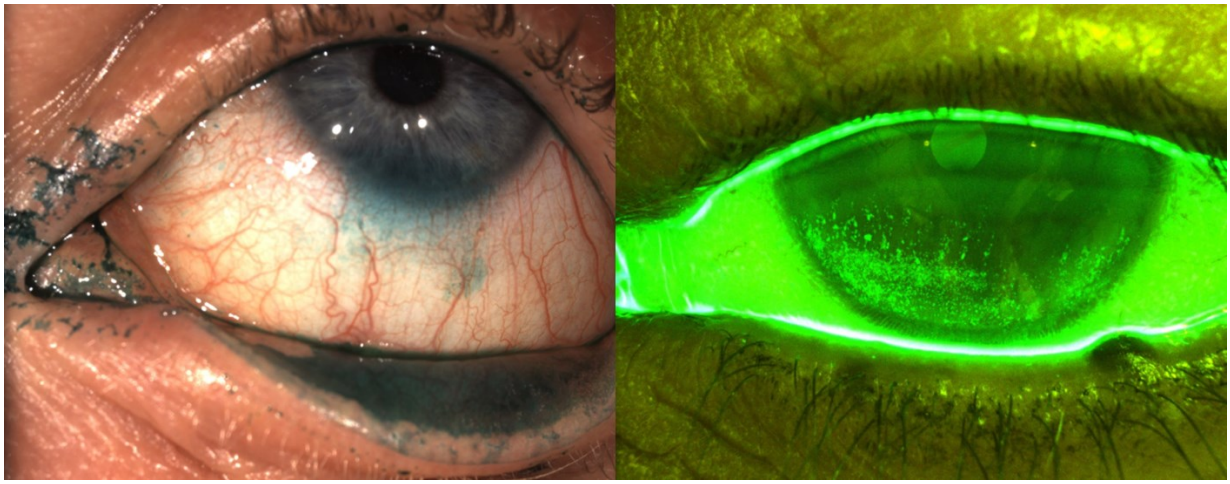


Figure 1.4. Ocular staining with lissamine green (left) and sodium fluorescein (right).

1.6.4.4. Tear ferning

Visual assessment of a small quantity of an air-dried tear sample indicates its chemical composition (Alanazi et al., 2019), which can be graded according to its pattern when viewed microscopically on a glass plate (Masmali et al., 2014). Dutta et al. (2019) demonstrated that the technique was repeatable and that it did not correlate with TBUT and symptomology in dry eye.

1.6.4.5. Biomarkers of dry eye

A raft of biological molecules have been studied as biomarkers for dry eye, including various cytokines, chemokines, degradative enzymes, growth factors, novel proteins and steroids (Fong et al., 2020). Inflammation is known to be an important element of the pathophysiology of DED (Bron et al., 2017) and is included in its definition (Craig et al., 2017a).

Clinical features elicited by imaging techniques, for example changes in non-invasive tear breakup time, tear meniscus height, meibography, tear lipid layer thickness, conjunctival redness, ocular surface staining and in-vivo confocal microscopy features, can also be considered biomarkers in DED (Villani et al., 2020).

1.6.4.5.1. Matrix metalloproteinase-9 (MMP-9)

Matrix metalloproteinase-9 is probably the most well-known biomarker in DED. MMP-9 is a proteolytic enzyme, which breaks down corneal basement membrane proteins and tight junctions, leading to epithelial cell death, and is a key factor in both inflammatory ocular surface diseases and also normal tissue modelling and wound healing (Fong et al., 2020). The InflammaDry test, which is approved by the US Food and Drug Administration for the diagnosis of dry eye, provides a positive result if MMP-9 levels exceed 40 ng/ml, but is non-specific as to the source of inflammation (Wolffsohn et al., 2017).

Sambursky et al. (2014) conducted a prospective clinical trial comparing InflammaDry with clinical testing, to determine the presence or absence of DED, and to ascertain its ease of use by untrained ophthalmic technicians. InflammaDry was compared with clinical tests (FBUT, anaesthetised Schirmer and corneal fluorescein staining), and analysed with and without the inclusion of OSDI questionnaire scores. Two hundred and thirty-seven participants were recruited, with a mean age of 53 yrs. When including OSDI in the criteria for mild dry eye, it was reported that InflammaDry had a positive agreement with clinical testing of 81% and a negative agreement of 98%. However, some shortcomings can be identified in this trial.

The assessment of TBUT could have been made more objective by using non-invasive means, such as automated videokeratography. Additionally, the use of the anaesthetised Schirmer test may have induced changes in the ocular surface characteristics being measured, due to its invasive nature. Schargus et al. (2015) noted that the diagnostic use of MMP-9 would likely miss many cases of mild or early-stage DED, compared to other biomarkers such as tear osmolarity. For this reason, it is not included in the TFOS DEWS II diagnostic criteria, as non-invasive measurements such as tear meniscus height and breakup time are likely to give a more accurate representation of a patient's clinical status (Wolffsohn et al., 2017).

1.7. Subclassification

Once a diagnosis of DED is established, the management is dependent on causal factors and subclassification as evaporative or aqueous deficient dry eye. Some cases present with elements of both, however there is a predilection for EDE (Craig et al., 2017a).

1.7.1. Evaporative dry eye

1.7.1.1. Meibomian gland dysfunction

EDE secondary to MGD is the commonest form of DED and can be identified by changes in the morphology and physiology of the meibomian glands. Features suggestive of MGD include shortening and loss of meibomian gland tissue, thickened, granular or inspissated secretions, lid margin keratinisation and tear lipid layer abnormalities (Knop et al., 2011, Magno et al., 2022).

1.7.1.2. Meibography and lid margin examination

Meibography can be achieved using infra-red illumination, for example with the aid of the Oculus K5M (Figure 1.5), and reveals the glandular tissue of the meibomian glands, and any shortening and dropout (Mathers et al., 1991). Pressing on the eyelids should result in the expulsion of some meibum, which can be graded in terms of expressability, colour and consistency (Knop et al., 2011).

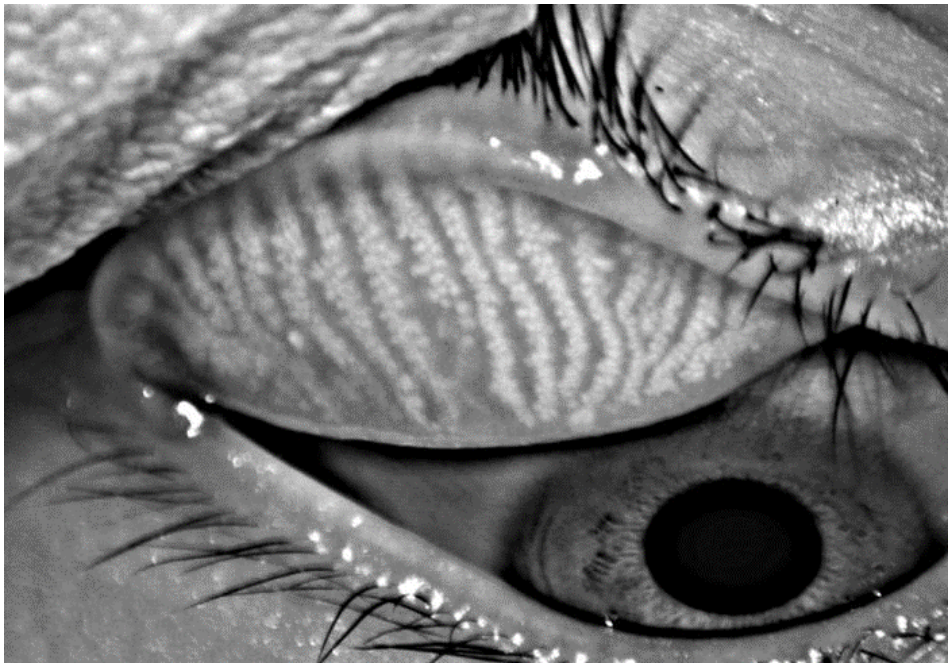


Figure 1.5. Meibography image taken with the Oculus K5M, showing meibomian gland architecture under infra-red illumination.

1.7.1.3. Tear film lipid layer

The tear lipid layer can be evaluated for quality and quantity by means of tear film interferometry, and graded using the Guillon-Keeler system (Guillon, 1998). Examination of the interferometry pattern under optical or digital magnification, for example using the K5M, allows the clinician to estimate the thickness of the lipid layer, which is normally around 40 nm, with a range of 15 to 157 nm (King-Smith et al., 2010).

1.7.2. Aqueous deficient dry eye

1.7.2.1. Tear meniscus height

The majority of the tear volume (75-90%) resides in the tear menisci (Niedernolte et al., 2021) therefore tear meniscus height gives a good indication of total tear volume, which helps in determining the presence and degree of aqueous deficiency. The most accurate method for measuring TMH is anterior eye ocular coherence tomography (Niedernolte et al., 2021). TMH can also be measured using specialised videokeratography software, however many optometry practices lack this kind of instrumentation. Practitioners may instead estimate TMH using slit-lamp biomicroscopy, by comparing the tear meniscus with a slit of known height, for example 0.3 mm (Niedernolte et al., 2021). A TMH of under 0.2 mm is taken as the diagnostic cut-off value for ADDE (Wolffsohn et al., 2017), as seen on the right hand side of Figure 1.3.

1.8. Management

After symptoms begin, they tend to fluctuate depending on various factors, however DED is generally a lifelong condition. DED presents as evaporative, aqueous deficient or hybrid, with evaporative dry eye predominating (Craig et al., 2017). Regardless of the subtype and aetiology, artificial tears are typically the mainstay of management, being easily accessible in a wide range of formulations, and having a low risk-profile (Jones et al., 2017). Most artificial tear preparations have been found to be effective in reducing the symptoms and signs of DED, however, there have been relatively few high quality randomised controlled trials (RCT) comparing different products with each other (Jones et al., 2017; Pucker et al., 2016).

Numerous other treatment modalities have been applied to dry eye, including home remedies, complementary therapies, pharmacological agents, thermal, mechanical and electronic devices; however many are not fully validated compared to alternative treatment options, due to a lack of clinical evidence (Jones et al., 2017). This makes the job of the practitioner more difficult. Whilst many patients seem to benefit from basic first-line treatments such as artificial tear supplementation and warm compresses, the extent and duration of symptomatic relief can vary quite considerably from one individual to another. Table 1.3 presents the array of management options identified by the TFOS DEWS II Management and Therapy Report (Jones et al., 2017). It is often difficult for practitioners to choose between treatment options for a given patient, due to a lack of high quality evidence.

A TFOS international survey (Wolffsohn et al., 2021a) was conducted between 2018 and 2019, as part of the follow-up work from TFOS DEWS II, to investigate clinical DED management and prescribing patterns around the world. A total of 1139 clinicians from 51 different nations responded to the survey. The most widely recommended management strategies included

general advice (87%), low (85%) and high (80%) viscosity unpreserved lubricants, and lid wipes/scrubs (81%). Surprisingly, recommendations for homemade warm compresses outnumbered those for commercial products, which maintain their temperature much better (Bitton et al., 2016).

Table 1.3. Treatment modalities for dry eye disease. Adapted from TFOS DEWS II Management and Therapy Report (Jones et al., 2017).

- **Treatments for tear insufficiency**
  - Tear replacement approaches
    - Artificial tear substitutes
      - Aqueous supplementation
      - Lipid supplementation
    - Biological tear substitutes
      - Autologous serum
      - Adult allogeneic serum
      - Umbilical cord serum
      - Platelet preparations
    - Other agents
      - Mucolytics
      - TRPV1 receptor antagonist
  - Tear conservation approaches
    - Punctal occlusion
      - Punctal occlusion with plugs
      - Surgical punctal occlusion
    - Moisture chamber spectacles and humidifiers
  - Tear stimulation approaches
    - Topical secretagogues
      - Aqueous secretagogues
      - Mucin secretagogues
    - Lipid stimulation
    - Oral secretagogues
    - Nasal neurostimulation
    - Various tear stimulation methods
- **Treatments for lid abnormalities**
  - Anterior blepharitis
    - Lid hygiene
      - Bacterial over-colonisation
        - Topical antibiotics
      - Demodex infestation
        - Tea tree oil
        - Ivermectin
  - Meibomian gland dysfunction
    - Ocular lubricants
    - Warm compresses
      - Blephasteam
      - MGDRx EyeBag
      - EyeGiene mask
      - Infrared warm compression device

        - Physical treatments
            - Forceful expression
            - LipiFlow
            - Intense pulsed light (IPL)
            - Intraductal probing
            - Debridement scaling
    - Blinking abnormalities and ocular exposure
        - Treatment for corneal exposure
        - Entropion and ectropion
        - Contact lenses
            - Therapeutic soft contact lenses (bandage lenses)
            - Rigid gas permeable scleral lenses
- **Anti-inflammatory therapy**
    - Topical glucocorticoids
    - Non-glucocorticoid immunomodulators
        - Ciclosporin A
        - Tacrolimus
        - Non-steroidal anti-inflammatory drugs
        - Biologics
        - Neuropeptides
    - Lymphocyte function-associated antigen 1 (LFA-1) antagonist
        - Lifitegrast
    - Inflammatory modulation with systemic and topical antibiotics
        - Tetracycline therapy
    - Macrolide therapy
- **Surgical approaches**
    - Tarsorrhaphy
    - Surgical treatment for conjunctivochalasis
    - Essential blepharospasm treatment with botulinum neurotoxin
    - Lid corrections
        - Dermatochalasis
        - Blepharoptosis (ptosis)
        - Lower lid blepharoplasty
    - Conjunctival surgery and amniotic membrane grafts
    - Mechanical dacryoreservoirs
    - Major salivary gland transplantation
        - Parotid duct transposition
        - Microvascular submandibular gland transplantation
    - Minor salivary gland autotransplantation
- **Dietary modifications**
    - General hydration state
    - Essential fatty acids
    - Lactoferrin
    - Other dietary considerations
- **Local environmental considerations**
    - Chronic topical medications
    - Systemic medications
    - Decreased blink rate
    - Desiccating conditions and environmental pollutants
    - Contact lens wear

- **Complementary medicines**
  - Herbal and natural products
  - Honey
  - Milk
  - Acupuncture
- **Management of psychological aspects of DED**

TFOS DEWS II suggests a staged management plan, as shown in Table 1.4, in order to guide the practitioner through an evidence-based algorithm, rather than a haphazard or scattergun approach. A detailed review of all known DED therapies was beyond the scope of this thesis, therefore the focus was limited to the following treatment algorithm; especially steps one and two.

Table 1.4. Staged management & treatment recommendations for dry eye disease[a,b,c]. Adapted from TFOS DEWS II Management and Therapy Report (Jones et al., 2017).

Step 1:

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:

If above options are inadequate consider:

- Non-preserved ocular lubricants to minimise preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
  - Punctal occlusion
  - Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)
- In-office intense pulsed light therapy for MGD
- Prescription drugs to manage DED[d]
  - Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
  - Topical corticosteroid (limited duration)
  - Topical secretagogues
  - Topical non-glucocorticoid immunomodulatory drugs (such as ciclosporin)
  - Topical LFA-1 antagonist drugs (such as lifitegrast)
  - Oral macrolide or tetracycline antibiotics

Step 3:
If above options are inadequate consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
    - Soft bandage lenses
    - Rigid scleral lenses

Step 4:
If above options are inadequate consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (e.g. tarsorrhaphy, salivary gland transplantation)

a. Potential variations within the disease spectrum are acknowledged to exist between patients and the management options listed above are not intended to be exclusive. The severity and aetiology of the DED state will dictate the range and number of management options selected from one or more steps.
b. One or more options concurrently within each category can be considered within that step of the dry eye disease state. Options within a category are not ranked according to importance and may be equally valid.
c. It should be noted that the evidence available to support the various management options differs and will inevitably be lower for newer management options. Thus, each treatment option should be considered in accordance with the level of evidence available at the time management is instigated.
d. The use of prescription drugs needs to be considered in the context of the individual patient presentation, and the relative level of evidence supporting their use for that specific indication, as this group of agents differs widely in mechanism of action.

1.8.1. Step 1

1.8.1.1. Education regarding the condition, its management, treatment and prognosis

Patient education can be important in the management of any disease, and can be achieved through a variety of means. The provision of written information to take away is often useful, as patients tend to forget details of what has been discussed in consultations (Watson and McKinstry, 2009). For example, patient educational leaflets for conditions including dry eye and blepharitis are produced by the College of Optometrists (College of Optometrists, 2022). Some risk factors are modifiable (see Table 1.1), for example screen use, which induces several ocular symptoms via a variety of mechanisms, such as reduced blink rate and incomplete blinking (Mehra and Galor, 2020). Patient education is key to addressing harmful behaviours and introducing measures to mitigate against them, for example blinking exercises and workstation humidifiers (Hirayama et al., 2013).

1.8.1.2. Modification of local environment

Bron et al. (2017) state that all forms of dry eye may be considered to be evaporative, as tear hyperosmolarity results from tear evaporation in both ADDE and EDE, and that EDE is a hyper-evaporative state. It follows that any environmental condition which increases evaporation from the ocular surface is likely to increase the incidence and severity of dry eye (McCulley et al.,

2006). Examples include heat, air pollution, wind, low relative humidity and high altitude. During the COVID-19 pandemic, many populations have been required to spend more time indoors, with increased reliance on technology for occupational and educational purposes.

Another measure adopted to reduce the spread of infection is the use of face masks. Boccardo (2022) analysed the data from 3605 questionnaires, showing that 67.9% of respondents had dry eye symptoms, of which 26.9% felt their symptoms were worse when wearing a mask. Presumably, mask-associated dry eye results from warm airflow over the ocular surface, caused by each exhaled breath. A 2017 review paper, concluded that many indoor microclimates common to twenty first century society promote dry eye (Calonge et al., 2017). They also encouraged the use of controlled environment laboratories when investigating the ocular surface.

1.8.1.3. Education regarding potential dietary modifications

This relates to factors such as dehydration, intake of foods or supplements containing essential fatty acids, antioxidants and anti-inflammatory compounds. Omega-3 and omega-6 are types of polyunsaturated fatty acids, which can only be obtained by dietary intake. It is known that significant changes in diet and nutrition have taken place during the modern era. For example, it has been found that the ratio of omega-6 to omega-3 essential fatty acids consumption in North America has changed up to 30-fold over the course of the twentieth century (Blasbalg et al., 2011). This would suggest a relative deficiency of omega-3 in this population. The use of dietary supplements containing omega-3 and 6 has been examined for the treatment of dry eye, including the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid (Downie et al., 2019). The 2019 Cochrane systematic review of these treatments found a lack of strong clinical evidence and the potential for bias in many studies, but suggested that long-chain omega-3 supplements may still have a role in dry eye management (Downie et al., 2019).

Lactoferrin is an iron-binding glycoprotein found in a variety of exocrine secretions such as milk and tear fluid, which possesses anti-microbial, anti-inflammatory and anti-angiogenic properties (Masson et al., 1966). It has previously been found that lactoferrin is able to reduce inflammation of the lachrymal gland, by reducing oxidative stress in a mouse model (Kawashima et al., 2012). Another study, involving dietary supplements containing lactoferrin and other components, showed beneficial effects on tear secretion in rats and human dry eye patients (Kawashima et al., 2016). More recently, a trial involving oral lactoferrin supplementation, reported protective effects against dry eye induced in mice, as well as reduced inflammatory cytokines, modulation of gut microbiota and increased production of short-chain fatty acids (Connell et al., 2021). Of

course, the use of animal studies can limit the generalisability of the findings, and more studies involving human participants are needed.

1.8.1.4. Identification and potential modification/elimination of offending systemic and topical medications

It is well established that the use of certain systemic medications, such as antihistamines, betablockers and antidepressants can increase the likelihood of suffering from DED (Table 1.1) (Gomes et al., 2017, Stapleton et al., 2017). The same is also true of many topical drops and their preservatives. Benzalkonium chloride, for example, can produce toxic, proinflammatory and detergent effects, which may lead to or exacerbate DED (Baudouin et al., 2010b). A study into the ocular surface effects of topical antiglaucoma drops (Wong et al., 2018) found significant deleterious changes in non-invasive tear breakup time, tear osmolarity, bulbar conjunctival redness, eyelid margin abnormality score, tear meniscus height and anaesthetised Schirmer score compared to the untreated eye, in a cohort of 33 open-angle glaucoma or ocular hypertensive patients. The authors cited increased inflammation, and preservative toxicity caused by benzalkonium chloride as causative factors for their findings.

Hommer et al. (2018) found that switching from preserved to unpreserved topical antiglaucoma drops could reduce dry eye symptoms in an open-label trial population of well controlled patients. They recruited 30 participants diagnosed with open-angle glaucoma or ocular hypertension, treated with either latanoprost or bimatoprost; both preserved with 0.2% benzalkonium chloride. Measurements taken 4 and 12 weeks after switching to unpreserved tafluprost showed significant improvements in tear film thickness, tear breakup time, corneal staining scores and Dry-Eye-Related Quality-of-Life Score. Intraocular pressures did not change, showing that treatment efficacy with unpreserved tafluprost was not inferior to its preserved counterpart.

1.8.1.5. Ocular lubricants of various types

Artificial tears are generally aqueous, or lipid-based. Aqueous-based drops often contain viscosity enhancing agents, such as carbomer 940 (polyacrylic acid), carboxymethyl cellulose (CMC), dextran, hyaluronic acid, hydroxypropyl-guar (HP-guar), hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), polyvinylpyrrolidone and polyethylene glycol (PEG), which lubricate and increase their retention time in the eye (Jones et al., 2017). As mentioned, a relatively limited number of randomised controlled trials have compared individual artificial tear preparations with one another. Essa et al. (2018) conducted a randomised, single-masked crossover trial to compare difference artificial tear formulations. The test products provided similar improvements in symptoms and signs, however the osmolarity balanced drop

(TheraTears) performed better for ADDE and the liposomal spray (Tears Again) was more beneficial for EDE.

A recent multicentre randomised controlled trial compared the efficacy of a lipid and a non-lipid drop over the course of six months (Craig et al., 2021). Whilst both drops were found to be effective, only the lipid-containing drop produced increased tear lipid layer thickness with long-term use, and the effect was especially pronounced for participants with a deficient lipid layer at baseline. Interestingly, almost a third of participants were unresponsive to all the treatments, however this was apparent after 1 month, indicating that non-responders can be identified and moved onto alternative treatments after a 30-day trial.

A multicentre prospective crossover study compared liposomal sprays of different phospholipid concentrations, with respect to ocular comfort on a visual analogue scale (VAS) and non-invasive tear breakup time (Pult et al., 2021). The higher concentration formulation was found to be more effective, and was therefore recommended for use.

Further work to compare the efficacy of the wide range of artificial tear products with one another is warranted, in order to inform practitioners and patients choosing between the numerous options. For example, in a recent systematic review of hyaluronic acid-based artificial tears, Hynnekleiv et al. (2022) identified a lack of research evidence for the optimal frequency of instillation, and drop formulation. They recommended that researchers investigate concentration, drop frequency and molecular weight of hyaluronate, in patients with different severities and sub-types of DED.

1.8.1.6. Lid hygiene and warm compresses of various types

Traditionally many practitioners may have recommended the use of diluted baby shampoo for patients with marginal blepharitis, although a range of purpose-designed lid cleansing products have been available for a number of years. TheraTears SteriLid has been shown to be more effective than Johnson's baby shampoo in some metrics, with less adverse effects on conjunctival goblet cell function (Craig et al., 2017b). In another trial, Aryasit et al. (2020) found no significant difference in efficacy between Johnson's baby shampoo and OCuSOFT Lid Scrub Original Foaming Eyelid Cleanser. A randomised double-blinded crossover trial was conducted to examine whether dry heat or moist heat warm compresses were more effective at raising eyelid tissue temperature and blood flow (Leeungurasatien et al., 2020). This trial found no significant difference between the two types of warm compresses, suggesting both are suitable for lid warming.

A prospective trial comparing a chambered warm moist air device and warm towel treatment for MGD found that symptoms improved in both groups, however tear film stability improved only in the warm moist air device group, and tear lipid layer thickness increased by a greater extent with the device than with warm towel treatment (Matsumoto et al., 2006). A randomised controlled trial comparing Blephasteam, EyeGiene and warm towel treatment for MGD found that Blephasteam reduced dry eye symptoms more effectively than EyeGiene and warm towel treatment (Sim et al., 2014), however a later review pointed out flaws in this study, such as significant baseline differences between participant groups (Magno et al., 2022), hence limiting the reliability of these findings.

1.8.2. Step 2

1.8.2.1. Non-preserved ocular lubricants to minimise preservative-induced toxicity

Multidose topical eyedrops tend to contain preservatives such as benzalkonium chloride, chlorhexidine and polyaminopropyl biguanide to slow spoilation, prolong shelf-life and reduce the risk of infection during use. Unfortunately, preservatives used for this purpose are toxic to the ocular surface (Baudouin et al., 2010a). For this reason, there has been a move towards preservative-free and unit-dose formulations, due to the risk of toxic and allergic reactions, especially when frequent instillation is required (Jones et al., 2017). Newer preparations may contain less damaging preservatives such as polyquaternium, or 'vanishing' preservatives such as sodium perborate and Purite, or feature bottles which incorporate a one-way valve to prevent the entry of microorganisms (Kathuria et al., 2021). Preservative-free formulations are recommended, especially for dry eye sufferers or sensitive individuals (Gomes et al., 2017, Jones et al., 2017).

1.8.2.2. Tea tree oil treatment for Demodex

Demodex mites are very common human ectoparasites, which increasingly affect individuals with age. It is thought that Demodex infestation is an important risk factor for chronic blepharitis, which is a key reason for visits to eyecare practitioners (Tighe et al., 2013). Tea tree oil is a natural essential oil with various anti-infective and anti-inflammatory properties, and is effective for reducing the numbers of Demodex parasites in affected individuals (Jones et al., 2017), but is also toxic to the ocular surface, and can cause irritation and pain if used neat (Bron et al., 2017). It has been found that the most effective anti-demodectic component in tea tree oil is terpinen-4-ol, which is effective at concentrations of just 1% (Tighe et al., 2013), thus reducing the risk of adverse reactions. A Cochrane systematic review undertaken in 2020 found that the evidence for short-term tea tree oil treatment was weak, but recommended that diluted preparations are used, to avoid adverse reactions (Savla et al., 2020). An alternative approach is topical 1.0 %

Ivermectin (e.g. Soolantra cream), which is primarily used to treat rosacea and other skin conditions, but is also effective in Demodex blepharitis when applied nightly for three months (Smith et al., 2024).

1.8.2.3. Tear conservation

1.8.2.3.1. Punctal occlusion

Punctal occlusion is a well-established option for ADDE and has been the subject of clinical trials and systematic reviews. Ervin et al. (2019) state that most studies report positive results, but point out a shortfall of evidence and some common adverse effects, such as irritation, epiphora and plug loss. Several studies have compared punctal plugging with artificial tears (Qiu et al., 2013, Tsifetaki et al., 2003, Zhou and Yi, 2016), with punctal plugs being favourable with respect to symptoms, and tear film stability but not corneal staining.

A study comparing punctal plugging with topical ciclosporin and a combination of the two found that all three regimes produced improvements in Schirmer I test results and reduced artificial tear use in participants, whilst the combination therapy reduced artificial tear use still further. Punctal plugging alone failed to reduce rose bengal staining, but combination therapy was found to be effective at 3 and 6 months (Roberts et al., 2007). Unfortunately, the authors did not report on symptoms.

Punctal plugs have been compared with oral pilocarpine in a population with Sjögren's syndrome. In this study, oral pilocarpine performed better than punctal plugs, in terms of symptoms and rose bengal staining, however there was no significant difference with Schirmer I test results (Tsifetaki et al., 2003).

One study treated patients with either punctal plugs or botulinum toxin injected into the lower eyelid, and found that more patients in the botulinum group were satisfied with treatment than in the punctal plug group (Bukhari, 2014). It was also reported that a significant proportion of the punctal plug group suffered from adverse events, with some requiring plug removal. It seems clear that punctal plugging can be beneficial in some individuals, however treatment failure can occur due to adverse effects such as discomfort or plug loss.

1.8.2.3.2. Moisture chamber spectacles/goggles

The aim of moisture chamber spectacles is to produce a high humidity microclimate and reduce air circulation around the eyes, in order to reduce tear evaporation and conserve the aqueous tear layer. In a small prospective study involving 14 participants with dry eye, Ogawa et al. (2018) found that a new moisture chamber spectacle design was effective in reducing dry eye symptoms and signs induced by a simulated windy environment, produced using an electric fan.

The small number of participants involved in this study reduces the quality of evidence and the authors note several other shortcomings, therefore more studies examining the effects of moisture chamber spectacles on dry eye sufferers of different types and severities are required.

1.8.2.4. Overnight treatments

These include the use of viscous aqueous or oil-based gels or ointments for overnight use, and/or moisture chamber devices, such as those mentioned above, to reduce tear evaporation and desiccation of the ocular surface during sleep (Jones et al., 2017). Dry eye symptoms often vary throughout the course of the day, and can range from mild to severe at different times (Wolffsohn et al., 2017). For example, patients typically experience a shorter duration of clear vision between blinks and greater subjective blurring of vision in the evening, compared to earlier in the day (Walker et al., 2010). Some dry eye metrics, such as tear ferning grades, subjective discomfort and vision are also worse immediately after waking from sleep (Bitton et al., 2008). A number of manufacturers now produce viscous overnight gels paired with their artificial tear brands, which aim to provide 24hr symptomatic relief (Guillon and Shah, 2019), however more studies are required to compare the various products with each other.

1.8.2.5. In-office, physical heating and expression of the meibomian glands

Changes in meibomian glandular physiology, resulting in inspissated meibum can lead to gland blockage, a deficient or dysfunctional lipid layer and EDE (Magno et al., 2022). Patients can be offered in-office treatments if their condition is severe or not adequately controlled by self-treatment measures such as warm compresses. Such treatments include debridement-scaling and therapeutic meibomian gland expression (MGX) at the slit-lamp, and device-assisted methods such as LipiFlow, which combine heat and gland expression in an automated procedure (O'Neil et al., 2019).

Tixel (Novoxel, Netanya, Israel) is a thermomechanical device, which applies heat energy to the skin, via conduction from the points of pyramids imprinted into a titanium tip, which is heated to around 400 °C. Brief contact is made between the heated tip and the skin, causing dehydration of the stratum corneum and superficial epidermis and producing micropore channels, in a technique which is used for cosmetic improvements in periocular skin wrinkles (Elman et al., 2016). Tixel technology is now being applied to patients with evaporative dry eye, secondary to MGD. A prospective pilot study involving 40 participants with DED due to MGD receiving three treatments, two weeks apart, found significant improvements in symptoms and signs, and the treatment resulted in no serious adverse effects (Safir et al., 2022). The authors acknowledged that more evidence from randomised controlled double-masked clinical trials is needed.

1.8.2.6. In-office intense pulsed light therapy for MGD

Intense pulsed light therapy involves the use of a powerful flashlamp, which emits brief pulses of broadband light, which cause photocoagulation of superficial blood vessels by photothermolysis, whereby electromagnetic energy thermally damages haemoglobin and melanin selectively (Cote et al., 2020). It has therefore been extensively utilised in dermatology, for the treatment of conditions such as rosacea. Subsequently, patients being treated for rosacea, appeared to experience improvements in their dry eye symptoms, prompting further investigation (Toyos et al., 2015).

A randomised controlled trial comparing IPL therapy plus MGX to MGX alone found significantly greater improvements in subjective and objective measures of DED in the IPL group (Arita et al., 2019). A similar study comparing IPL plus MGX, with sham plus MGX also found IPL to be more effective than MGX alone (Liu et al., 2017), however a systematic review cited insufficient numbers of high quality trials, low certainty of evidence, statistical errors and risk of bias (Cote et al., 2020).

Xue et al. (2020) conducted a double-masked placebo-controlled trial, which enrolled 87 symptomatic dry eye patients and treated them with a course of four rounds of IPL or placebo in both eyes. Results from each group were compared to baseline at regular intervals over the course of 105 days. Significant improvements occurred in the treatment group for OSDI, SPEED and SANDE scores, meibomian gland capping and tear lipid layer thickness.

Zarei-Ghanavati et al. (2021) found that a combination of warm compresses, lid hygiene and artificial tears was equally effective with or without the addition of IPL, aside from small differences in ocular redness. A further systematic review and meta-analysis found that IPL combined with MGX may be an effective short-term treatment for MGD-related dry eye, and treatment effects diminished over time, with retreatment required after around 6 months (Leng et al., 2021).

1.8.2.7. Prescription drugs to manage DED

1.8.2.7.1. Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis

Reduction of the bacterial load of the eyelids for blepharitis treatment is usually achieved by means of lid hygiene, however some cases require the prescription of topical antibiotics such as fusidic acid, ofloxacin and azithromycin (Jones et al., 2017, Jackson, 2009). Combination drops containing antibiotic and corticosteroid anti-inflammatory drugs such as azithromycin and dexamethasone are also available.

Azithromycin has an interesting therapeutic profile, having both anti-infective and immunomodulatory properties. It is prescribed for a variety of conditions, including respiratory diseases, sexually transmitted infections, as well as ocular diseases (Juurlink, 2014). It is an efficacious anti-infective, with bacteriostatic effects on a wide range of gram-positive and gram-negative bacteria, atypical bacteria, and some protozoa (Bakheit et al., 2014, McMullan and Mostaghim, 2015). Uniquely, azithromycin has also been found to stimulate immortalised meibomian gland epithelial cells in culture (Liu et al., 2015).

1.8.2.7.2. Topical corticosteroid (limited duration)

The pathophysiology of DED involves a self-perpetuating vicious cycle of ocular surface inflammation and damage (Bron et al., 2017). Anti-inflammatory therapy, by way of topical corticosteroids, is a means of breaking this cycle of inflammatory and immune responses (Jones et al., 2017). Limiting the duration to a temporary course reduces the risk of steroid-induced complications such as raised IOP and cataract formation. A 2022 Cochrane review (Liu et al., 2022) included 22 RCTs involving topical corticosteroid DED therapy, with a total of 4169 participants from around the world. The findings suggested a small to moderate improvement in symptoms, compared to artificial tears, and probable improvements in corneal staining and tear breakup time, but not osmolarity. Topical corticosteroids can be prescribed before (Sheppard et al., 2014a), and in the early stages of, ciclosporin use – as this takes several months to achieve therapeutic efficacy.

1.8.2.7.3. Topical secretagogues

Another method of restoring homeostasis is to stimulate tear secretion, which may take the form of aqueous, mucin or lipid secretagogues, targeting a given insufficient layer within the tear film. Examples include diquafosol, which promotes the production of aqueous and mucin; rebamipide, which stimulates corneal epithelial cells to secrete mucin-like glycoproteins; and insulin-like growth factor-1 and topical testosterone, which have been shown to have lipid stimulating effects on meibomian gland cells in clinical trials (Jones et al., 2017).

A 2021 systematic review of biological tear substitutes and topical secretagogues resulted in the analysis of 39 randomised controlled trials, with a total of 3693 patients (Jongkhajornpong et al., 2021). The interventions examined included autologous and allogeneic serum, cord blood serum, autologous platelet lysate, platelet rich plasma, diquafosol, rebamipide, eledoisin, 3-isobutyl-1-methylxanthine, recombinant human nerve growth factor (rhNGF), and small molecule nerve growth factor peptidomimetic, as well as combination interventions: diquafosol plus artificial tears and rebamipide plus artificial tears. In this review, biological tear substitutes were found to produce better results than topical secretagogues, with risks of adverse events

being equal, however the authors noted low or very low certainty of evidence, by reason of study limitation, indirectness, inconsistency and imprecision.

1.8.2.7.4. Topical non-glucocorticoid immunomodulatory drugs (such as ciclosporin)

Ciclosporin has dual uses in dry eye, as it reduces inflammation by inhibiting calcineurin, and also acts as an aqueous secretagogue, which benefits patients with ADDE (Matsuda and Koyasu, 2000, Moawad et al., 2021). Sixty patients with Sjögren's syndrome took part in a randomised controlled trial with two study arms (Moawad et al., 2021). Patients in one arm were assigned tacrolimus (another immunomodulatory drug) 0.03% drops in one eye and placebo drops in the other, whilst those in the other study arm received ciclosporin 0.05% in one eye and placebo in the other. Outcome measures were OSDI symptom scores, artificial tear use, FBUT, ocular staining, Schirmer I and meibum quality and expressibility. In this study population, both drops were equally effective.

1.8.2.7.5. Topical LFA-1 antagonist drugs (such as lifitegrast)

Lifitegrast is a lymphocyte function-associated antigen antagonist drug with anti-inflammatory properties, which has been formulated into a topical ophthalmic drop for DED (Xiidra, Novartis) available in North America. The efficacy and safety of lifitegrast 5.0% has been shown by three phase III clinical trials, OPUS-1 (Sheppard et al., 2014b), OPUS-2 (Tauber et al., 2015) and OPUS-3 (Holland et al., 2017). In a pooled analysis of five randomised controlled trials, Nichols et al. (2019), examined data from a total of 2464 adults with DED and found that 5.0% lifitegrast ophthalmic solution was safe and well tolerated, with side effects such as irritation resolving within a few minutes of instillation.

1.8.2.7.6. Oral macrolide or tetracycline antibiotics

Macrolides such as azithromycin and tetracyclines such as doxycycline have immunomodulatory and anti-infective properties, which can be beneficial in the treatment of anterior marginal blepharitis and dry eye (Jones et al., 2017). Macrolide drugs are typically used as anti-infectives due to their bacteriostatic action (Dang et al., 2022), however azithromycin, which is available in topical and systemic forms, has shown promising results for the treatment of MGD and also mixed anterior-posterior blepharitis (Onghanseng et al., 2021). Oral azithromycin can be prescribed as a pulse or low dose therapy for ocular surface disease (Dang et al., 2022). Similarly, when prescribed at low doses of around 20–50 mg once or twice daily, oral doxycycline is a useful and cost-effective anti-inflammatory, with very low side effects (Dang et al., 2022). As mentioned in section1.8.2.7.1, azithromycin is a unique antibacterial agent, as it not only possesses anti-infective and immunomodulatory properties, but has also been found to stimulate meibomian gland epithelial cells, however a systematic review by Wladis et al. (2016)

found limited evidence of the usefulness of oral antibiotics against ocular surface disease related to meibomian gland dysfunction.

1.8.3. Step 3

1.8.3.1. Oral secretagogues

Oral pilocarpine or cevimeline, which are cholinergic agonists, can be prescribed to stimulate tear secretion in ADDE, for example in Sjögren's syndrome. Both can lead to systemic adverse effects such as excessive sweating, but cessation of treatment for this reason is less common with cevimeline than with pilocarpine (Noaiseh et al., 2014). As mentioned in section1.8.2.3.1, Tsifetaki et al. (2003) found that pilocarpine was more effective than punctal plugs in this population, when considering symptoms and rose bengal staining.

1.8.3.2. Autologous/allogeneic serum eye drops

Drops produced from one's own (autologous) or donor (allogeneic) blood serum, have therapeutic advantages compared to artificial tears. The premise being that tears contain a complex mix of biological constituents such as anti-infective enzymes, vitamins, fibronectin and growth factors (Willcox et al., 2017) that, unlike artificial tears, are present in blood products such as serum. These are thought to aid wound healing, which is important in more severe cases of ocular surface disease (Metheetrairut et al., 2022). As mentioned in section 1.8.2.7.3, a 2021 systematic review and meta-analysis of studies involving biological tear substitutes and topical secretagogues found that biological tear substitutes produced better results compared to other tear promotion eye drops in the 39 trials included (Jongkhajornpong et al., 2021).

1.8.3.3. Therapeutic contact lens options

1.8.3.3.1. Soft bandage lenses

The use of contact lenses in the treatment of DED may seem counterintuitive, given that they are themselves a risk factor for its development. Indeed, extra care must be exercised when introducing a contact lens to an already compromised ocular surface, because of the risk of microbial keratitis, and for this reason are often reserved for more severe cases. The purpose of bandage contact lenses is to provide a physical barrier between the eye and its surroundings, resulting in a protective and comfort-enhancing shield, which facilitates wound healing. Silicone hydrogel lenses for extended wear would typically be used for this purpose (Foulks et al., 2003).

1.8.3.3.2. Rigid scleral lenses

Rigid scleral lenses not only provide the ocular surface with relief from mechanical damage, but also create a reservoir of tears between the eye and the lens. One advantage of rigid sclerals is that the lens vaults across the whole cornea, avoiding contact between the cornea and the contact lens. This treatment modality has been found to improve visual acuity and symptoms,

and to be well tolerated in cases of moderate or severe DED, which is refractory to other treatments (Bavinger et al., 2015, Alipour et al., 2012).

1.8.4. Step 4

1.8.4.1. Topical corticosteroid for longer duration

As mentioned previously, topical corticosteroids are useful in the treatment of inflammation in DED, but should be employed judiciously, due to potential adverse drug reactions such as ocular hypertension, cataract, immunosuppression and inhibited wound healing. Increasing the duration of treatment can increase the risk of adverse reactions but may be necessitated in the treatment of more severe or recurrent cases.

1.8.4.2. Amniotic membrane grafts

Amniotic membranes may be considered in cases of persistent corneal epithelial defects, which can result in ulceration, scarring and consequent sight loss, in conditions such as Stevens-Johnson syndrome and ocular graft-versus-host disease (Chen et al., 2021). Although not yet fully understood, it is thought that the amniotic membrane provides a scaffold, which encourages epithelial migration and re-epithelialisation, as well as containing beneficial cytokines and growth factors (Dang et al., 2022). Other indications include ocular chemical burns, which are a true ophthalmic emergency. After initial first aid measures, such as repeated liberal irrigation to prevent further damage, amniotic membrane transplantation may be carried out in addition to conventional treatments, in order to promote wound healing, reduce pain and improve visual outcomes (Sharma et al., 2018). Furthermore, dehydrated amniotic membrane can be temporarily applied to the ocular surface, using a specialised bandage contact lens, and has been found to improve both symptoms and signs of DED (Travé-Huarte and Wolffsohn, 2024).

1.8.4.3. Surgical punctal occlusion

Punctal occlusion can be achieved by punctal plugging, which commonly leads to side effects such as irritation, epiphora and plug loss (Ervin et al., 2019). Surgical punctal occlusion may be considered in severe cases, where patients have failed to tolerate or retain punctal plugs, and is most often achieved using disposable handheld thermal cautery devices (Jones et al., 2017).

1.8.4.4. Other surgical approaches

1.8.4.4.1. Tarsorrhaphy

This is the surgical closure of the eyelids, in order to protect the ocular surface from the external environment and facilitate healing. It may be applied to severe ocular surface diseases such as neurotrophic ulcers, exposure keratopathy, post penetrating keratoplasty, severe dry eye, radiation keratopathy, ocular cicatricial pemphigoid and Stevens-Johnson syndrome (Bartlett and Bartlett, 2015).

1.8.4.4.2. Salivary gland transplantation

The lacrimal gland is responsible for secreting the majority of the aqueous component of the tears, therefore if absent or impaired, severe desiccation and ocular surface damage can occur. Saliva has been found to have a similar composition to tears (Geerling et al., 2008), with the obvious addition of salivary amylase, which is not thought to harm the ocular surface. Therefore, in the absence of a functioning lacrimal gland, this complex surgical approach may be considered to ameliorate the most severe sequelae of ADDE.

1.8.5. Predictive management

The ability to predict the most effective treatment for a given patient is beneficial for both patients and practitioners. One way to achieve this could be to assess and analyse tear film biomarkers. The scope of current techniques for tear collection and analysis are limited by technical challenges, cost, reproducibility, and stimulation of reflex tears – which induces changes in tear film characteristics (Fong et al., 2020). If these challenges can be overcome, this field may illuminate avenues of diagnosis and management closed to most practitioners.

Some studies have shown evidence of the potential of predictive management in DED, by illustrating that patients with certain characteristics found at baseline have responded differently to treatments tailored towards the presumed aetiology of their dry eye. For example, the randomised controlled trial conducted by Essa et al. (2018) indicated that an osmolarity balanced artificial tear drop performed better for patients with ADDE and a liposomal spray was more beneficial for patients with a thinner baseline lipid layer. Craig et al. (2021) also conducted a RCT comparing aqueous and lipid containing artificial tears, and found a greater increase in tear lipid layer thickness in participants with a deficient lipid layer at baseline.

A post-hoc analysis of participants in clinical trials of lifitegrast 5.0% eye drops showed that it was possible to predict which patients would have a greater likelihood of response to treatment (Holland et al., 2021). Responders tended to be those who had higher symptom and corneal staining scores at baseline, with this group being 1.70 to 2.11 times more likely to achieve improvement in signs and symptoms with therapy.

The DEWS II Management and Therapy Report commented on a lack of randomised clinical trials comparing the efficacy of artificial tear products to each other (Jones et al., 2017b). However, most studies assess a formulation against a placebo or vehicle, such as sodium hyaluronate or saline (Essa et al., 2018). It would be desirable to be able to predict which treatment would deliver maximal therapeutic benefit to a given patient, based upon high quality evidence and easily pre-determined patient-specific biomarkers. Therefore, studies comparing treatments

with one another, and relating this to baseline patient characteristics, are useful for practitioners deciding between the array of products on the market.

1.9. Thesis overview

1.9.1. Chapter breakdown

There has been a great deal of advancement in the field of DED research, and interest and awareness has also increased markedly since the publication of the TFOS DEWS II reports in 2017. However, there are still gaps in the literature, as highlighted in this chapter. For example, there are still relatively few RCTs comparing different artificial tear formulations to one another, as opposed to a placebo or vehicle (Jones et al., 2017, Pucker et al., 2016). The literature review outlined in this chapter evaluated the extent of currently available research data relevant to this thesis, and identified important knowledge gaps.

Accurate diagnosis and subclassification are prerequisites for effective management, and practitioners increasingly rely upon time and space-saving technology, with new diagnostic equipment being developed continually. When a new device comes to market, clinicians must be able to rely upon its accuracy and reliability. The Topcon MYAH has many useful applications, including diagnostic measures for DED and myopia management, and digital imaging capabilities, but no data exists comparing it to the already validated K5M (Best et al., 2012, Tian et al., 2016), and to established traditional techniques. Chapter 2 describes an international multicentre randomised clinical trial comparing the diagnostic output of the novel Topcon MYAH device, to that of the previously validated K5M, and to established traditional techniques.

With the array of artificial tear products continuing to grow, but relatively little evidence to show which are the most effective, practitioners and patients are faced with an increasingly daunting task when it comes to choosing the best treatment. In chapter 3, a systematic review was undertaken, examining RCTs of artificial tear formulations.

Recently, there has been growing interest in the role of molecular weight in artificial tear constituents. A recent systematic review of hyaluronic acid-based artificial tears (Hynnekleiv et al., 2022) identified a lack of research evidence for the optimal frequency of instillation and drop formulation, and recommended that researchers investigate the molecular weight of sodium hyaluronate in artificial tears. Chapter 4 involves a prospective randomised double-masked crossover trial, which adds to the understanding of molecular weight in artificial tears.

It is increasingly clear that the bulk of DED is evaporative in nature, mainly due to MGD. Lipid-containing artificial tears are helpful; however, it is important to address the root cause, by conducting treatments such as lid warming and gland expression. A novel MGD treatment with

reusable heated attachments has become available, but there have been no high quality RCTs to assess its efficacy. Chapter 5 describes an important randomised clinical trial into this novel treatment for MGD.

Publication of the TFOS DEWS II reports led to significant developments in the field of DED. As part of the follow-up work, Wolffsohn et al. (2021a) surveyed and analysed clinical practice patterns in 2018-19, to gauge how well the learnings from TFOS DEWS II were being adopted in practice. Chapter 6 updates and tracks changes in clinical practice patterns in DED management.

Chapter 7 summarises and interprets the findings of each study, identifies their limitations, and maps the future research directions indicated, in order to further build upon the work in this thesis.

1.9.2. Research questions investigated

- Chapter 2: Accuracy of a new multifunctional diagnostic device compared to previously validated means of measuring DED metrics, such as NIBUT
- Chapter 3: Relative efficacy of specific artificial tear formulations, compared to one another, in improving the symptoms and signs of DED
- Chapter 4: Influence of the molecular weight of sodium hyaluronate in artificial tears, on the symptomology and ocular surface signs of patients with DED
- Chapter 5: Efficacy of the novel MGrx device, compared to traditional debridement and expression, for the treatment of MGD and EDE
- Chapter 6:
    - A. Comparison of clinical practice patterns in the management of DED between different territories around the world
    - B. Comparison of current and previous practice patterns, to identify and track any changes in recent years

1.9.3. Overall thesis aims

DED results in a substantial burden, which is likely to increase, due to aging populations and environmental/lifestyle factors, such as increasing VDU use. The appropriate management of DED has a far-reaching impact, yet adequate management of symptoms and signs remains challenging for practitioners and their patients. The overall aim of this thesis was to expand the research evidence-base, and translate it into patient care.

2. Evaluation of the dry eye capabilities of a new multifunctional diagnostic device

The work in this chapter relates to an international multicentre clinical study, for which the thesis author was the UK investigator, and conducted all data collection from all UK participants. Data collection at the Centre for Ocular Research & Education, Waterloo, and New Zealand National Eye Centre, Auckland, was conducted by co-investigators. The author also conducted all image processing and analysis of objective meibomian gland loss and objective corneal staining, using images obtained from two different diagnostic devices, at all three study sites in the UK, Canada and New Zealand. Image processing and analysis for other measures, such as tear breakup time and tear meniscus height were conducted by co-investigators.

2.1. Introduction

Optometric practice increasingly relies upon a growing suite of diagnostic equipment, for applications such as digital imaging and biometric measurements such as autorefraction and keratometry. Practitioners with an interest in the diagnosis and management of dry eye now have several multifunctional devices to choose from, including the Keratograph 5M (K5M) (Oculus, Optikgeräte, Wetzlar, Germany), which has previously been clinically validated (Tian et al., 2016, Best et al., 2012). Recently, a new multifunctional diagnostic instrument was developed; the MYAH (Figure 2.1; Topcon Healthcare, Visia Imaging, San Giovanni Valdarno, Italy), which has many useful applications, including diagnostic measures for DED and myopia control, and digital imaging capabilities. Like the K5M, the MYAH offers a small footprint, and time and labour-saving functions, such as automated non-invasive tear breakup time measurement.

The MYAH device has some unique selling points, as it is marketed as an all-in-one device for myopia management, and DED, with features including biometry for tracking myopia progression, as well as a suite of dry eye diagnostics (Topcon Healthcare, 2025). Full details of the MYAH device can be found on the Topcon website: www.topconhealthcare.eu. When investing in new practice equipment, it is critical to be able to rely upon the accuracy of its data output and usability of its functions. Hence, the purpose of this study was to compare the MYAH to the already validated K5M, and to established traditional techniques.

Figure 2.1. The Topcon MYAH, left, with a screenshot of the meibography manual markup function, right.

2.2. Objectives

The objective of the study was to compare the dry eye diagnostic outputs of the MYAH device to those of the Oculus K5M, and to other commonly used assessment techniques.

2.3. Outcome variables

- Non-invasive tear breakup time as determined from automated analysis by the MYAH and K5M devices (primary outcome variable).
- Non-invasive tear breakup time from subjective measurements taken using live viewing of the video feed, for K5M only.
- Tear meniscus height, using the calliper tools of the MYAH and K5M at time of image capture, and subsequent analysis.
- Corneal fluorescein staining with the MYAH and K5M, and subsequent image grading using the Oxford scale.
- Meibomian gland imaging of the upper and lower lids, including manual grading of the images acquired with the MYAH and K5M. In addition, percentage gland loss was analysed using the semi-automated feature of the MYAH, and also using a third-party software for both images acquired with the MYAH and the K5M.
- Conjunctival fluorescein staining.
- Meibomian gland expressability, assessed using the Meibomian Gland Evaluator (Tear Science, Johnson and Johnson Vision, CA, USA) and graded using the meibomian gland secretion score (range 0-45).

All outcome variables were analysed for the right eye only, unless otherwise stated.

2.4. Materials and methods

Ethical clearance was obtained through the associated institutional review boards at each of the three study sites, prior to commencement of the study (REC ID: 1820). Informed consent was obtained from all participants prior to enrolment in the study and prior to any study data collection. Participant eligibility was determined at a screening visit according to the inclusion and exclusion criteria.

2.4.1. Study design

2.4.1.1. Overall design

This was a prospective, observational, device order randomised, multicentre study that involved 150 participants across three study sites. Each site enrolled 50 study participants, in a ratio of up to 10 asymptomatic and at least 40 symptomatic participants.

The study included two study visits, a screening/baseline visit (V1) that was attended by all participants, and a second visit (V2) for a subset of thirty eligible participants (10 per site) during which the repeatability of a number of tests was assessed.

2.4.1.2. Randomisation

The order of assessments with the MYAH and K5M was randomised using pairwise randomisation, with the order of the MYAH and K5M being randomised for each pair of study participants, i.e. for each pair, one participant started with the MYAH and one with the K5M.

2.4.2. Participants

Because no previous data on NIBUT with the MYAH instrument were available, the sample size calculation was based on previously reported data on NIBUT assessments obtained with two different devices, the Oculus K5M, in comparison to the Tearscope (Keeler, Windsor, UK) (Wolffsohn et al., 2017). Using repeated measures analysis of variance (ANOVA) with two groups (symptomatic & asymptomatic) and two instruments, power of 0.80, α=0.95, a variance of 0.8 and error in variance of 15, it was determined that a total sample size of 150 participants was required to complete the study.

Study participants were recruited from each respective study site's research participant databases, University staff and student populations, the University eye clinics, local optometric practices, and via advertising approved by the institutional research ethics boards. Informed consent was obtained for all participants prior to their enrolment in the study. Participants were only considered as enrolled in the study and assigned a study identification code after they had signed the informed consent document.

The first thirty of the 150 eligible participants were invited for a second visit (V2; n=10 per site) during which a subset of measurements was repeated to assess repeatability compared to the results from visit 1.

2.4.2.1. Eligibility criteria

A person was eligible for inclusion in the study if they:

1. Were at least 18 years of age and had full legal capacity to volunteer
2. Had read and signed an information consent letter
3. Were willing and able to follow instructions and maintain the appointment schedule

A person was excluded from the study if they:

1. Participated in any concurrent clinical or research study
2. Wore contact lenses in either eye within 48 hours, or were not willing to refrain from contact lens wear until completing the study
3. Had any known active ocular disease and/or infection
4. Used topical ocular medications, including rewetting drops or artificial tears, that might have interfered with the study outcomes, or were deemed to be contraindicated for participation, within 3 hours of the study visit
5. Had a systemic condition or disease considered unstable by the investigator
6. Used any systemic medications, topical medications, vitamins or supplements where a stable dosing regimen had not been established or which may have had an impact on the outcome variables; including but not limited to antihistamines, antimuscarinics, beta-blocking agents, etc. Dosing was considered to not be stable if a participant started, stopped, or changed dose and/or drug within 30 days of screening visit, or if a participant anticipated starting, ending or changing a regimen during the study if they also took part in the repeatability visit. Medications which were taken on an "as required" basis, e.g. paracetamol, were acceptable
7. Had a known sensitivity to a diagnostic pharmaceutical, e.g. sodium fluorescein, used in the study

2.4.3. Group assignment

At the screening visit, participants were assigned to the asymptomatic or symptomatic group based on their symptom score from the Ocular Surface Disease Index questionnaire (Schiffman et al., 2000) only, according to the following categorisation based on the recommendations of the TFOS DEWS II Diagnostic Methodology report (Wolffsohn et al., 2017):

- Asymptomatic Group: OSDI <13
- Symptomatic Group: OSDI ≥13

The homeostatic markers that have been recommended as tests for dry eye diagnosis (Wolffsohn et al., 2017) were not included in the symptom group assignment at visit 1, when confirming eligibility for this study; group assignment to the asymptomatic and symptomatic groups was solely based on a participant's OSDI score, so that the intended approximate 4:1 ratio of

symptomatic to asymptomatic participants at each site could be reached. Hence, 150 eligible participants, underwent dry eye testing procedures at each study site.

The diagnostic criteria that were established as part of the TFOS DEWS II Diagnostic Methodology report (Wolffsohn et al., 2017; Figure 1.3) were then used when evaluating whether a participant met any of the criteria for the diagnosis of dry eye, during post-analysis.

2.4.4. Study visits

This study had a total of one or two study visits, including a screening/baseline visit (V1) that was attended by all 150 participants, and a second visit (V2) for a subset of 30 eligible participants (n=10 per site) to evaluate the repeatability of some of the dry eye assessments that were obtained with the MYAH and the K5M. A summary of the visit schedule is shown in Table 2.1.

Table 2.1. Summary of visit schedule.

Visit code	Visit	Approximate Duration	Day	Total number of participants
1	Screening & Baseline	2 hours	0	150 (50/site)
2	Repeatability	1.5 hours	>24hr and ≤7 days after V1; same time of day ±2h	Subset of 30/150 (10/site)

To minimise the risk of successive testing impacting the results at the study visits, there was a mandated order of tests and wait periods between some assessments, to allow the tear film to return to baseline status. Details for visits 1 and 2 are described below.

2.4.4.1. Screening and baseline visit (V1)

The study investigator determined participant eligibility using the inclusion and exclusion criteria during the screening portion of visit 1. Ineligible participants were discontinued as screen failures from the study. Those participants who met all eligibility criteria continued to the baseline portion of the visit, where they were randomised to the order of device used for each assessment. Once randomised, dry eye measurements were performed, using both the MYAH and K5M in randomised order, and other dry eye measurements using other standard clinical assessments.

2.4.4.2. Repeatability visit (V2)

The first thirty participants (n=30; 10 per site) returned to each study site to undergo certain assessments that were used to assess repeatability compared to the results from visit 1. This

visit was scheduled between >24 hours and ≤7 days after the screening visit, at approximately the same time of day (±2 hours).

Following the same procedures as for visit 1, the assessments were conducted for the right eye only (unless otherwise stated) and were ordered from least to most invasive, to minimise any order effect. The order of devices used was the same as in visit 1.

2.4.5. Study procedures

The primary focus of this study was the comparison of those dry eye metrics that could be obtained with both devices. To allow for the assessment of all the recommended dry eye metrics, as per the TFOS DEWS II Diagnostic Methodology report (Wolffsohn et al., 2017), all dry eye metrics that could not be collected with both devices were obtained using traditional methods or, if the device included this feature, with just the MYAH or just the K5M.

At both study visits, measurements for the individual dry eye metrics were performed in the order from least to most invasive, for the right eye only, except for visual acuity and slit-lamp biomicroscopy. Unless otherwise noted, measurements for each metric were completed subjectively first, to prevent observer bias, before the same measurement was taken with each device as applicable. To minimise participant and investigator movement, while keeping a counter-balanced sequence between devices, assessments with the MYAH and K5M were performed according to the order of procedures shown in Table 2.2. Fluorescein live-grading was performed only after fluorescein imaging – which was not graded at the visit – so that images could be acquired after the same, single application of fluorescein.

After all the measurements for a metric, or closely related metrics, had been completed, i.e. subjective and with the two devices, measurements for the next metric were started (Table 2.2). At the repeatability visit, the dry eye metrics were assessed in the same instrument order as at visit 1.

Table 2.2. Order of procedures for MYAH and K5M.

Measurement	**First**	**Second**
NIBUT (MYAH & K5M; subjective & automated)	Device B	Device A
Fluorescein: corneal staining image capture (MYAH & K5M)	Device A	Device B
Subjective staining grade (fluorescein at slit-lamp)	N/A (slit-lamp)	
Meibomian gland expressibility (at slit-lamp)	N/A (slit-lamp)	
Meibomian gland imaging (MYAH & K5M)	Device B	Device A
Biomicroscopy of cornea & conjunctiva (at slit-lamp)	N/A (slit-lamp)	

Device A and B as per randomisation, starting with Device A for TMH. If MYAH was randomised to be Device A, the K5M was Device B, and vice versa.

2.4.5.1. Non-invasive tear breakup time

At both devices, measurements were performed by asking the participants to blink and then to refrain from blinking for as long as they were able, while the automated detection feature of each device detected any areas of tear film breakup that occurred between the start of the video and a device-initiated end of the video, e.g. due to a very unstable tear film or if a participant blinked.

In addition, a subjective (visual) measurement of NIBUT was performed during the automated NIBUT measurements at the K5M. During each of the three automated NIBUT measurements, the study investigators observed the video feed from the K5M monitor, to subjectively assess the first breakup time using a stopwatch. To prevent bias, the display settings were set so that no device-detected breakups were displayed during this subjective assessment. The subjective measurement of NIBUT was not considered to be a primary outcome variable, but the results from these subjective assessments are included for completeness and to facilitate comparison between all NIBUT data.

In total, the following four NIBUT outcome variables were collected:

i. MYAH: automated time until first breakup
ii. MYAH: automated time until 5% area breakup
iii. K5M: automated time until first breakup
iv. Subjective: time until first breakup (using stopwatch; live view of K5M video feed)

In all four measurement procedures, three measurements were collected for the right eye and the mean calculated (Table 2.6).

2.4.5.2. Tear meniscus height

Tear meniscus height measurements were performed at the MYAH and K5M (as per randomisation order) by taking an image of the inferior tear meniscus of the right eye. TMH measurements were performed both during the study visit at the time of image capture as well as after study completion as part of the post analysis. TMH measurements were collected at both visits.

During the study visit, TMH was measured using each device's digital calliper tool. Three calliper measurements were taken from a single image at the lower lid margin, within ±1 mm of the pupil centre. The mean of the three calliper measurements was used for data analysis. The calliper tool was accessed via the touchscreen for the MYAH, and using a mouse for the K5M.

In order to evaluate whether the use of the touch screen procedure impacted TMH measurements for the MYAH, a separate analysis of TMH was performed, by analysing the images from all three sites using a physical mouse, rather than the device's touch screen. For completeness, images obtained with the K5M were also analysed for a second time.

2.4.5.3. Corneal fluorescein staining

Corneal fluorescein staining was assessed by grading images captured with the K5M and MYAH as well as by live grading at the slit-lamp biomicroscope during visits. After instillation of sodium fluorescein to the superior bulbar conjunctiva, an image of the right eye of each participant was obtained with the fluorescein image capture feature of the MYAH and the K5M. After image capture at the MYAH and K5M had been completed, the participant's level of staining was live graded during the study visit at the slit-lamp biomicroscope, while viewing with blue light through a yellow barrier filter. Grades were assigned in each of five zones (nasal, temporal, superior, inferior and central) by comparing the participant's eye to the six grade panels of the Oxford grading scheme (Bron et al., 2003) (Figure 2.2) and assigning the grade that most closely corresponded to the depicted severity level. Thus, a total of five zonal grades were obtained, which were then averaged for analysis.

The staining images captured with the MYAH and K5M at all sites were reviewed and graded in the same way, by the author. This process helped to reduce variability and maximise repeatability of the grading of the images from each device.

2.4.5.4. Meibomian gland dropout

Imaging of the meibomian glands for the purpose of assessing meibomian gland dropout was performed at both visits. The upper and lower everted eyelids were imaged in the right eye only, with the MYAH and K5M devices, using infra-red light. This process resulted in a total of 720

images obtained across all three study sites: V1 = 150 each for upper and lower lid with the two devices (total of 600); V2 = 30 each for upper and lower lid with the two devices (total of 120). These images were analysed in two different ways after the study:

i. Subjective grading of gland loss – Pult scale
ii. Objective image analysis software – percentage loss

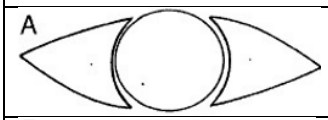
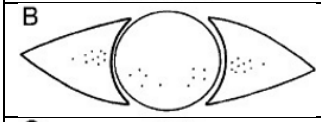
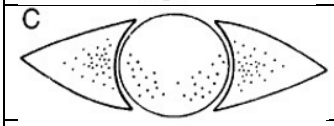
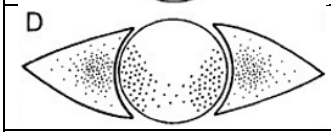
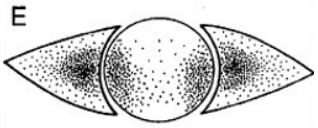
Panel	Grade	Criteria	Dot Count	Log	Verbal Descriptor
	0	Equal to or less than panel A	1	0	Absent
	1	Equal to or less than panel B; greater than A	10	1.0	Minimal
	II	Equal to or less than panel C; greater than B	32	1.5	Mild
	III	Equal to or less than panel D; greater than C	100	2.0	Moderate
	IV	Equal to or less than panel E; greater than D	316	2.5	Marked
>E	V	Greater than panel E	>316	>2.5	Severe

Figure 2.2. Oxford grading scheme, modified from Bron et al. (2003).

2.4.5.4.1. Subjective grades

Subjective grading of all 720 images was performed by a single, masked, expert observer, to reduce variability and maximise repeatability during this subjective assessment. The scale used was Pult's Meiboscale (Pult and Riede-Pult, 2012) (Figure 2.3) which consists of five grades from 0 to 4, with a grade 0 corresponding to no dropout. Grades 1 to 4 each correspond to a specified range of percentage dropout in 25% steps.

2.4.5.4.2. Objective image analysis

The digital meibography images were also analysed objectively by the author, to quantify the percentage gland dropout. A third-party software (Advanced Ophthalmic Systems (AOS), Croydon, UK) was used to analyse the meibography images obtained with both the K5M and

MYAH (n=600 at V1 and 120 at V2; 720 images in total), to allow for an objective analysis comparison between images obtained with each device. In addition, the author analysed the MYAH images after study completion, using the MYAH's built-in semi-automated meibography image analysis feature (Figure 2.1), which requires the user to manually mark up each image, before the MYAH calculates the drop-out percentage (n= 300 at V1 and 60 at V2; 360 images in total).

2.4.6. Data analysis

The majority of analyses in this report are based on the full study cohort data of all 150 participants, including comparisons between the two devices, with descriptive statistics used for demographic data e.g. age and sex. Data that were collected at both visits, to evaluate the repeatability of the data from the subset of 30 participants who attended both study visits, are presented to provide information on the repeatability of the measurements, using Wilcoxon Matched Pairs (WMP) analyses.

The following measurements were collected with the MYAH and K5M and compared between devices:

a. NIBUT – during the visit
b. TMH – during visits at time of image capture, and during post analysis
c. Corneal fluorescein staining – during the visit at the slit-lamp, and during post analysis
d. Meibomian gland area loss for upper and lower lid – post analysis

Additionally, the homeostatic markers of dry eye that were collected with both devices were compared to evaluate whether each participant's diagnosis would have matched between the two devices.

Testing for normality revealed that data for several outcome variables were not normally distributed, therefore non-parametric statistical analysis tests were used throughout for consistency.

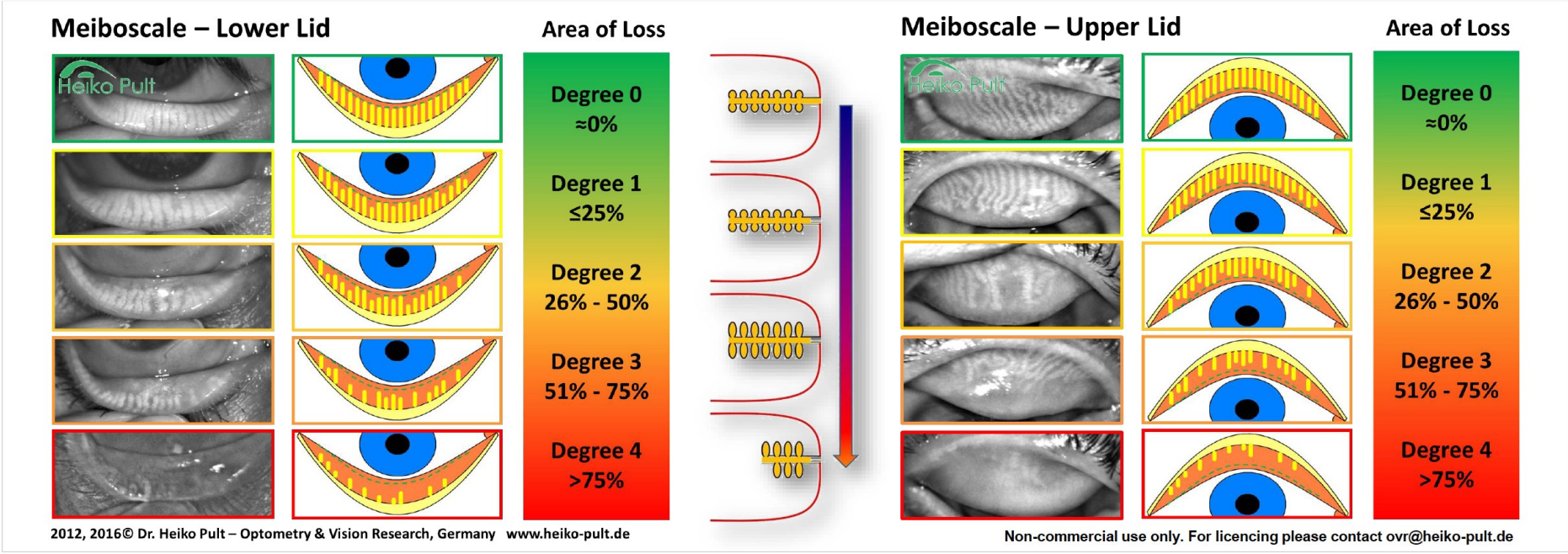


Figure 2.3. Pult Meiboscale (Pult and Riede-Pult, 2012), used with permission.

2.5. Results

2.5.1. Participants

2.5.1.1. Demographics

One hundred and fifty participants were enrolled in the study (107 female, 43 male). The mean age of all participants was 32.7 ± 15 years (median 26 years, range 18 to 78 years). Table 2.3 summarises the participant characteristics; the top section shows the distribution for sex and by age for all 150 participants, and the bottom section shows the same distribution, but only for those 30 participants who attended both study visits.

Table 2.3. Participant demographics.

	SEX			**AGE**
V1 (full cohort)	**Female**	**Male**	**Total**	Mean ± SD Median (range)
Canada	36	14	**50**	34 ± 14 27.5 (19 – 69)
New Zealand	36	14	**50**	37 ± 17 29.5 (19 – 78)
United Kingdom	35	15	**50**	27 ± 12 21 (18 – 65)
TOTAL	**107**	**43**	**150**	**33 ± 15** **26 (18 – 78)**
V1&V2 subset	**Female**	**Male**	**Total**	Mean ± SD Median (range)
Canada	7	3	**10**	40 ± 14 39 (21 – 63)
New Zealand	8	2	**10**	27 ± 9 25 (20 – 52)
United Kingdon	8	2	**10**	30 ± 12 27 (20 – 53)
TOTAL	**23**	**7**	**30**	**33 ± 13** **28 (20 – 63)**

2.5.1.2. OSDI scores

The OSDI questionnaire was used to categorise participants into those who were symptomatic of dry eye (SYMP) and those who were not (ASYMP), based purely on their symptoms. Using this categorisation, the study included 122 participants with OSDI scores of ≥13 (SYMP) and 28 participants with OSDI scores of ≤12 (ASYMP; Table 2.4), with none of the study sites enrolling more than 10 asymptomatic participants, hence meeting the requirements of the study protocol.

There was no difference in age between the two groups (p>0.05; Mann-Whitney U test), with median ages (range) of 26.5 (18 – 78) and 26 (19 – 63) years for the symptomatic and asymptomatic group, respectively.

Table 2.4. Descriptive statistics - OSDI scores & age by group.

OSDI scores (V1) Mean ± SD Median (range)	**All participants** (n=150)	**SYMP** (OSDI ≥13, n=122)	**ASYMP** (OSDI <13; n=28)
Canada SYMP: n=40; ASYMP: n=10	27.4 ± 18.2 27 (0 – 83)	34.0 ± 14.6 29.5 (17 – 83)	2.2 ± 3.1 1 (0 – 9)
New Zealand SYMP: n=42; ASYMP: n=8	26.9 ± 17.6 27 (0 – 71)	31.3 ± 15.7 29.0 (13 – 71)	3.9 ± 3.1 4 (0 – 9)
United Kingdom SYMP: n=40; ASYMP: n=10	28.5 ± 20.5 25 (0 – 85)	34.7 ± 17.9 30 (14 – 85)	2.6 ± 2.8 2 (0 – 7)
TOTAL	27.6 ± 18.7 26 (0 – 85)	33.3 ± 16.0 29 (13 – 85)	2.8 ± 3.0 2 (0 – 9)
Median age (range), years	26 (18 – 78)	26. 5 (18 – 78)	26.0 (19 – 63)

SYMP = Symptomatic of dry eye; ASYMP = Asymptomatic of dry eye.

OSDI scores were also collected at the repeatability visit. There was a significant difference in numerical OSDI scores between visit 1 and 2 (Wilcoxon Matched Pairs test; p=0.04). However, despite this statistical difference, because all participants still fell into the same symptom category at visit 2 that they had been associated with at visit 1, this difference between median values of 1 unit was inconsequential for the symptom groups in the study.

Based on these data, the repeatability analysis in all sections below is composed of 25 symptomatic participants with OSDI scores of ≥13 and 5 asymptomatic participants with OSDI scores of ≤12, (n=30 participants) (Table 2.5).

Table 2.5. OSDI repeatability – comparison between V1 and V2 (n=30).

	OSDI score Mean ± SD Median (range)	**# participants with OSDI score ≥13** **SYMP**	**# participants with OSDI score ≤12** **ASYMP**
Baseline V1 *(n=30)*	25.6 ± 16.2 25 (0 – 66)	25	5
Repeatability V2 *(n=30)*	23.2 ± 14.6 24 (0 – 65)	25	5
p value (WMP)	**0.04**		

WMP = Wilcoxon Matched Pairs test.

2.5.2. Comparisons MYAH VS K5M

2.5.2.1. Non-invasive breakup time

Descriptive statistics for all four NIBUT measurement procedures are shown in Table 2.6 and compared in Table 2.7.

Table 2.6. NIBUT - Descriptive statistics for V1 (n=150).

NIBUT (seconds) Mean ± SD Median (range)	**Subjective** **First breakup**	**K5M** **First breakup**	**MYAH** **First breakup**	**MYAH** **5% area**
All participants *(n=150)*	10.32 ± 5.93 8.65 (1.44 – 27.24)	9.68 ± 5.34 8.54 (2.42 – 24.92)	3.49 ± 3.13 2.35 (0.75 – 21.80)	10.15 ± 7.23 8.04 (1.37 – 30.17)
SYMP *(n=122)*	9.40 ± 5.19 8.32 (1.44 – 25.23)	9.20 ± 5.25 7.83 (2.44 – 24.92)	3.39 ± 2.81 2.43 (0.75 – 14.90)	9.44 ± 6.77 7.47 (1.37 – 30.17)
ASYMP *(n=28)*	14.31 ± 7.29 14.58 (3.00 – 27.24)	11.80 ± 5.30 12.00 (2.42 – 21.31)	3.49 ± 4.28 2.03 (1.20 – 21.80)	13.26 ± 8.41 12.24 (1.90 – 29.87)

Table 2.7. Comparison of NIBUT data across acquisition methods (V1 only; n=150).

Wilcoxon Matched Pairs (significance)	Subj First breakup	K5M First breakup	MYAH First breakup	MYAH 5% breakup
Subj First breakup		**0.023**	**<0.001**	0.89
K5M First breakup	**0.023**		**<0.001**	0.49
MYAH First breakup	**<0.001**	**<0.001**		**<0.001**
MYAH 5% breakup	0.89	0.49	**<0.001**	

Statistically significant differences were found, depending on the specific NIBUT metric compared. The automated detection of first breakup for the MYAH was found to be significantly shorter than all other methods (all $p<0.001$). There was no difference between the MYAH's 5% NIBUT measurement when compared to the first breakup time measured with the K5M and the subjective stopwatch method (Table 2.7 and Figure 2.4).

There were significant differences in NIBUT between symptomatic and asymptomatic groups for MYAH 5% area, K5M first breakup and subjective first breakup (all $p \leq 0.02$; Mann-Whitney-U test); however, there was no difference between symptom groups based on the MYAH first breakup data ($p > 0.05$; Mann-Whitney-U test).

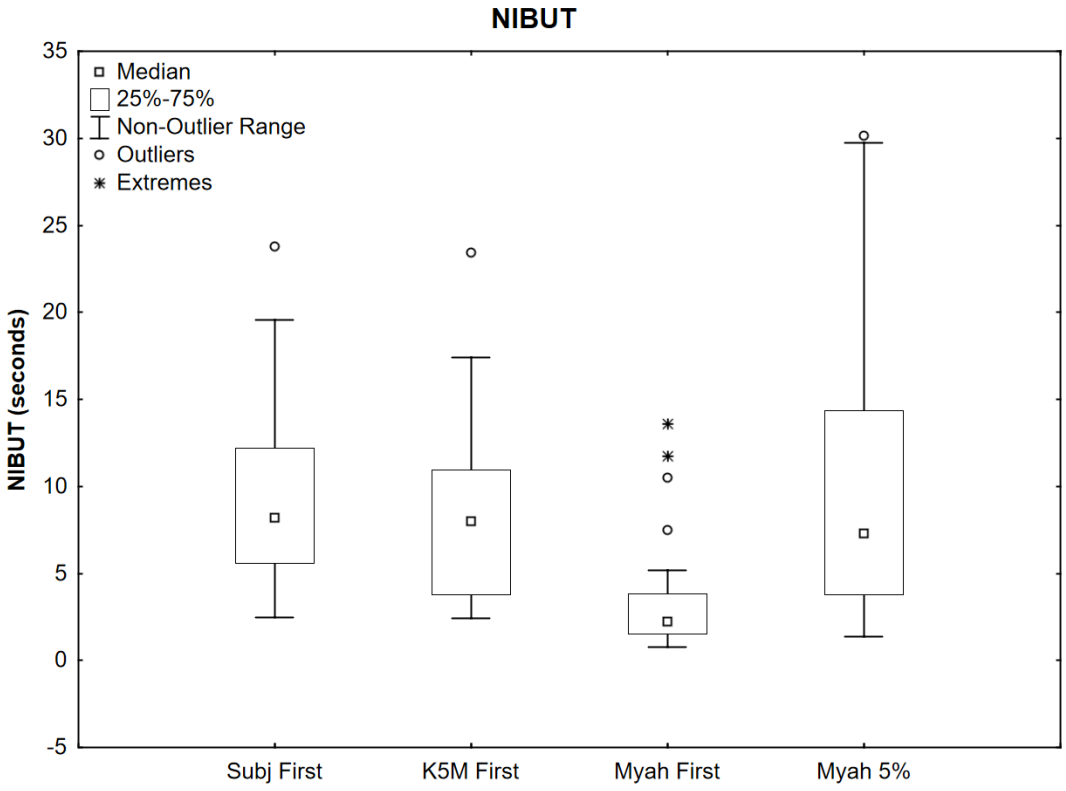


Figure 2.4. Box plots for NIBUT data across acquisition methods. Time to first breakup with the MYAH was significantly shorter than for the other three NIBUT assessments.

The difference between the MYAH first breakup data compared to all other acquisition methods is also apparent in the Bland-Altman Limit of Agreement plots (Figure 2.5), which show a clear bias towards shorter times for the first breakup time with the MYAH, which increase as the average tear breakup time increases; as apparent from the angled pattern of the dots that seem to have a linear boundary.

When assessing repeatability within the subset of 30 participants who attended both visits, there was a significantly shorter NIBUT for the MYAH 5% area breakup time at visit 2 compared to visit 1. There was no difference between visits for the other assessment methods (Table 2.8).

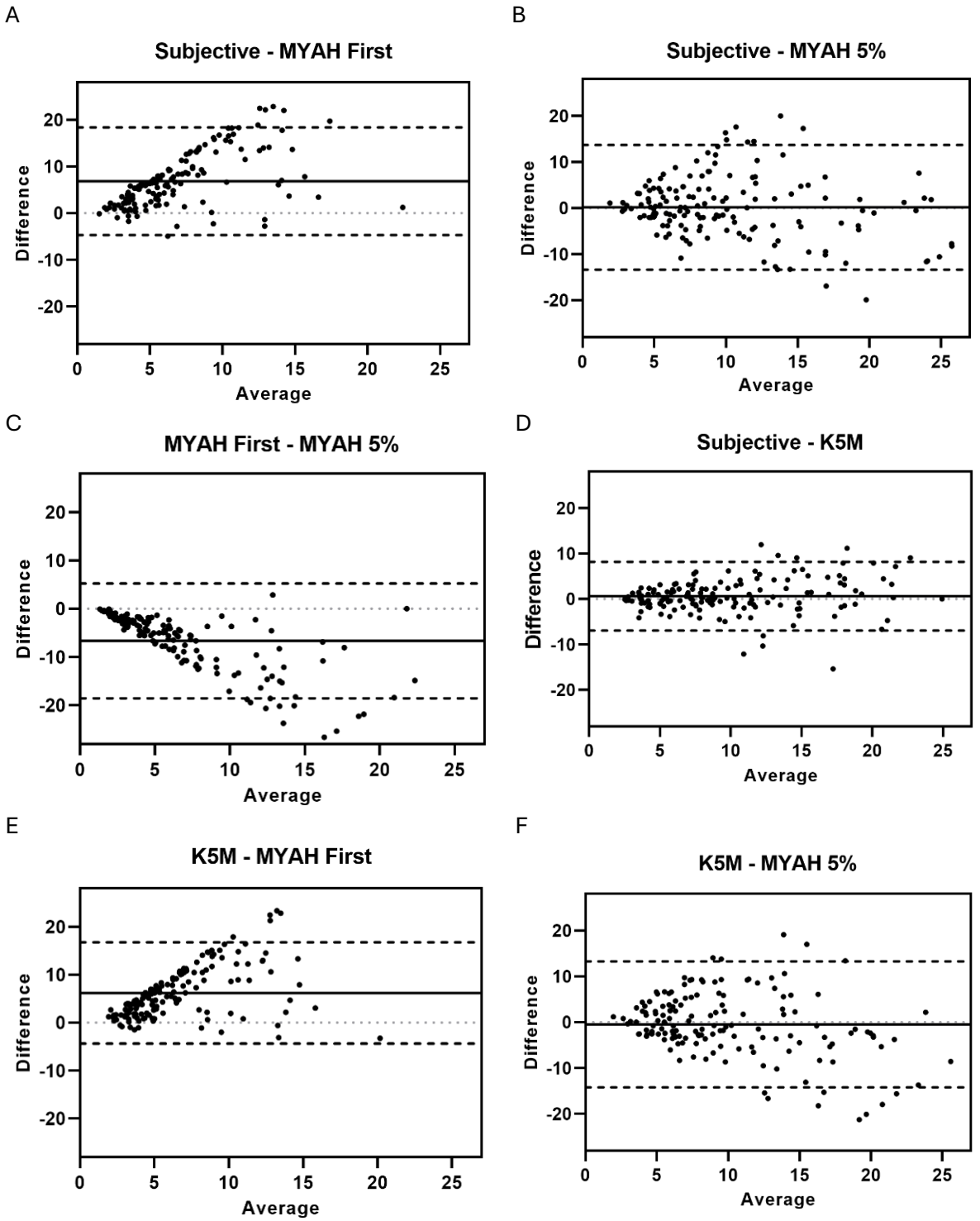


Figure 2.5. Bland-Altman Limit of Agreement plots: the full line represents the mean of the differences between the two measurement methods; the dashed lines represent the upper and lower limit of agreement for each comparison. The dotted grey line corresponds to zero (i.e. no difference) between each pair of measurements. A: comparison between subjective and MYAH first NIBUT. B: comparison between subjective and MYAH 5% NIBUT. C: comparison between MYAH first and MYAH 5% NIBUT. D: comparison between subjective and K5M NIBUT. E: comparison between K5M and MYAH first NIBUT. F: comparison between K5M and MYAH 5% NIBUT.

Table 2.8. NIBUT repeatability – comparison between V1 and V2 (n=30).

NIBUT	Subjective First breakup	K5M First breakup	MYAH First breakup	MYAH 5% area
Baseline V1 *(n=30)*	9.43 ± 5.26 8.21 (2.47 – 23.80)	8.49 ± 5.20 7.99 (2.42 – 23.43)	3.46 ± 3.23 2.22 (0.75 – 13.60)	10.21 ± 8.29 7.30 (1.37 – 30.17)
Repeatability V2 *(n=30)*	9.04 ± 4.57 7.66 (3.50 – 20.58)	7.88 ± 4.27 6.80 (2.72 – 21.47)	2.46 ± 2.45 1.88 (1.20 – 14.60)	8.13 ± 6.71 5.92 (1.40 – 28.17)
p value (WMP)	0.53	0.77	0.07	**0.04**

2.5.2.2. Tear meniscus height

TMH was significantly greater when measured with the K5M than with the MYAH, for the measurement at the time of image capture during the study visit (difference between the means: 0.04mm) and for the post-study image analysis (difference between the means: 0.06mm) (Table 2.9 and Figure 2.6). Comparing TMH measured during the visit to the post-analysis measurements for each device, showed statistically significant differences of 0.01mm for both MYAH and K5M (Table 2.9).

Table 2.9. TMH measurements (mm) for Baseline (V1) data (n=150).

TMH at V1 (*n=150)* *Mean ± SD* *Median (range)*	**At time of image capture**	**Post analysis**	**p value** (WMP)
MYAH *(mm)*	0.23 ± 0.10 0.21 (0.05 – 0.78)	0.22 ± 0.10 0.20 (0.09 – 0.76)	**p=0.01**
K5M *(mm)*	0.27 ± 0.13 0.24 (0.09 – 1.15)	0.28 ± 0.13 0.25 (0.13 – 1.28)	**p<0.001**
p value (WMP)	**p<0.001**	**p<0.001**	

There was no difference in TMH between symptomatic and asymptomatic group for the MYAH or the K5M. There was also no difference between the TMH as measured during the study visit compared to the post-study measurement (Table 2.10; all p>0.05).

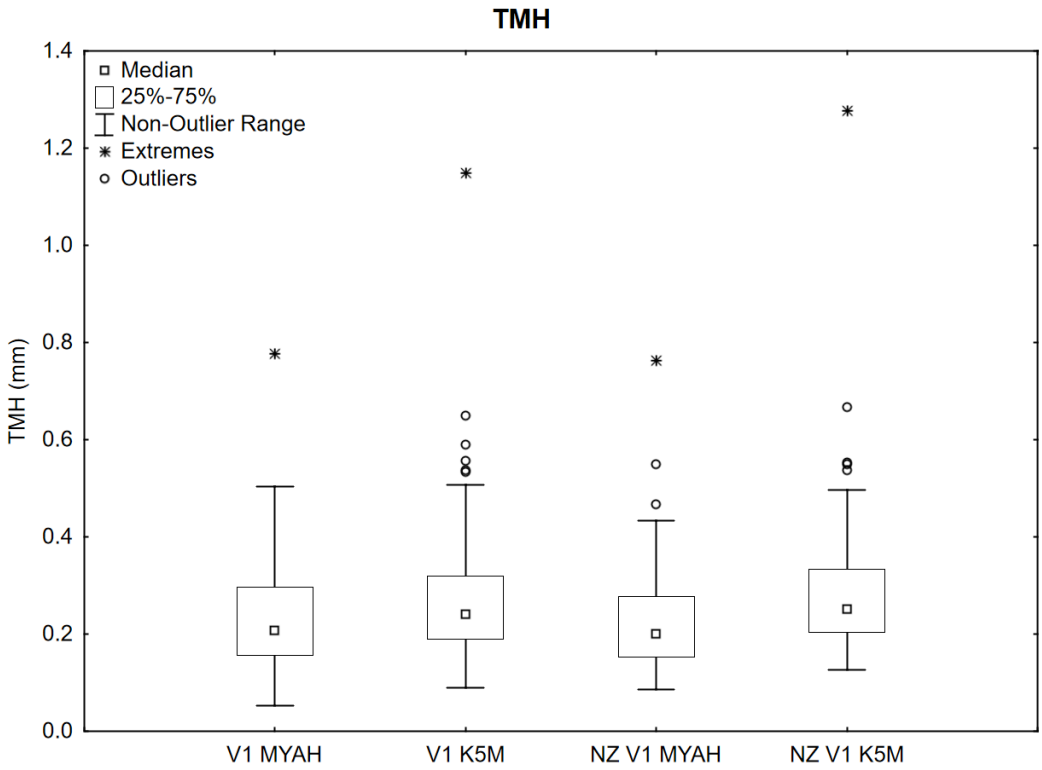


Figure 2.6. Box plots for TMH for MYAH and K5M. TMH was significantly larger for the K5M.

Table 2.10. TMH stratified by symptomatic and asymptomatic group.

TMH (mm) *Mean ± SD* *Median (range)*	**MYAH**		**K5M**	
	At time of image capture	**Post analysis**	**At time of image capture**	**Post analysis**
SYMP *(n=122)*	0.23 ± 0.10 0.21 (0.05 – 0.78)	0.22 ± 0.10 0.20 (0.09 – 0.76)	0.27 ± 0.13 0.24 (0.09 – 1.15)	0.29 ± 0.13 0.26 (0.13 – 1.28)
ASYMP *(n=28)*	0.24 ± 0.08 0.22 (0.09 – 0.41)	0.22 ± 0.08 0.20 (0.10 – 0.40)	0.26 ± 0.09 0.23 (0.12 – 0.56)	0.27 ± 0.09 0.25 (0.15 – 0.55)
p value (MWU)	0.34	0.99	0.78	0.78

MWU = Mann-Whitney U Test.

There was no difference when comparing TMH measurements between visits for the subset of 30 participants who attended both V1 and V2 for any device, nor for the time of measurement (Table 2.11).

Table 2.11. TMH repeatability – comparison between V1 and V2 (n=30).

TMH *Mean ± SD* *Median (range)*	**MYAH**		**K5M**	
	At time of image capture	**Post analysis**	**At time of image capture**	**Post analysis**
Baseline V1 *(n=30)*	0.22 ± 0.09 0.19 (0.11 – 0.40)	0.21 ± 0.08 0.18 (0.11 – 0.37)	0.24 ± 0.10 0.21 (0.11 – 0.51)	0.25 ± 0.08 0.24 (0.15 – 0.45)
Repeatability V2 *(n=30)*	0.21 ± 0.07 0.20 (0.12 – 0.40)	0.20 ± 0.06 0.20 (0.12 – 0.40)	0.24 ± 0.07 0.23 (0.12 – 0.44)	0.25 ± 0.08 0.24 (0.15 – 0.45)
p value (WMP)	0.67	0.49	0.64	0.91

2.5.2.3. Corneal fluorescein staining

The averaged grade of all 5 zones for the right eye of each participant was used for statistical analysis. Because of the use of averaged grades, and to better visualise the differences between devices, data are presented using 1 decimal point rather than rounding to the next available scale step (Table 2.12).

Table 2.12. Corneal staining grades (Oxford scale) for Baseline (V1) data (n=150).

Corneal staining (0-5; unit steps) Mean ± SD Median (range)	**Slit-lamp** During visit; each site	**MYAH** Post analysis; UK site	**K5M** Post analysis; UK site
All participants *(n=150)*	0.4 ± 0.5 0.2 (0.0 – 2.8)	0.1 ± 0.1 0.0 (0.0 – 0.6)	0.1 ± 0.1 0.0 (0.0 – 0.6)
SYMP *(n=128)*	0.4 ± 0.5 0.2 (0.0 – 2.8)	0.1 ± 0.1 0.0 (0.0 – 0.6)	0.1 ± 0.2 0.0 (0.0 – 0.6)
ASYMP *(n=22)*	0.2 ± 0.3 0.2 (0.0 – 1.0)	0.0 ± 0.1 0.0 (0.0 – 0.4)	0.0 ± 0.1 0.0 (0.0 – 0.4)

Corneal staining grades were found to be significantly lower when staining was assessed from the MYAH and K5M images in comparison to the live assessments at the slit-lamp, for the whole participant sample and also when stratified by symptom group (Table 2.13; both $p<0.001$).

Table 2.13. Comparison of Oxford scale corneal staining grades (V1 only).

p values (WMP) all participants; SYMP; ASYMP	**Slit-lamp** During visit; each site	**MYAH** Post analysis; UK site	**K5M** Post analysis; UK site
Slit-lamp		**<0.001**	**<0.001**
MYAH	**<0.001**		>0.05
K5M	**<0.001**	>0.05	

There was no significant difference in Oxford scale corneal staining grades between symptomatic and asymptomatic groups for subjective grading at the slit-lamp and from the MYAH and K5M images (Mann-Whitney U test; all $p>0.05$).

There was also no difference when comparing corneal staining grades between visits for the subset of 30 participants who attended both visits for any device (Table 2.14 and Table 2.16; all $p>0.05$).

In addition, the images captured with the MYAH and K5M were analysed using a third-party objective staining analysis software (Advanced Ophthalmic Systems (AOS), Croydon, UK). The software uses algorithms that are applied to each pixel of the image to determine whether the shape and intensity of the pixel can be considered as punctate (AOS, 2023). The algorithms also use intensity and sensitivity thresholds to eliminate certain artefacts which might be due to camera and image digital noise. Once processed, the software outputs a staining (punctate) spot count for the whole eye, which was used for the comparison between spot counts from the K5M and MYAH.

Overall, the number of detected punctate spots (or pixels) was very low, with the maximum number being 196 for any participant or device. Despite the small range of counts, significantly fewer spots were detected from images captured by the MYAH, compared to the K5M, both for the participant sample as a whole and for the symptomatic participants (Table 2.15).

Table 2.14. Corneal staining repeatability, Oxford scale – comparison between V1 and V2 (n=30).

Corneal staining (0-5; unit steps) Mean ± SD Median (range)	**Slit-lamp** During visit	**MYAH** Post analysis	**K5M** Post analysis
Baseline V1 *(n=30)*	0.4 ± 0.4 0.3 (0.0 – 1.8)	0.1 ± 0.1 0.0 (0.0 – 0.6)	0.1 ± 0.1 0.0 (0.0 – 0.2)
Repeatability V2 *(n=30)*	0.4 ± 0.3 0.3 (0.0 – 1.0)	0.1 ± 0.1 0.0 (0.0 – 0.6)	0.1 ± 0.1 0.0 (0.0 – 0.6)
p value (WMP)	0.33	0.79	0.77

Table 2.15. Comparison of corneal staining automated punctate spot counts (V1 only; n=150).

Corneal staining (dot count) Mean ± SD Median (range)	**MYAH** Post analysis	**K5M** Post analysis	**p value** (WMP)
All participants *(n=150)*	1.6 ± 11.2 0 (0 – 133)	6.3 ± 24.0 0 (0 – 196)	**p<0.001**
SYMP *(n=128)*	1.9 ± 12.4 0 (0 – 133)	7.6 ± 26.5 0 (0 – 196)	**p<0.001**
ASYMP *(n=22)*	0.4 ± 1.9 0 (0 – 10)	0.8 ± 3.6 0 (0 – 19)	0.18

There was no significant difference in automated corneal staining spot counts between symptomatic and asymptomatic groups, from the MYAH images or from the K5M images (Mann-Whitney U test, both p>0.05).

There was no difference between V1 and V2 when comparing the automated corneal spot counts from images taken with both the MYAH and K5M for the subset of 30 participants who attended both visits (Table 2.16).

Table 2.16. Corneal staining repeatability, automated spot count - comparison between V1 & V2 (n=30).

Corneal staining (dot count) Mean ± SD Median (range)	**MYAH** Post analysis	**K5M** Post analysis
Baseline V1 *(n=30)*	0.2 ± 0.5 0 (0 – 2)	3.0 ± 11.3 0 (0 – 61)
Repeatability V2 *(n=30)*	1.5 ± 7.0 0 (0 – 38)	3.5 ± 10.5 0 (0 – 54)
p value (WMP)	0.28	0.58

2.5.2.4. Meibomian gland dropout

Subjective grades of meibomian gland dropout were statistically significantly greater for the MYAH images compared to the K5M images for the lower lid (Table 2.17; $p<0.001$), but there were no statistical differences between devices for the upper lid grades ($p>0.05$). The difference in gland dropout grades between the MYAH and K5M for the lower lid are unlikely to be clinically meaningful; it must also be noted that unlike the lower lid grading scheme, the Pult scale upper lid grading scheme has not been validated in the literature.

Table 2.17. Meibomian gland dropout - subjective grades from images (Pult Meiboscale; n=150).

Meibomian gland dropout *Subjective (Pult 0-4 scale)*		**MYAH** Post-study grading	**K5M** Post-study grading	**p value** (WMP)
All participants *(n=150 each)* Mean ± SD Median (range)	Upper lid	1.3 ± 0.9 1 (0 – 4)	1.2 ± 0.9 1 (0 – 4)	0.33
	Lower lid	1.5 ± 0.9 1 (0 – 4)	1.3 ± 0.9 1 (0 – 4)	**<0.001**
SYMP *(n=122 each)* Mean ± SD Median (range)	Upper lid	1.2 ± 0.9 1 (0 – 4)	1.2 ± 0.9 1 (0 – 4)	0.47
	Lower lid	1.6 ± 0.9 1 (0 – 4)	1.3 ± 0.9 1 (0 – 4)	**<0.001**

ASYMP *(n=28 each)* Mean ± SD Median (range)	Upper lid	1.3 ± 0.8 1 (0 – 3)	1.2 ± 0.7 1 (0 – 3)	0.48
	Lower lid	1.4 ± 0.8 1 (0 – 4)	1.1 ± 0.9 1 (0 – 4)	**<0.001**

There was no significant difference in meibomian gland dropout between symptomatic and asymptomatic groups, neither for MYAH nor K5M (Mann-Whitney U test, all p>0.05).

There was no difference in subjective grades of meibomian gland dropout in upper and lower lid when comparing grades between visits for the subset of 30 participants who attended both visits, for both MYAH and K5M (Wilcoxon Matched Pairs test; all p>0.05).

The results of the objective post-analysis of meibomian gland dropout – using the MYAH's built-in software for images captured on the MYAH, and the AOS software for both the MYAH and K5M images – is presented in Table 2.18.

Table 2.18. Meibomian gland percentage dropout – objective analysis n=150).

Meibomian gland % dropout *Objective analysis (%)* Mean ± SD Median (range)		**MYAH** Post analysis; MYAH built-in software	**MYAH** Post analysis; AOS software	**K5M** Post analysis; AOS software
All participants *(n=150 each)* Mean ± SD Median (range)	Upper lid	35.8 ± 13.8 34 (7 – 84)	36.4 ± 11.0 34 (16 – 69)	19.1 ± 10.7 17.5 (0 – 66)
	Lower lid	33.1 ± 12.6 32 (8 – 67)	31.6 ± 12.5 31 (6 – 62)	14.7 ± 11.0 12 (0 – 53)
SYMP *(n=122 each)* Mean ± SD Median (range)	Upper lid	35.9 ± 14.3 34 (7 – 84)	35.7 ± 11.1 33 (16 – 69)	19.4 ± 11.5 18 (0 – 66)
	Lower lid	33.5 ± 13.1 32.5 (8 – 67)	32.2 ± 12.9 31.5 (6 – 62)	14.5 ± 10.4 12 (0 – 51)
ASYMP *(n=28 each)* Mean ± SD Median (range)	Upper lid	35.4 ± 11.9 32.5 (15 – 70)	39.3 ± 10.5 40 (23 – 61)	17.5 ± 6.8 17 (1 – 31)
	Lower lid	31.3 ± 10.4 29.5 (10 – 54)	29.0 ± 10.7 30.5 (8 – 51)	15.3 ± 13.7 11.5 (1 – 53)

For the upper lid (Table 2.19 upper panel & Figure 2.7), there was significantly less percentage gland dropout for K5M images analysed with the AOS software compared to the MYAH images, independent of whether the AOS software or the MYAH software was used (Wilcoxon Matched Pairs; $p<0.001$); these differences would be considered as clinically significant. Percentage dropout for MYAH images was similar between the AOS software and the built-in software for the participants as a whole, and for the symptomatic group, however AOS analysis gave significantly higher dropout than the built-in software for the asymptomatic group ($p=0.04$).

For the lower lid (Table 2.19 lower panel & Figure 2.7), there was significantly less percentage gland dropout for K5M images analysed with the AOS software compared to the MYAH images, independent of whether the AOS software or the MYAH software was used (Wilcoxon Matched Pairs; $p<0.001$). Percentage dropout for MYAH images was similar between the AOS software and the built-in software for the symptomatic and asymptomatic groups (both $p>0.05$) however, the difference was significant for the participants when analysed as a whole group ($p=0.04$).

There was no difference in the percentage of meibomian gland dropout in upper and lower lid when comparing between visits for the subset of 30 participants who attended both visits, for both MYAH analyses, and for the K5M (Wilcoxon Matched Pairs test; all $p>0.05$).

There was also no difference in the meibomian gland dropout between asymptomatic (OSDI <13) and symptomatic (OSDI ≥13) participants, neither when using subjective scale grades, nor percentage dropout from objective analysis (Mann-Whitney U test; all $p>0.05$).

2.5.2.4.1. Conversion of percentage dropout into Pult scale grades

The Pult Meiboscale employs five scale steps, which are based on percentage gland loss (Figure 2.3). To allow comparison between the subjective grades and the objectively derived dropout percentages using the AOS software and the built-in analysis feature, these percentages were converted into Pult Meiboscale grades according to the scale descriptors (Table 2.20). For example, an image with 37% dropout was converted to a Pult scale grade 2 (26-50%) and an image with 75% gland loss was converted to a Pult scale grade 3 (51-75%).

Table 2.19. Statistical comparison of meibomian gland percentage dropout from different objective analysis methods (V1 only).

Upper Lid - p-values (WMP)	**MYAH** Post analysis; MYAH built-in software		**MYAH** Post analysis; AOS software		**K5M** Post analysis; AOS software
MYAH Post analysis; MYAH built-in software			**SYMP 0.04**	All & SYMP >0.05	**<0.001**
MYAH Post analysis; AOS software	**ASYMP 0.04**	All & SYMP >0.05			**<0.001**
K5M Post analysis; AOS software	**<0.001**		**<0.001**		
Lower Lid - p-values (WMP)	**MYAH** Post analysis; MYAH built-in software		**MYAH** Post analysis; AOS software		**K5M** Post analysis; AOS software
MYAH Post analysis; MYAH built-in software			**All 0.04**	SYMP&ASYMP >0.05	**<0.001**
MYAH Post analysis; AOS software	**All 0.04**	SYMP&ASYMP >0.05			**<0.001**
K5M Post analysis; AOS software	**<0.001**		**<0.001**		

WMP = Wilcoxon Matched Pairs test; All = all participants; SYMP = symptomatic; ASYMP = asymptomatic.

Table 2.20. Meibomian gland dropout – Pult scale grades (subjective and converted).

Meibomian gland dropout *Subjective (Pult 0-4 scale) (n=150 each)*					
Mean ± SD Median (range)	**MYAH** Subjective	**MYAH** Built-in Converted	**MYAH** AOS converted	**K5M** Subjective	**K5M** AOS converted
Upper lid	1.3 ± 0.9 1 (0 – 4)	2.0 ± 0.6 2 (1 – 4)	2.0 ± 0.5 2 (1 – 3)	1.2 ± 0.9 1 (0 – 4)	1.2 ± 0.5 1 (0 – 3)
Lower lid	1.5 ± 0.9 1 (0 – 4)	1.8 ± 0.6 2 (1 – 3)	1.8 ± 0.6 2 (1 – 3)	1.3 ± 0.9 1 (0 – 4)	1.1 ± 0.4 1 (0 – 3)

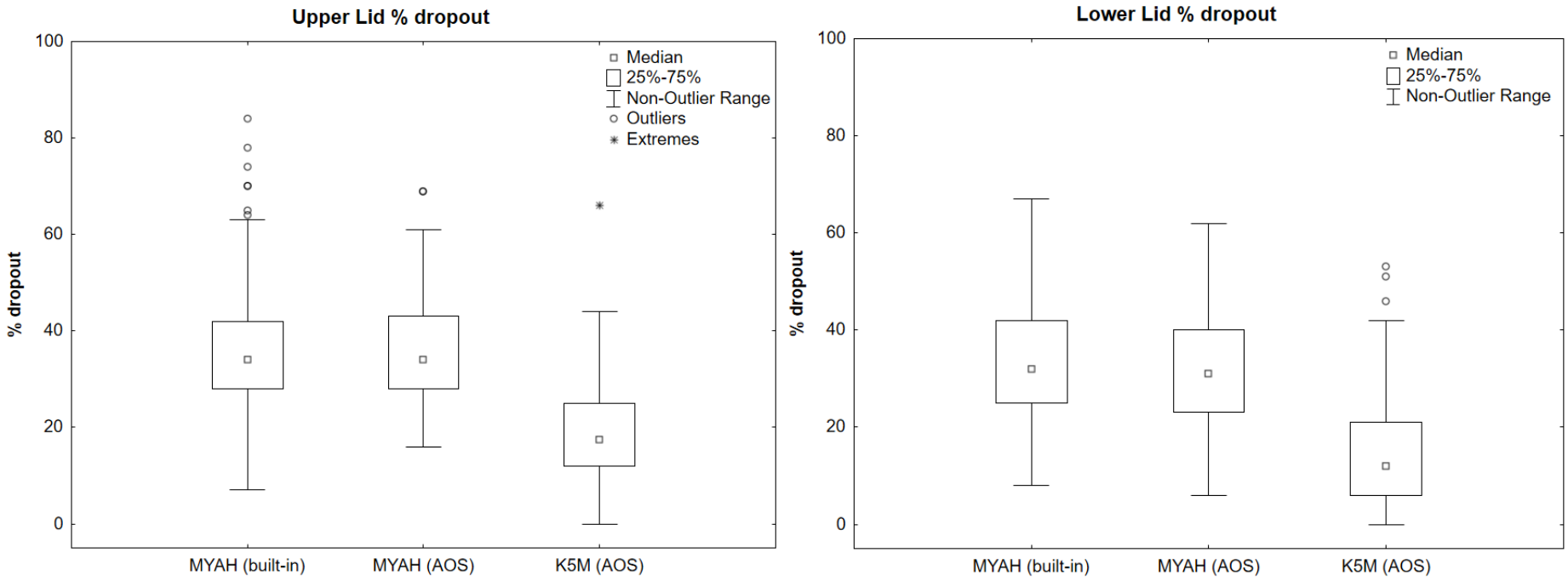


Figure 2.7. Meibomian gland percentage dropout from objective analysis (n=150).

Pult scale grades converted from K5M percentages obtained from the AOS software analysis were found not to differ from the subjective grades, either for the lower or the upper lid (Table 2.21 and Figure 2.8; both $p>0.05$).

Pult scale grades converted from MYAH percentages obtained from objective analysis using both the AOS software and the semi-automated built-in analysis of the MYAH were found to be significantly greater for upper and lower lid than the subjectively assigned grades (Table 2.21 and Figure 2.8; all $p<0.01$); these differences are clinically significant.

Table 2.21. Statistical comparison of subjective and objective-converted Pult scale grades (V1 only; n=150).

Upper Lid p-values (WMP)	**MYAH** Subjective	**MYAH** Built-in converted	**MYAH** AOS converted	**K5M** Subjective	**K5M** AOS converted
MYAH Sub		**<0.001**	**<0.001**	0.33	0.84
K5M Sub	**<0.001**	**<0.001**	**<0.001**		0.60
Lower Lid p-values (WMP)	**MYAH** Subjective	**MYAH** Built-in converted	**MYAH** AOS converted	**K5M** Subjective	**K5M** AOS converted
MYAH Sub		**0.002**	**0.01**	**<0.001**	**<0.001**
K5M Sub	**<0.001**	**<0.001**	**<0.001**		0.23

Sub = subjective.

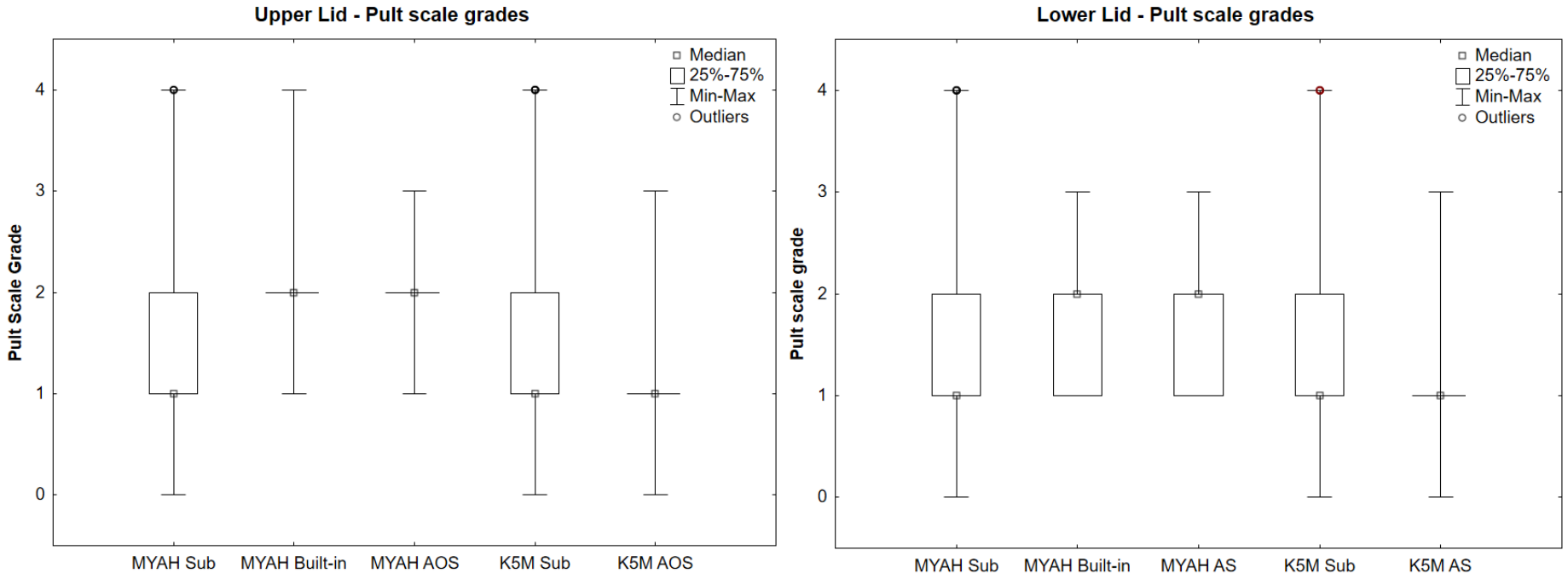


Figure 2.8. Meibomian gland dropout – Pult scale grades (subjective and objective-converted).

2.5.2.5. Dry eye classification – MYAH Vs K5M

A total of 150 participants were enrolled into the study, including 28 asymptomatic and 122 symptomatic participants, with the group assignment based solely on the participant's OSDI score (asymptomatic ≤12 or symptomatic ≥13) and not considering any clinical dry eye markers. Because markers of dry eye were only evaluated as part of the study and were not available in advance, clinical testing to diagnose dry eye was only possible after completion of the data collection. The MYAH and K5M allow for the capture of two of the three homeostatic markers of dry eye, NIBUT and the corneal surface staining component of the ocular surface staining assessment. This section explores whether there were differences in dry eye diagnosis when comparing NIBUT and ocular surface staining from the MYAH and from the K5M.

The criteria for dry eye diagnosis (Wolffsohn et al., 2017) according to TFOS DEWS II (Figure 1.3) that could be assessed to compare the MYAH and K5M are as follows:

- Symptomatic based on DEQ-5 ≥6 and/or OSDI ≥13 **plus one of the following**
- NIBUT <10s
- Ocular surface staining (fluorescein)
    - > 5 corneal spots

2.5.2.5.1. NIBUT

For the purpose of this device-specific analysis, only parameters that could be captured with both the MYAH and K5M were included. Therefore, the data in this section only relate to NIBUT as a standalone homeostatic marker, but do not consider ocular surface staining for the diagnosis of dry eye. According to the TFOS DEWS II diagnostic criteria (Wolffsohn et al., 2017), a patient with a NIBUT of <10 seconds and OSDI of ≥13 is considered to have DED. Any participant who meets dry eye criteria for only one (NIBUT of <10s or OSDI score ≥13) or neither criterion would be considered as not having dry eye.

Table 2.22 shows the number and percentage of symptomatic participants (those with an OSDI ≥13; n=122) who also met the NIBUT criterion for dry eye. Use of the MYAH first NIBUT resulted in 115/122 (or 94.3%) of symptomatic participants meeting the criterion for dry eye, with a NIBUT of <10 seconds, while the other three NIBUT measurements only resulted in roughly 2/3 of the symptomatic participants having a NIBUT of <10 seconds (Table 2.22).

Table 2.22. The number (percentage) of symptomatic participants (based on OSDI ≥13; n=122) who also met the NIBUT criterion for dry eye.

OSDI & NIBUT <10s Count (%)	Subjective First breakup	K5M First breakup	MYAH First breakup	MYAH 5% area breakup
Symptomatic *(n=122)*	78 (63.9%)	79 (64.8%)	115 (94.3%)	82 (67.2%)

To evaluate whether a participant would have had the same dry eye diagnosis independent of which method (Subjective, K5M first, MYAH first or MYAH 5%) was used to determine NIBUT, each pair of NIBUT variables – e.g. MYAH first vs K5M first – were compared to see whether the same dry eye diagnosis would have been reached with this combination of paired measures (Figure 2.9). For example, when comparing the first NIBUT as measured with the MYAH and the K5M (Figure 2.9, top row), 66% of the 150 participants would have been assigned to the same dry eye group. The greatest percentage of matches (5/6 or 83.3%) was determined when comparing the first breakup times measured subjectively and with the K5M, with all other combinations resulting in similar ratios of around 65%.

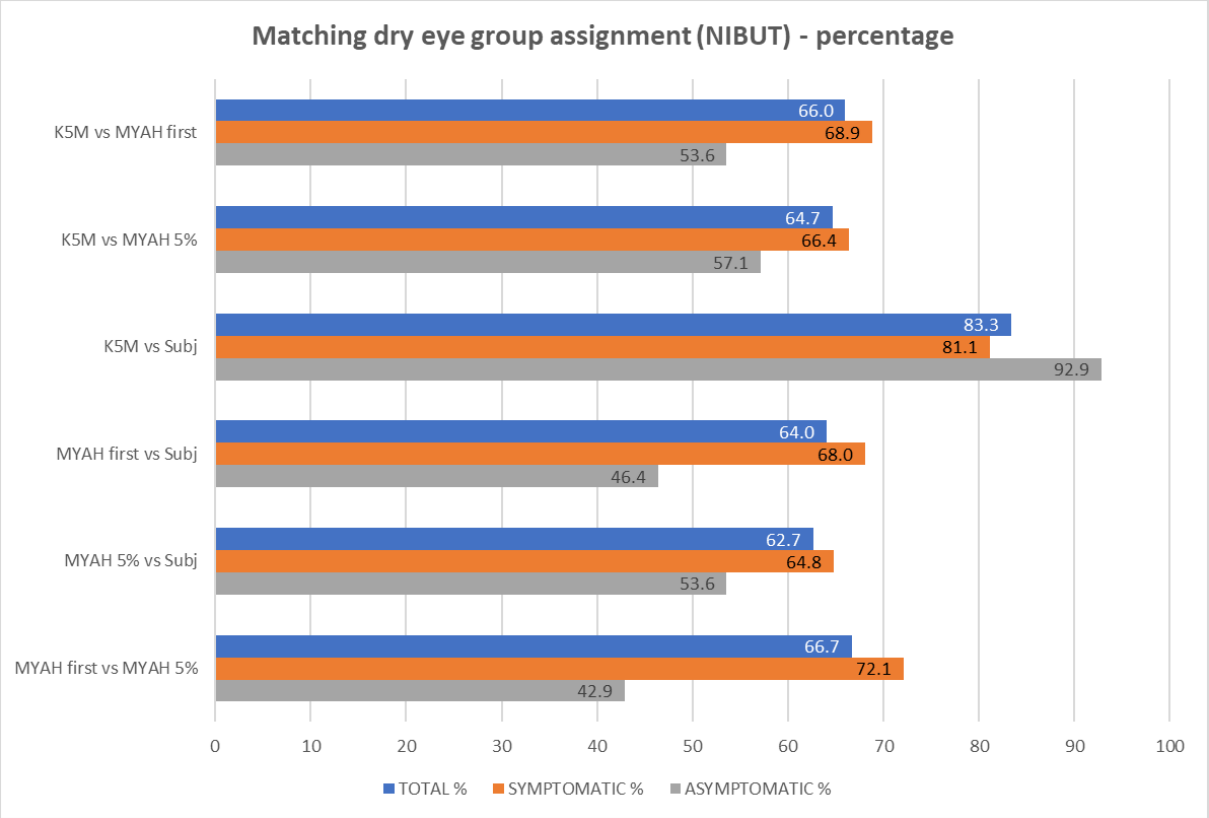


Figure 2.9. Percentage of dry eye group matches for each paired combination of NIBUT metrics and devices.

2.5.2.5.2. Corneal staining with fluorescein

As in section 2.5.2.5.1. for NIBUT, the data in this section only relate to the subjective grading of corneal staining as a standalone homeostatic marker, but do not consider NIBUT or the remaining ocular surface staining parameters (e.g. conjunctival; lid margin) for the diagnosis of dry eye.

According to the TFOS DEWS II diagnostic criteria (Wolffsohn et al., 2017), a patient with more than 5 corneal staining spots and OSDI ≥13 is considered to have DED. Any participant who meets the dry eye criteria for only one (>5 corneal staining spots or OSDI score ≥13) or neither criterion would be considered not to have dry eye.

The Oxford grading scheme (Bron et al., 2003) (Figure 2.2) shows approximate dot counts that are associated with each severity grade, with grade 1 being associated with a count of 10 staining dots across the ocular surface. For the purpose of statistical analysis, an Oxford corneal staining grade of 1 in at least one of the five corneal zones was used to diagnose a participant as having dry eye (based on corneal surface staining), in accordance with the TFOS DEWS II criterion for corneal staining of >5 corneal staining spots. This criterion was met by 68% of participants when staining was assessed during the visit at the slit-lamp biomicroscope. When corneal staining was graded after conclusion of the study, from photographs taken with the MYAH and K5M, the criterion was met in 18.9% and 20.5% of participants, respectively.

To evaluate whether a participant would have had the same dry eye diagnosis independent of which device (slit-lamp, K5M, MYAH) was used to assess corneal staining, each pair of corneal staining grades – e.g. slit-lamp vs MYAH – were compared to see whether the same dry eye diagnosis would have been obtained with this combination of measures (Figure 2.10). Using the assessments of corneal staining at the slit-lamp as the gold standard, there were less than 50% of matches between slit-lamp grades and grades obtained from MYAH and K5M images for those participants who reported symptoms of dry eye (orange bar).

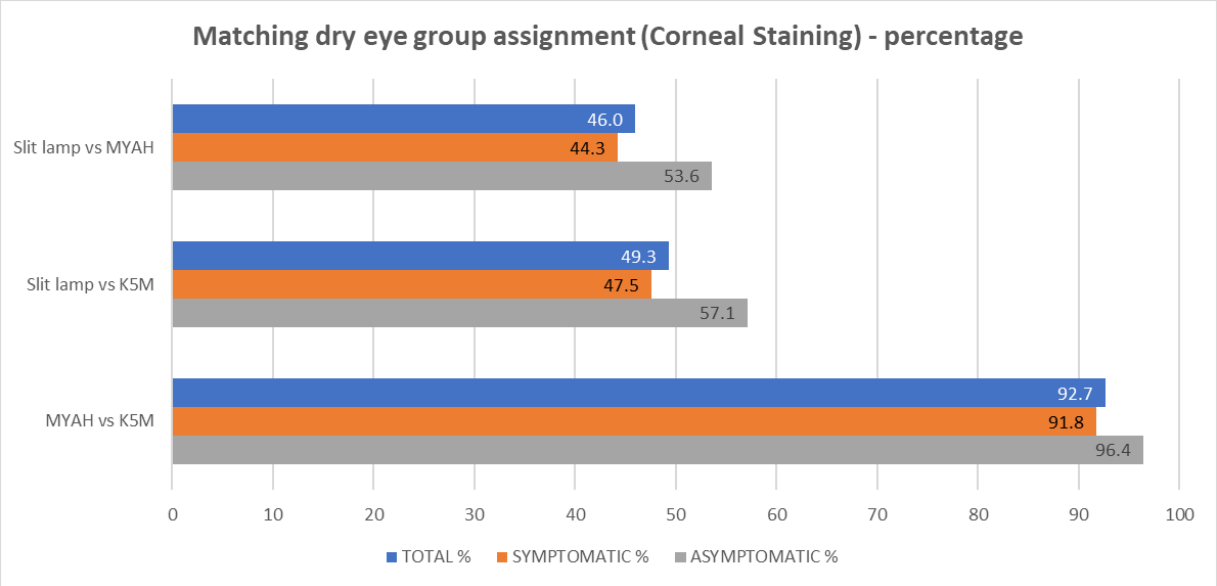


Figure 2.10. Percentage of dry eye group matches for each paired combination of corneal staining assessments with MYAH, K5M and slit-lamp.

2.6. Discussion

The MYAH and K5M are two multifunctional devices that allow for the assessment of multiple dry eye measurements used in the diagnosis of DED in clinical practice. They both offer increased convenience, with space and cost savings by combining these features into a single instrument. The objective of the study was to compare the dry eye diagnostic assessment features of the MYAH to those of the K5M, and to some other commonly used assessment techniques. An extensive analysis of the data collected using the MYAH device revealed some hardware and software deficiencies of relevance to practitioners. The MYAH first NIBUT result could not be relied upon, as it did not correlate with that of the previously validated K5M (Best et al., 2012, Tian et al., 2016), nor subjective measurement using a stopwatch. This resulted in gross overdiagnosis of DED. Tear meniscus height was significantly greater when measured with the K5M than with the MYAH. Corneal fluorescein staining was underestimated with both the MYAH and K5M. Meibomian gland loss was overestimated, when using images produced by the MYAH, compared to the K5M.

This study included a total of 150 participants across three sites, with 122 of these being symptomatic of dry eye, based on an OSDI score of at least 13 (Wolffsohn et al., 2017). Participants ranged in age from 18 to 78, with a median age of 26 years. Aging is a well-known risk factor for dry eye (de Paiva, 2017, Stapleton et al., 2017, Sullivan et al., 2017) however the median

age in this study was relatively young. Female sex is considered a significant risk factor for the development of dry eye (Sullivan et al., 2017, Stapleton et al., 2017) and roughly 71% of all participants were female, suggesting this sample was representative in terms of gender.

An important outcome variable of this study was NIBUT, which is one of the three homeostatic markers recommended in the TFOS DEWS II Diagnostic Methodology report (Wolffsohn et al., 2017). In clinical research, NIBUT has historically been measured by observing the reflection of Placido disc rings while using a stopwatch to measure the time until the first post-blink interruption of the tear film is noticed, or the participant blinks. More recent instrumentation advances now allow for NIBUT to be measured automatically.

The MYAH provides two NIBUT outcome variables; time until first breakup, and time until 5% area breakup. Time to first breakup is also reported as part of the K5M NIBUT measurements. The K5M has previously been reported to provide repeatable and reproducible NIBUT values, especially in patients with DED (Best et al., 2012, Tian et al., 2016). There was no difference between the MYAH 5% area breakup and the first breakup times that were measured using the K5M and the subjective stopwatch method.

Conversely, time to first breakup with the MYAH was significantly shorter compared to the other three NIBUT outcome variables. The median time for MYAH first breakup was only 2.35 seconds, which was at least 5.59 seconds shorter than the other NIBUT outcome variables. The difference between these NIBUT variables becomes best apparent in the Bland-Altman plots, which show a closely linear trend towards increasingly greater differences between the MYAH first breakup time as the other three NIBUT values increase. This suggests that the algorithm used in the MYAH to detect the first breakup may be too sensitive or produce false positive detections of tear breakup that result in an underestimated reading. Because the MYAH does not offer an opportunity to review the captured NIBUT video, the specific cause for these underestimated breakups could not be determined in this study.

The shorter first breakup time with the MYAH also impacted the diagnosis of DED. According to the TFOS DEWS II criteria, a patient with a NIBUT of <10 seconds and OSDI ≥13 is considered have DED (Wolffsohn et al., 2017). The percentage of symptomatic study participants who were found to have a NIBUT of <10 seconds was almost identical for the subjective first, K5M first and MYAH 5% area NIBUT values, with roughly 2 out of 3 symptomatic participants meeting the TFOS DEWS II criterion for tear breakup time. However, based on the MYAH first breakup time, almost 95% of the symptomatic participants met the NIBUT criterion for dry eye, thereby overestimating

the number of participants with dry eye based on currently accepted criteria. In addition, the MYAH time to first breakup was the only NIBUT variable that failed to show a significant difference between the symptomatic and asymptomatic groups. These findings suggest that the MYAH time to first breakup is not a suitable outcome variable for clinical practice, in the diagnosis of dry eye.

Another homeostatic marker that can be assessed with both the MYAH and K5M is corneal staining, which is one of the three ocular surface staining parameters that may be used for DED diagnosis according to TFOS DEWS II (Wolffsohn et al., 2017). Corneal staining was assessed in this study using the Oxford 0-5 grading scheme (Bron et al., 2003). Grades were assigned in real time at the slit-lamp biomicroscope, and also after study completion by the author, who graded the images captured with the MYAH and K5M. The author also objectively quantified the staining depicted in images acquired with the MYAH and K5M, using the Advanced Ophthalmic Systems (AOS) software package. Staining grades were significantly lower when staining was graded from the MYAH and K5M images, compared to the live grading at the slit-lamp biomicroscope, but not different between the K5M and MYAH. Similarly, there was no difference between images captured by the MYAH and K5M in the automated staining dot count using the AOS software.

According to the TFOS DEWS II diagnostic criteria (Wolffsohn et al., 2017), a patient with more than 5 corneal staining spots and an OSDI ≥13 is considered to have DED. For the purpose of statistical analysis, the equivalent Oxford corneal staining grade of 1 (corresponding to at least 10 staining dots) in at least one of the five corneal zones was used as the clinical sign to diagnose a participant with dry eye. Assessment of corneal staining at the slit-lamp is often part of a typical routine eye examination in clinical practice. Using this methodology in this study, 83 (68%) of the symptomatic participants were found to have a corneal staining grade of ≥1 in at least one corneal zone, thus meeting the TFOS corneal staining criterion for dry eye. Looking at the staining grades for the images of those 83 symptomatic participants with grade ≥1 staining at the slit-lamp, this corneal staining would have been missed in 65 (78.3%) and 61 (72.6%) cases for the MYAH and K5M, respectively. This is a clear indication that the built-in fluorescein imaging feature of neither the MYAH nor K5M is a sensitive enough replacement for the live slit-lamp assessment of corneal staining.

Fluorescein imaging with the MYAH, and K5M, may be a useful option to photograph corneal staining or rigid lens fitting for clinics without a dedicated slit-lamp camera. While imaging rigid lenses is possible with both K5M and MYAH, the finding that some staining could be seen during the live exam at the slit-lamp biomicroscope but not in the MYAH and K5M images, suggests that contrast and illumination may have been insufficient when acquiring these images. Because the

MYAH and K5M images were acquired before the live grading at the slit-lamp, the study investigators had no prior knowledge of the location of any staining when capturing the images. It is possible that prior knowledge of the target staining may have led to better image capture. The K5M allows adjustments of exposure (in ms) and gain (in %) using sliders that are easily accessible within the fluorescein imaging interface, allowing immediate modifications to account for variables such as iris colour that impact the visibility of overlying corneal staining. The MYAH device would benefit from the availability of similar functions, in the image capture screen.

Tear meniscus heights were significantly greater with the K5M compared to the MYAH, with an average difference of 0.04mm to 0.06 mm for the measurements during the study visit and for the post-analysis measurements respectively. Considering that the mean TMH measurements ranged between 0.22 and 0.28 mm, this difference makes up roughly 20% to 25% of the total measurement. Although this difference appears to be systematic, it would likely not impact monitoring this variable over time, if the same device was used consistently. Further investigations are warranted to determine the accuracy of this measurement. As with all measurements, TMH measurements were performed back-to-back in randomised device order, and therefore this difference between devices was not due to an order effect. Because TMH measurements with both devices were performed using each device's built-in ruler, it appears that one of the devices (or both) may not be accurately calibrated for this measurement, but it is not known whether the MYAH or K5M may require recalibration by the manufacturer.

The touch screen option for the MYAH's TMH measurement made fine adjustments of the calliper lines more difficult. Trialling the measurement process with a mouse appeared much easier and resulted in revision of TMH post-analysis parameters in the study protocol. TMH measurements during study visits were performed with the touch screen only. While there was a small but significant difference in the TMH between touchscreen measurements during visits, and mouse-operated measurements during post-analysis (0.01mm; not considered clinically meaningful), K5M measurements were performed with a mouse during both the visit and post analysis, so it is unclear whether touchscreen use impacted the results.

The assessment of meibomian gland dropout showed significant differences between the MYAH and K5M for subjective grades and objective percentage dropout. For the lower lid, the subjective grades with the Pult Meiboscale, as well as the percentage dropout measured with the AOS software, were significantly greater for the MYAH images than for the K5M images. For the upper

lid, percentage dropout was also greater for objective analysis of the MYAH images compared to the K5M images, while there was no difference in subjective grades.

One explanation for these differences in percentage dropout may be related to the software algorithms employed by the MYAH and the AOS software. However, the difference in percentage dropout for the MYAH images with AOS and built-in software was within 1.5% of each other, while being roughly 17% greater compared to percentage dropout detected for the K5M image, suggesting that this difference is independent of the software used for analysis. This indicates that the difference between MYAH and K5M images is due to a difference of image quality between the two devices, with some glands that are detected in K5M images not being as easily detected in MYAH images.

Conversion of the dropout percentages into Pult Meiboscale grades also suggests a difference in image quality between MYAH and K5M images. For the MYAH, the converted grades were found to be significantly greater for upper and lower lid than the subjectively assigned grades. For the K5M images on the other hand, there were no differences in converted and subjective Pult grades for upper and lower lid. This suggests that some of the glands that were visible to the clinician when grading dropout in the MYAH images were not accurately detected during the automated gland detection with AOS or with the MYAH's built-in analysis; these glands seem to have been detected in the K5M images, by both the investigator and the AOS software, which is why the dropout grades were lower based on K5M images. There are a number of possible explanations for this, for example lower contrast (and/or brightness) levels in the MYAH images. Another explanation may be a possibly greater depth of field on the K5M which could lead to more of the glandular structure being in focus in a single image.

In conclusion, the MYAH incorporates a variety of imaging and measurement features for the assessment of DED, in a compact device, making it an appealing option for clinicians. However, there were significant differences for some of the dry eye variables between the MYAH and the K5M, most notably in first NIBUT, meibomian gland dropout and TMH.

For NIBUT, the MYAH's first breakup time variable was found to be overly sensitive as it detected breakup more than 5 seconds earlier than the other two methods. The MYAH's 5% area NIBUT was more aligned with the values from other methods, which necessitates further investigation.

There was greater gland dropout reported when using the MYAH images for objective analysis compared to using K5M images. This suggests better resolution was achieved in the K5M images.

While both the K5M and MYAH provided repeatable results for TMH, they were significantly different between devices, with larger TMH values measured with the K5M. This appeared to be a systematic difference between devices, which warrants confirmatory calibration of the TMH callipers.

Overall, the MYAH would benefit from a number of modifications and updates, in order to further improve its functionality and user-friendliness. Consequently, the decision was made to use the Oculus K5M for the measurement of key tear film and ocular surface metrics such as NIBUT in subsequent chapters.

Following diagnosis and subclassification of DED, using methods such as those outlined in this chapter, it is necessary to consider appropriate treatment options. Artificial tears are still the mainstay of management, but with the number of different formulations growing rapidly, and little evidence to show which are the most effective, practitioners and patients face a daunting choice. The following chapter details a systematic review of the literature on RCTs comparing artificial tears to one another, rather than a placebo or vehicle.

3. Artificial Tears: A Systematic Review

This chapter was published as a peer-reviewed paper in the journal Clinical Optometry in 2023. The thesis author was responsible for conducting literature searches, assessment and collation of the numerous search results, conducting Cochrane risk of bias analyses and drafting the main body of the paper. Co-authors provided significant contributions, such as written content, conducting independent literature searches, and review and submission of the final manuscript.

The full text article can be found, using the following details:

David A Semp, Danielle Beeson, Amy L Sheppard, Debarun Dutta & James S Wolffsohn (2023). Artificial Tears: A Systematic Review, Clinical Optometry, 15:, 9-27, DOI: 10.2147/OPTO.S350185

3.1. Introduction

Artificial tear drops are most commonly associated with the management of dry eye. Artificial tears are typically included in first-line management options for dry eye, as they are easy to use, accessible in a wide range of formulations, and have a low risk-profile (Jones et al., 2017). Most artificial tear preparations have been found to be effective in reducing the symptoms and signs of DED, however the Tear Film and Ocular Surface Society dry eye workshop in 2017 concluded there had been relatively few high quality randomised controlled trials comparing different formulations with each other (Jones et al., 2017). Furthermore, few clinical trials have compared the efficacy of different artificial tear products, and attempted to correlate this with patient characteristics, in order to aid management decisions (Essa et al., 2018, Craig et al., 2021). The issue with this is that both practitioners and patients are faced with a bewildering array of different products with varying ingredients, and little or no clear way of knowing which is the most effective. Practitioners will often be asked "which is the best drop for dry eye" but have little scientific evidence on which to base their answer. Other aspects that influence practitioner and patient choices are:

- formulation
    - percentage concentration (Hynnekleiv et al., 2022)
    - molecular weight (Hynnekleiv et al., 2022)
    - preservative used (Gomes et al., 2017)
- and storage bottle design (Dietlein et al., 2008, Connor and Severn, 2011, Kashiwagi, 2019).

Patients therefore face a trial-and-error approach to product selection, incurring mounting costs and frustration in the process. This will be felt most keenly by patients who are highly price sensitive, since over-the-counter products are no longer easily available via National Health Service subsidised prescriptions (NHS, 2021) in the UK. A recent study (Bilkhu et al., 2022a) on the reported experience of dry eye management across four continents identified that on average, DED still caused a moderate impact on an individual's quality of life (median impact 3/10); less than half of the individuals in any country had undergone a consultation with an eye or health-care practitioner about their dry eye; about half had tried dry eye treatment, with artificial tears being the most common, followed by warm compresses, and both therapies were rated as reasonably effective (median 5–7/10).

3.1.1. Formulation

The majority of artificial tear products are aqueous-based and contain viscosity-enhancing agents, such as carbomer 940, carboxymethyl cellulose, dextran, hyaluronic acid, sodium hyaluronate (which has a smaller molecular size), hydroxypropyl guar, hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone (PVP) and polyethylene glycol, which aid lubrication and increase on-eye retention time (Jones et al., 2017). Other ingredients may include osmotic agents, osmoprotectants, antioxidants, preservatives and inactives such as pH buffers, excipients and electrolytes (Jones et al., 2017). Aqueous-based artificial tears target principally the muco-aqueous phase of the tear film, but have been shown to improve dry eye symptoms related to all subtypes of DED (Pucker et al., 2016). In recent years, there has been an increase in the popularity and availability of lipid-based drops, which target the superficial tear lipid layer (Lee et al., 2012, Moshirfar et al., 2014) as the emphasis on meibomian gland dysfunction and its role in evaporative dry eye continues to increase (Jones et al., 2017). It has been demonstrated in randomised controlled trials that lipid-based drops are more effective at managing DED classified as evaporative (Essa et al., 2018, Craig et al., 2021). These can take the form of emulsion drops or liposomal sprays, which are applied to the closed eye and may be easier for those who struggle to instil drops, for example those with reduced manual dexterity or hand tremor. A completely water-free drop comprised of 100% lipid (perfluorohexyloctane) is available now, with the added benefit of being preservative-free (Agarwal et al., 2019).

3.1.2. Preservatives

Multidose eye drops, including artificial tears and medicated preparations, commonly contain preservatives to maintain sterility and prolong shelf life, however, these are also known to produce toxicity. Benzalkonium chloride, commonly found in multidose drops, can produce toxic, proinflammatory and detergent effects, which may actually lead to or exacerbate DED (Baudouin et al., 2010b). For this reason, there has been a move towards preservative-free and unit-dose formulations, due to the risk of toxic and allergic reactions, especially when frequent instillation is required. Newer preparations may contain less damaging preservatives such as polyquaternium, or “vanishing” preservatives such as sodium perborate and Purite, or feature specially designed bottles, which prevent the entry of microorganisms (Kathuria et al., 2021). Preservative-free formulations are recommended for all types of dry eye, however this is even more important in severe cases or sensitive individuals, and more details can be found in the TFOS DEWS II iatrogenic report (Gomes et al., 2017).

3.1.3. Ideal properties

It is important that artificial tear drops behave in a similar way to natural tears. One aspect of this is the physical property of rheology, which refers to the way fluids and soft solids flow. The viscosity of human tears is high between blinks, but reduces during each blink cycle in order to protect the ocular surface from damage due to fluid turbulence (Jones et al., 2017). In other words, they display non-Newtonian fluid properties. Hyaluronic acid has been the subject of a significant amount of research and has been shown to exhibit these non-Newtonian shear-thinning properties (Pisarcik et al., 1995), making it behave like the tear film and hence suitable for use in artificial tears (Arshinoff et al., 2021). Hyaluronic acid, a common constituent of artificial tears, is a naturally occurring glycosaminoglycan, which is found in and around body cells and tissues, for example in synovial fluid, and vitreous and aqueous humour (Rah, 2011). Its use in ophthalmology was pioneered by Andre Balazs in the late 1960s (Balazs et al., 1972), with Polack and McNiece (Polack and McNiece, 1982) being the first to report its use in dry eye. Hyaluronic acid is water soluble and is capable of binding large quantities of water, compared to its own weight, but its physical properties vary depending upon its molecular weight (Müller-Lierheim, 2020). There is evidence to suggest that high molecular weight hyaluronic acid (HMWHA) is clinically superior in the treatment of DED compared to its low molecular weight counterpart (Kojima et al., 2020). Furthermore, HMWHA has been found to be protective against corneal cell apoptosis due to benzalkonium chloride toxicity, ultraviolet light radiation and chemical burns (Pauloin et al., 2009, Pauloin et al., 2008, Wu et al., 2013), as well as being anti-inflammatory and having a role in reducing pain sensation (Gomis et al., 2004b, Kojima et al., 2020).

3.1.4. Artificial tears for dry eye disease

There have been several systematic reviews (Pucker et al., 2016, Song et al., 2017, Ang et al., 2017, Alves et al., 2013) conducted over the past decade, concluding that artificial tears are a safe and effective way of treating DED. A meta-analysis concluded that the effectiveness of sodium hyaluronate did not differ based on its preparation (Ang et al., 2017) and another (Liu et al., 2017) suggested that CMC appeared to be better than hyaluronic acid in treating DED, but the results were not statistically significant. Two recent reviews (Yang et al., 2021, Hynnekleiv et al., 2022) both identified that while hyaluronic acid was effective in reducing the symptoms of DED, the ideal drop frequency and formulation (both concentration and molecular weight) for different ages and severities were yet to be investigated.

3.2. Aims and objectives

The aim of this study was to conduct a systematic review of the literature, with respect to randomised controlled trials comparing different artificial tear formulations to each other, rather than a placebo or vehicle. This is of interest to anyone involved in treating DED.

3.3. Methods

With the objective of better understanding the evidence for the effect of different artificial tears in managing dry eye, a search was made of the Web of Sciences databases (Clarivate Analytics, Philadelphia, USA) which includes the Science Citation Index Expanded covering over 9200 of the world's most impactful journals from 1900 to the present day, along with PubMed (including MEDLINE) from its inception. The systematic review was prospectively registered on PROSPERO (ID: CRD42022369619; see appendix 1) and was conducted in the format prescribed by PRISMA (2020) (Page et al., 2021). A search for "artificial tear*" AND "randomi?ed" identified 481 unique results which were screened independently by two researchers (DB and DS) and verified by a third (JSW). Studies were eligible to be accepted if they were in full paper form (not abstracts or book chapters), compared two or more artificial tears against each other (not just a placebo) and involved randomisation to avoid bias. This resulted in 64 papers being accepted (Figure 3.1) and the full text scrutinised for the key factors, which were tabulated in a spreadsheet and are summarised in Table 3.1. The study design, artificial tears compared, number and age profile of participants completing the trial, duration of use and dosing, tests conducted which showed a significant difference/did not differentiate between the products or change from baseline and general comments (dyes used for ocular surface staining, adverse events when reported and sub-analyses) were extracted. Missing information is highlighted in the table and risk of bias analysis performed with the Cochrane tool reported (see appendix 2) (Higgins et al., 2011). No data synthesis was attempted due to heterogeneity particularly in drop duration.

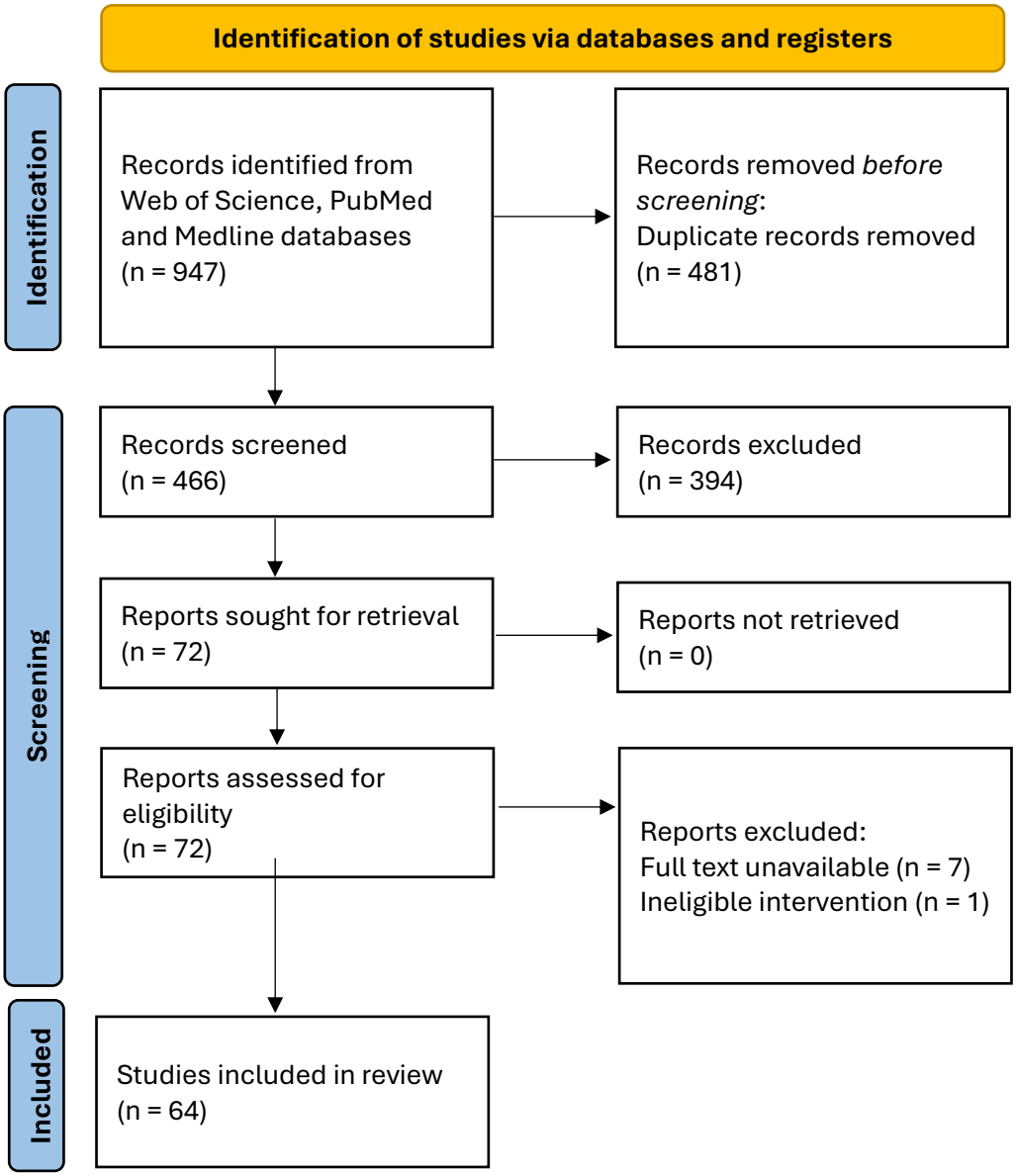


Figure 3.1. PRISMA 2020 flow diagram of the systematic review search results. PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10). Creative Commons.

3.4. Results

All studies are prospective (as expected) and involve parallel groups (unless stated otherwise) of dry eye patients (diagnosed using National Eye Institute, arbitrary or recently TFOS DEWS II criteria). However, less than half are registered with a clinical trials database, and those which are registered have high risk of bias characteristics (Higgins et al., 2011), hence the certainty of the result is generally low. The lack of a definitive severity classification has been identified as a factor in differentiating the effectiveness of the available artificial tears (Alves et al., 2013), but previous attempts at a severity matrix table in TFOS DEWS I (Lemp and Foulks, 2007) led to patients being graded at different levels of severity by different tests and was abandoned in TFOS DEWS II (Wolffsohn et al., 2017); severity to a dry eye patient is based upon their symptoms, whereas it is more likely to be based upon signs on the ocular surface to a cataract surgeon, for example. While the intention of many of the analysed studies is to demonstrate non-inferiority compared to an established treatment, some are underpowered – see TFOS sample size recommendations (Wolffsohn et al., 2017) – and/or include both eyes without accounting for the correlation (Armstrong, 2013) between the eyes of an individual (Angel Sanchez et al., 2010, Brignole et al., 2005, Calvao-Santos et al., 2011, Pinto-Bonilla et al., 2015, Mihάltz et al., 2018). In most studies, fluorescein sodium is used for assessing corneal staining (although an appropriate blue light with a peak around 395nm [not cobalt blue whose peak is ~450nm] and yellow filter with a cut off around 500nm is often not stated) (Peterson et al., 2006). Most studies use lissamine green for conjunctival staining (unless otherwise stated in Table 3.1) which is the recommended practice (Wolffsohn et al., 2017), but few state the brand, which can dramatically affect the staining observed (Delaveris et al., 2018). Some studies (Perez-Balbuena et al., 2016, Troiano and Monaco, 2008) report differences even when they do not meet the standard criteria of $p < 0.05$ and therefore any “difference” should be considered as noise in the data. While many trials comparing artificial tears are manufacturer initiated or sponsored, unless the research was conducted by the company or not conducted by a reputable research organisation, this should not lead to concerns regarding bias.

Table 3.1. Description of randomised controlled trials and their findings.

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Amrane et al. (2014)	Randomised, open-label, multi-centre study	Cationic Emulsion - Cationorm PVA-Povidone - Refresh	N = 44 N = 35	61.3 ± 15.4 61.9 ± 12.5	4 weeks (4x/day)	Symptoms, TBUT, eyelid erythema, conjunctival staining with Cationorm	Schirmer's, corneal staining			Sub-analysis with MGD participants CLINICAL TRIAL NOT REGISTERED
Aragona et al. (2020)	Randomised, double-masked, multi-centre study	CMC + HA - Optive Fusion UD CMC - Refresh Optive Sensitive/Optive UD	N = 180 N = 184	59.4 ± 13.8 57.5 ± 13.7	90 days (2x/day)	Lower ocular pain/discomfort with CMC-HA	OSDI, TBUT , ocular surface staining, Schirmer's II	OSDI, symptoms (VAS), TBUT, ocular surface staining	Schirmer's II	10% minor adverse events CLINICAL TRIAL NOT REGISTERED
Baeyens et al. (2012)	Randomised, double-masked, multi-centre study	SH 0.18% - Vismed Carbomer 0.3% NaCL	N = 100 N = 96 N = 96	59.3 ± 15.0 (across groups)	84 days	Symptoms & corneal staining with SH vs saline	Symptoms, corneal and conjunctival staining, Schirmer's, TBUT SH vs carbomer	Symptoms, corneal staining	Conjunctival staining, Schirmer's, TBUT	CLINICAL TRIAL NOT REGISTERED
Barabino et al. (2014)	Randomised, double-masked, multi-centre study	CMC 0.5% / glycerine 0.9% - Optive HA 0.2% / tamarind seed (TS) polysaccharide 0.2% - Xiloial	N = 25 N = 23	57.1 ± 17.4 52.2 ± 14.9	3 months (4x/day)	Symptoms with HA+TS	TBUT, ocular surface staining, Schirmer's	OSDI, TBUT, ocular surface staining	Schirmer's	CLINICAL TRIAL NOT REGISTERED
Baudouin et al. (2012)	Randomised, investigator-masked, multi-centre study	CMC 0.5% & Osmoprotectant – Optive SH 0.18% - Vismed Multi	N = 37 N = 29	58.1 ± 14.2 55.4 ± 13.4	3 months	None	Osmolarity, Schirmer's I, OSDI, staining	Osmolarity, Schirmer's I, OSDI, staining	None	Clinical Trial NCT00987727 - only symptom primary and secondary outcomes & day 35 data missing Cochrane Risk of Bias R?C?M–O?I–S–B?

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Benelli et al. (2010)	Randomised Investigator-masked, single-centre study	CMC 0.5% - Cellufresh PEG 400 2.5% - Blink Intensive HP-guar 0.18%/PEG 400/PG - Systane	N = 20 N = 20 N = 20	Not stated	30 days (up to 4x/day)	Osmolarity with PEG400	VA, aberrometry, staining, TBUT, Schirmer's	Aberrometry	Osmolarity, VA, staining, TBUT, Schirmer's	CLINICAL TRIAL NOT REGISTERED
Brignole et al. (2005)	Randomised, masked-observer, single-centre study	CMC 1% - Celluvisc SH 0.18% - Vismed	N = 11 N = 10	69 ± 2 57 ± 2	2 months (3x/day)	CD44 antigen, comfort (only at day 7), keratitis recovery with SH	All other inflammatory markers, corneal & conjunctival staining, TBUT, corneal topography, tear meniscus height	Symptoms and ocular surface staining	None	Moderate dry eye and keratitis patients CLINICAL TRIAL NOT REGISTERED
Brodwall et al. (1997)	Randomised, investigator-masked, single-centre study	Polyacrylic acid 0.2% - Visco Tears PVA 1.4%	N = 38 N = 41	60.2 61.8	4 weeks (Drops/day a study variable; average 3-5)	Symptoms (16/27 study days), hyperaemia, Rose Bengal staining, compliance with polyacrylic acid	TBUT, Schirmer's	Symptoms & signs (unspecified)	TBUT, Schirmer's	CLINICAL TRIAL NOT REGISTERED
Bron et al. (1998)	Randomised, double-masked, multi-centre study	Carbomer 940 0.2% - Lacrinorm/GelTears, Laboratoire Chauvin Carbomer 940 0.2% - Viscotears/Vidisic/ Lacrigel	N = 92 N = 87	58.6 ± 16.2 64.0 ± 14.0	4 weeks (4x/day)	None	Symptoms, TBUT, Schirmer's, corneal & conjunctival staining	Symptoms, TBUT, Schirmer's, fluorescein/ lissamine green staining	None	Adverse events in n=21 4 in Lacrinorm group & 17 in Viscotears group CLINICAL TRIAL NOT REGISTERED
Calvao-Santos et al. (2011)	Randomised, open-label, single-centre study	Tears Again [lipidic] Opticol [aqueous] Optive [mucin] No treatment	N = 7 N = 6 N = 7 N = 7	24 to 53 years	30 days (not stated)	None	OSDI, TBUT, Schirmer's	Symptoms, Schirmer's for tears again	TBUT	Patients with digital eye strain. Compared drops primarily acting on one tear layer CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Chiambaretta et al. (2017)	Randomised, investigator-masked, multi-centre study	HA-trehalose HA	N = 52 N = 49	60.0 ± 12.2 58.5 ± 13.4	84 days (3-6x/day; average 4)	Symptoms with HA-trehalose	Cornea & conjunctival staining	OSDI [Schirmer's, TBUT, staining, hyperaemia, no statistics presented]	None	Adverse events: 3 with HA-trehalose vs 24 with HA Clinical Trial NCT02023268 - only staining as primary outcome & day 35 data missing Cochrane Risk of Bias R?C-M-O?I?S-B?
Christensen et al. (2004)	Randomised, double-masked, multi-centre study	PEG 400 0.4% / PG/HP-guar 0.3% - Systane CMC 0.5% - Refresh Tears	N = 42 N = 45	58.5 59.5	6 weeks (4x/day)	Lissamine green staining, dryness, refreshed & foreign body symptoms with 0.5% PEG	Fluorescein staining, use ratings, ocular signs or symptom frequency	Corneal & conjunctival staining only with 0.4% PEG	Conjunctival staining with CMC	CLINICAL TRIAL NOT REGISTERED
Cohen et al. (2014)	Randomised, double-masked, multi-centre study	CMC 1% - Refresh LiquiGel PEG 400 0.4%/ PG/HP-Guar 0.3% - Systane Gel	N = 70 N = 67	57.5±16.6 56.5±15.0	6 weeks (4x/day)	Corneal staining with PEG	Conjunctival staining, TBUT, symptoms	Corneal staining	Lissamine green staining, TBUT, symptoms	CLINICAL TRIAL NOT REGISTERED
Comez et al. (2013)	Randomised, patient-masked, 2 group contralateral, single-centre study	PG 0.3% & PEG 0.4% - Systane SH 15% - Eyestil HPMC - Tears Naturale CMC 0.5% - Refresh Tears	N = 17 N = 13	47.4±14.5 46.3±15.5	12 weeks (5x/day)	None	OSDI, osmolarity, Schirmer's, TBUT	OSDI, osmolarity, Schirmer's, TBUT	None	~30% drop-out CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Craig et al. (2021)	Randomised, double-masked, multi-centre study	Aminomethylpropanol, HP-guar - Systane Ultra Dimyristoyl phosphatidylglycerol, HP-guar, mineral oil, polyoxyl 40 stearate - Systane Complete	N = 49 N = 50	43 ± 17 45 ± 16	6 months (4x/day +)	Lipid thickness	Symptoms, TMH, lipid, osmolarity, hyperaemia, expressibility, blinking	Symptoms (OSDI, DEQ-5, SANDE) NIBUT, LWE, corneal & conjunctival staining	TMH, osmolarity, hyperaemia, expressibility, blinking	Symptoms improved @1+ month, LWE @ 2+ months, lipid @ 3+ months staining @ 4+ months. 1 in 3 had no benefit in signs or symptoms. Those with lipid layer grade ≤ 3 benefit more from lipid-based drop Clinical Trial ACTRN12619000390189 - additional questionnaire, acuity and lid data presented Cochrane Risk of Bias R+C+M+O+I+S-B+
Dausch et al. (2006)	Randomised, investigator-masked, crossover, multi-centre study	Liposomes - Tears Again Carbomer triglycerides - Liposic	N = 74 with deficient lipid layer	n=1 <25 years n=9 25-45 years n=16 46-60 years n=49 >60 years	6 weeks (3x/day)	Symptoms, LIPCOF, TBUT, Schirmer's, lid margin inflammation with Tears Again		Symptoms, LIPCOF, TBUT, Schirmer's, lid margin inflammation	-	Photo sequence of phospholipid liposomes sprayed on eyelid reaching ocular surface CLINICAL TRIAL NOT REGISTERED
Davitt et al. (2010)	Randomised, double-masked, single-centre study	PEG 400/PG/HP-guar CMC 0.5% - Optive	N = 52 N = 53	33 x 18-64 years, 19 x ≥65 years 41x 18-64 years, 12 x ≥65 years	6 weeks (4x/day)	Corneal & conjunctival staining with PEG 400/PG/HP-guar group	Symptoms, TBUT	Symptoms	TBUT	CLINICAL TRIAL NOT REGISTERED
Diaz-Llopis et al. (2019)	Randomised, investigator-masked, multi-centre study	Seawater spray - Quinton CMC 0.5% -Viscofresh	N = 60 N = 60	68.1 ± 6.3 66.8 ± 8.4	12 weeks (5x/day)	OSDI, IL-1 β & IL-6 with seawater spray	Cornea & conjunctival staining, Schirmer I, osmolarity, TBUT, TMH	OSDI, corneal & conjunctival staining	Schirmer I, osmolarity, TBUT, TMH	CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Downie et al. (2020)	Randomised, double-masked, multi-centre study	CMC, glycerine, flaxseed oil and castor oil and osmoprotectants (levocarnitine, Erythritol & trehalose) (OM3) Refresh Optive Advanced (ROA)	N = 120 N = 122	54.3 ± 17.3 52.8 ± 16.7	90 days (2x/day +)	Combined corneal / conjunctival staining with OM3	OSDI, TBUT	OSDI, TBUT, combined corneal / conjunctival staining	None	Adverse events (OM3 0% vs ROA 4.1%) Clinical Trial NCT02553772 Cochrane Risk of Bias R+C+M+O+I+S+B?
Dumbleton et al. (2009)	Randomised, double-masked, single-centre study	PEG 400 0.25% - Blink gel tears CMC 1% - Refresh Liquigel	N = 56 N = 54	46.3 ± 19.3 47.2 ± 19.1	30 days (3x/day)	Symptoms with PEG	Phenol red test, TMH, NIBUT, hyperaemia, corneal and conjunctival staining		Hyperaemia, corneal & conjunctival staining	No notable adverse events CLINICAL TRIAL NOT REGISTERED
Essa et al. (2018)	Randomised, investigator-masked, crossover, single-centre study	SH 0.4% - Clinitas Soothe SH 0.15% - Hyabak Phospholipid liposomes -Tears Again CMC - TheraTears	N = 50 (for all treatments)	60.8 ± 14.2	4 weeks (drops/day a study variable; average 2-3)	None	OSDI, NIBUT, FBUT, TMH, phenol red, LIPCOF, ocular surface staining, lipid layer grading, osmolarity (baseline visit only)	OSDI, LIPCOF, conjunctival staining	NIBUT, FBUT, TMH, phenol red, lipid layer grading	Artificial tears performed similarly. However, osmolarity balanced preferred in those with low baseline tear volume and liposomal spray for those with lipid layer deficiency. Clinical Trial NCT02420834 Cochrane Risk of Bias R?C?M-O?I+S+B?
Fogt et al. (2019)	Randomised, observer-masked, crossover, non-dispensing, single-centre study	Omega 3 - Refresh Optive MEGA-3 Refresh Optive	N = 19 with thin lipid	46.5 ± 8.7	60 minutes (Single application)	Lipid layer thickness (overall), symptoms with MEGA-3	None	Lipid layer thickness, symptoms	Symptoms, Schirmer's	Clinical Trial NCT03380624 - 15 min data missing Cochrane Risk of Bias R?C?M-O?I+S-B?

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Fondi et al. (2018)	Randomised, patient-masked, crossover single-centre study	SH and trehalose - Thealoz Duo HA, trehalose & carbomer - Thealoz Duo Gel	N = 40 (for both treatment)	43.7 ± 12.3	1 week (actual 3.2 ± 2.6x/day HT & 1.9 ± 2.2x/day HTC-gel)	None	Corneal / conjunctival staining, TBUT, sleep quality	Corneal / conjunctival staining, TBUT, sleep quality	None	Clinical Trial NCT02980913 Cochrane Risk of Bias R?C?M-O?I?S+B?
García-Lázaro et al. (2011)	Randomised, investigator masked, crossover, single-centre study	PEG 400 2.5% - Blink Intensive Tears HPMC 0.3% - Artificial Tears	N = 20	57.5 ± 8.4	1 month (3x/day)	Tear meniscus volume with PEG	None	Tear meniscus volume	None	CLINICAL TRIAL NOT REGISTERED
Gensheimer et al. (2012)	Randomised, double-masked, contralateral, non-dispensing, single-centre study	Glycerine 1% with PLL-g-PEG - Eyeon PG 0.3% & PEG 0.4% - Systane	N = 16	44.5	120 mins (single application)	NIBUT, TBUT with glycerine	None	NIBUT with glycerine	TBUT	CLINICAL TRIAL NOT REGISTERED
Gokul et al. (2018)	Randomised, double-masked, contralateral, non-dispensing, single-centre study	Systane Balance Systane Ultra	N = 30	27 ± 9	30 mins (following 2.5 mins in adverse conditions)	Lipid thickness with liposomal Systane Balance	NIBUT	Lipid thickness, NIBUT	Glare acuity, temperature variation, TMH	CLINICAL TRIAL NOT REGISTERED
Grene et al. (1992)	Randomised, double-masked, single-centre study	CMC 1.0% - Celluvisc Lubricant HPMC 0.3% - Tears Naturale 2	N=28? N=28? severe	??	2 months (8x/day)	Symptoms, corneal erosions & impression cytology grades with CMC	Schirmer's, corneal & conjunctival staining, lid & conjunctival swelling	Corneal staining, symptoms, impression cytology grade (CMC only)	Schirmer's	CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Iester et al. (2000)	Randomised, open-label?, multi-centre, study	HPMC 0.3% HA 0.4%	N = 55 N = 58	56.4 ± 12.8 52.2 ± 10.6	2-3 months (6x/day)	Symptoms, tear ferning osmolarity, impression cytology with HA	TBUT, staining, Schirmer's I	TBUT, staining, Schirmer's I, symptoms, impression cytology	-	Ferning, osmolarity and impression cytology only measured in ~33% of sample each CLINICAL TRIAL NOT REGISTERED
Jacobi et al. (2012)	Randomised, open-label? single-centre study	HP-guar - Systane UD Tamarindus indica seed polysaccharide 1% - VISINE INTENSIV	N=14 N=14	44 ± 8 overall	3 months (5x/day)	TBUT with HP-guar	OSDI, Schirmer's II, LIPCOF, corneal & conjunctival (rose Bengal)	TBUT, LIPCOF, OSDI with HP-guar	Schirmer's II, LIPCOF, corneal & conjunctival (rose Bengal)	CLINICAL TRIAL NOT REGISTERED
Jerkins et al. (2020)	Randomised, double-masked, multi-centre study	Systane Balance Refresh Optive advanced	N = 117 N = 114	56.7 ± 14.7 55.6 ± 16.4	35 days (4x/day)	TBUT with Systane	Symptoms	Symptoms, TBUT	None	2 lipid-based drops Clinical Trial NCT02776670 - exploratory lid wiper epitheliopathy and questionnaire additionally reported Cochrane Risk of Bias R+C+M?O?I−S+B?
Johnson et al. (2006)	Randomised, double-masked, contralateral, single-centre study	SH 0.1% SH 0.3% NaCL 0.9%	N = 13 (for all treatments)	Range 21-34	6 hours (single application)	NIBUT (0.3% SH performed better than 0.1% SH)	Symptoms	Symptoms, NIBUT	None	CLINICAL TRIAL NOT REGISTERED
Johnson et al. (2008)	Randomised, double-masked study, single-centre study	Carbomer 934 0.3% - Lacryvisc SH 0.18% - Vismed	N = 33 N = 32	Median 36 Median 39 Range 21-64	1 month (drops/day a study variable; median 2.1-2.3)	Corneal & conjunctival staining with SH	Symptoms, NIBUT, TBUT	Symptoms, corneal & conjunctival staining	NIBUT TBUT	CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Khaireddin and Schmidt (2010)	Randomised, multi-centre study	HA - Vismed light Phospholipid - Tears Again	N = 103 N=113 Evaporative	n=9 <25 years, n=26 25-45 years, n=42 46-60 years, n=139 >60 years	3 months 3x/day +	LIPCOF, lid inflammation NIBUT with Tears Again	Schirmer's	LIPCOF, lid Inflammation, NIBUT	Schirmer's	CLINICAL TRIAL NOT REGISTERED
Khanal et al. (2007)	Randomised, investigator-masked, single-centre study	Castor oil 0.1.25% HPMC 0.32% - Artelac Single Dose Unit	N = 27 N = 26	Unclear from text	1 month (3x/day)	Tear evaporation with HPMC	Schirmer's, osmolarity	Tear evaporation; Lipid layer with castor oil	Schirmer's, osmolality	CLINICAL TRIAL NOT REGISTERED
Labetoulle et al. (2018)	Randomised, double-masked, multi-centre study	HP-guar - HA dual-polymer – Systane Hydration SH 0.15% - Hyabak	N = 50 N = 49	61.7 ± 12.3 56.7 ± 14.3	6 weeks (4x/day)	None	Symptoms, TBUT, ocular surface staining	Ocular surface staining	Symptoms, TBUT	Fluorescein dye only Clinical Trial NCT02470429 - exploratory end points additionally reported in n=30 Cochrane Risk of Bias R+C+M?O?I+S+B?
Laihia et al. (2020)	Randomised, double-masked, single-centre study	Sacha inchi microemulsion (SIME) HA 0.2%	N = 26 N = 26	53.3 ± 12.6 overall	1 month (3x/day)	Ocular protection index with SIME	Symptoms, corneal & conjunctival staining, TBUT	Symptoms, osmolarity in hyperosmolar subgroup. Corneal and conjunctival (nasal) staining, TBUT & lid redness only with SIME	Osmolarity, conjunctival temporal staining	Fluorescein dye only Clinical Trial NCT03569202 Cochrane Risk of Bias R+C+M+O+I+S+B+
Lee et al. (2011)	Randomised, observer-masked, single-centre study	CMC 0.5% - Refresh Plus SH 0.1% - Hynex	N = 33 N = 32	39 ± 14.6 37 ± 13.4	2 months (6x/day)	None	Corneal & conjunctival staining TBUT symptoms	Cornea & conjunctival staining TBUT symptoms	None	Fluorescein staining only CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Lievens et al. (2019)	Randomised, double-masked, multi-centre study	CMC 1.0% and glycerine (CMC-GLY) 0.9% CMC 1.0%	N = 94 N = 94	≥ 18 years of age	1 month (2x/day +)	Symptoms, corneal staining, TBUT with CMC-GLY at day 7 only	Symptoms, corneal staining, TBUT at all other time points	Symptoms, corneal staining, and TBUT	None	Clinical Trial NCT02280473 Cochrane Risk of Bias R+C+M+O+I+S+B+
Marner et al. (1996)	Randomised, open-label, crossover, multi-centre study	Carbomer gel - Lubrithal PVA 1.4% - Lacril/Liquifilm	N=54 (for all treatment)	64.3, range 38-89	2 weeks (drops/day a study variable (carbomer 3.9 vs PVA 4.6x)	Symptoms, TBUT, instillation frequency with carbomer	Schirmer's I, ocular surface staining, corneal sensitivity	Schirmer's I, TBUT, ocular surface staining, symptoms	None	Rose Bengal only used Adverse events 33% with carbomer, 8% with PVA CLINICAL TRIAL NOT REGISTERED
Mihältz et al. (2018)	Randomised, investigator-masked, single-centre study	Carbomer, triglycerides - Artelac Lipids UD SH - Artelac Splash Edo UD	N=10 N=13	55.5 ± 11.3 53.8 ± 17.9	3 months (4x/day +)	None	Schirmer's, TBUT, ocular surface staining, symptoms MG dropout aberrations	Schirmer's, TBUT, ocular surface staining	None	Lipid drops better for those with >50% meibomian gland dropout improving Schirmer's & aberrations CLINICAL TRIAL NOT REGISTERED
Muntz et al. (2020)	Randomised, double-masked, contralateral crossover, single-centre study	Lipid, PG, HP-guar and mineral oil - Systane Complete PEG 400, PG and HP-guar - Systane Ultra	N = 28 (for all treatments)	29 ± 9	Single application – adverse environment	Symptoms, lipid layer quality, NIBUT with Systane complete	TMH Hyperaemia	Symptoms, NIBUT Lipid layer quality only with Systane Complete	TMH Hyperaemia	Clinical Trial ACTRN12619000361101 Cochrane Risk of Bias R+C+M+O+I+S+B?
Nelson and Farris (1988)	Randomised, double-masked, multi-centre study	PVA 1.4% - Liquifilm SH 0.1%	N = 16 N = 20	52.3 ± 16.4 64.8 ± 10.8	8 weeks 8x/day +	-	Symptoms, Osmolality, TBUT, rose bengal staining, Schirmer's I, impression cytology	Symptoms, osmolality, TBUT, rose bengal staining, Schirmer's I	Impression cytology	CLINICAL TRIAL NOT REGISTERED
Ousler et al. (2007)	Randomised, double-masked crossover, single-centre study	PEG & HP-guar - Systane CMC - Refresh Tears CMC - Refresh Endura	N = 50	62.7	Single application	TBUT, ocular protection index with Systane	Blink rate	No comparison presented		No difference between CMC products CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Park et al. (2017)	Randomised, investigator-masked, multi-centre study	SH 0.1% SH 0.15% SH 0.3% Ciclosporin (CS) 0.05%	N = 43 N = 41 N = 47 N = 45	44.1 ± 13.9 46.2 ± 14.0 44.8 ± 16.2 45.2 ± 15.4	12 weeks (5-6x/day)	Schirmer's (0.15% SH group)	Corneal & conjunctival staining TBUT	Corneal & conjunctival staining, TBUT	Schirmer's	Adverse events 13% 0.1% SH. 20% 0.15% SH, 13% 0.3% SH, 31% 0.05% CS group. Clinical Trial KCT0001796 Cochrane Risk of Bias R+C?M–O?I+S+B?
Perez-Balbuena et al. (2016)	Randomised, double-masked, multi-centre study	Xanthan gum 0.09 % and chondroitin sulphate 0.1 % PEG 400 0.4 % and PG 0.3%	N = 76 N = 72	49.9 ± 16.0 45.5 ± 12.7	2 months (4x/day)	None	Schirmer's, TBUT, Symptoms, Corneal & conjunctival staining	Schirmer's, TBUT, symptoms	Corneal & conjunctival staining	Clinical Trial NCT01657253 Cochrane Risk of Bias R+C?M+O?I+S+B+
Pinto-Bonilla et al. (2015)	Randomised, open-label, crossover, single-centre study	trehalose and SH 1.5mg/ml -Thealoz Duo PEG & HP-guar - Systane	N = 9 N = 8	45.3 ± 11.8 53.8 ± 14.6	1 week (5x/day) (Actual 3.7±0.9 / 3.5±0.9)	None	Symptoms, Corneal & conjunctival staining, Schirmer's, TBUT	Symptoms,	Schirmer's TBUT, Corneal & conjunctival staining	CLINICAL TRIAL NOT REGISTERED
Postorino et al. (2018)	Randomised, investigator-masked, single-centre study	HA crosslinked + CoQ10 HA 0.15% crosslinked	N = 20 N = 20	60.2 ± 13.6 60.9 ± 12.5	3 months (4x/day)	Symptoms, MGD assessment, corneal / conjunctival staining, epithelial hyperreflectivity & keratocytes with HA + CoQ10	Symptoms, corneal aesthesiometry TBUT	OSDI MGD assessment, corneal / conjunctival staining, epithelial hyperreflectivity & keratocytes with HA + CoQ10 only	Corneal aesthesiometry TBUT	Fluorescein staining only Clinical Trial NCT03074344 - meibomian gland assessment and confocal additionally reported Cochrane Risk of Bias R+C+M–O?I?S–B?
Pult et al. (2021)	Randomised, double-masked, crossover, multi-centre study	Phospholipid 0.98% - Tears Again Phospholipid 0.12% - Ocuvers	N=30 (all treatments)	33.2±1.8	Single application	Symptoms, NIBUT with high concentration lipid	None	Symptoms, NIBUT with high concentration lipid only	None	CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Robert et al. (2016)	Randomised, investigator masked, multi-centre study	Cationic Emulsion (CE; Cationorm) SH 0.18% - Vismed	N = 37 N = 37 Moderate to severe	60.0 ± 14.6 65.3 ± 11.1	3 months (4x/day)	Symptoms at 1 month with SH	TBUT, Schirmer's, Corneal & conjunctival staining, Osmolarity, Impression cytology	Symptoms, corneal & conjunctival staining	Schirmer's, TBUT, Osmolarity, Impression cytology	Adverse events 18% CE, 27% HS >10% drop-out Clinical Trial EudraCT 2011-A00955-36 Cochrane Risk of Bias R+C?M–O?I+S+B?
Safarzadeh et al. (2017)	Randomised patient-masked, single-centre study	Dextran 70, 1 mg/ml and HPMC – Tears Naturale Dextran 70, 0.1 mg/ml & 0.3 g HPMC – Tearlose	N = 41 N = 47	44.1 ± 6.3 45.8 ± 8.4	4 weeks (2x/day)	None	Symptoms, TBUT, Schirmer's Corneal & conjunctival staining	Symptoms, TBUT, corneal & conjunctival staining	Schirmer's	Fluorescein staining only CLINICAL TRIAL NOT REGISTERED
Sanchez et al. (2010)	Randomised, investigator-masked, single-centre study	CMC 0.5% (Viscofresh) HA 0.15% (Lubristil)	N = 7 N = 8	51.8 ± 14.1 71.8 ± 12.2	1 month (4x/day)	TBUT, corneal staining, and HLA-DR with CMC	Schirmer's Other inflammatory markers	HLA-DR, TBUT & corneal staining with CMC	Schirmer's, Tear clearance,	No adverse events CLINICAL TRIAL NOT REGISTERED
Schmidl et al. (2015)	Randomised, double-masked, single-centre study	Trehalose and SH 1.5mg/ml -Thealoz Duo SH, 0.15% - Hyabak NaCL 0.9% - Hydrabak	N = 20 N = 20 N = 20	43.6 ± 13.3 42.9 ± 12.0 41.8 ± 9.9	240 minutes Single application	Tear film thickness (SH+trehalose to 240min and SH to 40min only)	TBUT, Schirmer's	Tear film thickness (both SH products)	TBUT, Schirmer's	CLINICAL TRIAL NOT REGISTERED
Simmons and Vehige (2007)	Randomised, double-masked, crossover & parallel groups, multi-centre studies	CMC 1.0% CMC 0.5% (Refresh Tears)	N = 43 single application Parallel N = 53 N = 50	mean 62 Not stated	60 minutes (single application) 1 month (4x/day)	Ocular protection index (low viscosity to 20min, high viscosity to 30min. Corneal & conjunctival staining with higher viscosity	Symptoms	Symptoms, corneal and conjunctival staining	None	Fluorescein staining only. More adverse events with high viscosity – visual disturbance 23vs4%; discharge 13vs2% CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Simmons et al. (2015a)	Randomised, investigator-masked, multi-centre study	CMC (Refresh Optive Advanced Sensitive), unit-dose CMC (Refresh Optive Sensitive), unit-dose CMC (Refresh Optive Advanced Sensitive), multi-dose CMC (Refresh Optive Sensitive), multi-dose	N = 105 N = 103 N = 51 N = 56	54.4 ± 14.8 55.8 ± 14.1 55.2 ± 14.5 53.5 ± 13.9	30 days (2x/day +)	None	Symptoms, TBUT, Corneal & conjunctival staining Schirmer's	OSDI, TBUT	Corneal & conjunctival staining, Schirmer's	No clinically significant differences in safety, effectiveness, and acceptability between lipid and aqueous artificial tears Clinical Trial NCT01459588 Cochrane Risk of Bias R+C?M–O?I+S+B?
Simmons et al. (2015b)	Randomised, double-masked, multi-centre study	CMC 0.5% + 0.1% HA (Optive Fusion) CMC 0.5% + 0.15HA CMC 0.5% (Refresh Tears)	N = 87 N = 87 N = 90	59.6 ± 14.5 59.2 ± 16.3 60.0 ± 13.3	3 months (2x/day +) (actual 4.3, 3.9, 3.8x/day)	Some symptoms with Fusion Corneal staining with Fusion vs Refresh	Conjunctival staining	Symptoms, corneal & conjunctival staining	None	Investigational formulations Clinical Trial NCT01294384 - visual disturbance questionnaire additionally reported Cochrane Risk of Bias R+C+M+O?I+S–B?
Szegedi et al. (2018)	Randomised, patient-masked, single-centre study	SH 0.18% + triglycerides, and phospholipids SH 0.18% - Vismed Sodium chloride 0.9% - Hydrabak	N = 20? N = 20? N = 20?	34.6 ± 11.7 40.5 ± 9.9 39.2 ± 12.8	40 minutes Single application	Tear film thickness 40min vs 20min vs 0min with phospholipids	TBUT, Corneal staining, Lipid thickness	Tear film thickness, TBUT, corneal staining, lipid thickness	None	Clinical Trial NCT03161080 Cochrane Risk of Bias R?C?M–O–I+S+B?
Tomlinson et al. (2013)	Randomised, double-masked, crossover, single-centre study	CMC 0.5% - Refresh Tears CMC 0.5%/castor oil - Optive Plus) Glycerine 1%/castor oil - Refresh Ultra	N = 18 with dry eye N = 19 controls For all treatments	41 ± 14 30 ± 12	2 weeks 3x/day	Evaporation for both CMCs	Symptoms, TBUT, NIBUT (except for controls), osmolarity	Symptoms, evaporation, TBUT, NIBUT (except for controls), osmolarity	Lipid thickness	Measures taken after adaptation to environmental centre CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Troiano and Monaco (2008)	Randomised, patient-masked, crossover, single-centre study	HA 0.4% 300mOsm/L HA 0.4% 150mOsm/L	N = 28 For all treatments	55.5 ± 7.3	7 days 4x/day	Foreign body & dryness symptoms and ocular surface staining with 150mOsm/L	None	Symptoms, hyperaemia, ocular surface staining	None	Reducing osmolarity effective Rose Bengal staining only CLINICAL TRIAL NOT REGISTERED
van Setten et al. (2020)	Substitution, open-label, multi-centre study	High molecular weight HA 0.15% - Comfort Shield Over habitual controls	N = 44 N = 40	57.7 ± 14.4 59.5 ± 12.5	8 weeks Actual 8.2 vs 6.5			Symptoms, visual acuity, nerve fibre length with high molecular weight HA	Corneal staining, TBUT, Schirmer's, Lid wiper epitheliopathy, mucocutaneous junction, osmolarity	Change from habitual optimal artificial tears. No change with controls CLINICAL TRIAL NOT REGISTERED
Waduthantri et al. (2012)	Randomised, double-masked, single-centre study	CMC 0.5% - Refresh Tears PEG 400 0.4% / PG/HP-guar 0.3% - Systane Ultra	N = 15 N = 15	54.7 ± 5.8 55.9 ± 5.3	6 weeks 4x/day	None	Symptoms Schirmer's TBUT, Corneal staining	Symptoms	Schirmer's TBUT, Corneal staining	Clinical Trial NCT00796926 - meibography, osmolarity and tear meniscus height not reported Cochrane Risk of Bias R+C?M+O+I+S–B+
Wang et al. (2007)	Randomised, open-label, single-centre study	Carbomer - Vidisic Ophthalmic Gel Cellulose - Artelac Ophthalmic Solution Mineral oil (lanolin) - Duratears Ointment	N = 22 N = 23 N = 22	55.9 ± 15.7 50.1 ± 14.3 60.3 ± 11.2	4 weeks (4x/day for Carbomer and Cellulose) (1x/day before sleep for mineral oil)	Schirmer's with Carbomer and Cellulose & TBUT with Carbomer	Schirmer's	Symptoms, TBUT, Schirmer's		Fluorescein staining only, but not reported in results CLINICAL TRIAL NOT REGISTERED
Wang et al. (2010)	Randomised, open-label, single-centre study	Carbomer + lipid gel - Liposic Ophthalmic Liquid Gel HP-guar gel - Systane Lubricant Eye Drops	N = 15 N = 15	40.4 ± 15.0 49.5 ± 12.2	2 months (4x/day)	Symptoms & Schirmer's with Carbomer + lipid	TBUT	Symptoms, Schirmer's, TBUT	None	Fluorescein staining only, but not analysed in results CLINICAL TRIAL NOT REGISTERED

Paper	Design	Comparators	Participants completing	Age (years)	Duration (Dosing)	Tests showing significant difference	Tests not differentiating products	Tests showing significant difference	Tests showing no change	General Comments
						Cross comparator		Compared to baseline		
Xiao et al. (2008)	Randomised, investigator-masked, single-centre study	Carbomer-based 0.4% gel CMC 1.0%	N = 30 N = 30	46.7 ± 2.3 46.6 ± 2.1	3 months 3x/day +	Symptoms, TBUT, Schirmer's, corneal staining, ocular residence time with carbomer gel	None	Symptoms, TBUT, Schirmer's corneal staining (but no statistics presented)	None	Method relating to precorneal residence time missing. Fluorescein staining only. CLINICAL TRIAL NOT REGISTERED

CMC = carboxymethyl cellulose, CoQ10 = coenzyme Q_{10} / ubiquinone, DEQ-5 = 5-item dry eye questionnaire, EudraCT = European Union Drug Regulating Authorities Clinical Trials, HA = hyaluronic acid, HLA-DR = human leukocyte antigen – DR isotype, HP-guar = hydroxypropyl guar, HPMC = hydroxypropyl methylcellulose / hypromellose, IL = interleukin, LIPCOF = lid-parallel conjunctival folds, LWE = lid wiper epitheliopathy, MGD = meibomian gland dysfunction, NaCl = sodium chloride, NIBUT = non-invasive tear breakup time, OSDI = ocular surface disease index questionnaire, PEG = polyethylene glycol, PG = propylene glycol, PLL-g-PEG = Poly-L-Lysine graft polyethylene glycol, PVA = polyvinyl alcohol, SANDE = symptoms assessment in dry eye questionnaire, SH = sodium hyaluronate, TBUT = tear breakup time, UD = unit-dose, VAS = visual analogue scale.

Cochrane Risk of Bias: R = random sequence generation, C = allocation concealment, M = masking of patient and personnel, O = masking of outcome assessment, I = incomplete outcome data, S = selective reporting and B = other bias; "+" = low risk of bias, "?" = unclear risk of bias and "–" = high risk of bias.

3.5. Discussion

From the studies summarised to date (with the caveat that the effects might be affected by dry eye severity and full artificial tear formulation, as well as the patient demographic) it would appear from direct comparisons between artificial tears that:

- Combination formulations are more effective than single active ingredient artificial tears.
    - The combination of CMC with hyaluronic acid is more effective than either in isolation (Aragona et al., 2020, Simmons et al., 2015b).
    - Hyaluronic acid (Chiambaretta et al., 2017) and sodium hyaluronate (Chiambaretta et al., 2017) benefit from the addition of trehalose.
    - CMC is enhanced by the addition of glycerine (Lievens et al., 2019).
    - CoQ10 enhances the effectiveness of hyaluronic acid (Postorino et al., 2018).
    - Newer versions of Systane (Complete and Balance) outperform earlier versions with less complexity (Ultra) (Gokul et al., 2018, Muntz et al., 2020).
- Some studies suggest sodium hyaluronate could be more effective than CMC40 and carbomers (Brignole et al., 2005), while others find no difference (Baudouin et al., 2012, Lee et al., 2011); the optimal percentage is not clear (Park et al., 2017, Johnson et al., 2006).
- PEG containing artificial tears are more effective than those containing CMC (Christensen et al., 2004, Christensen et al., 2009, Cohen et al., 2014, Davitt et al., 2010, Ousler et al., 2007, Benelli et al., 2010) and HPMC (Grene et al., 1992, García-Lázaro et al., 2011).
- Cationic formulations are more effective than sodium hyaluronate (for objective signs) (Robert et al., 2016) and polyvinyl alcohol (Amrane et al., 2014).
- Hyaluronic acid-containing artificial tears might be better than those with HPMC (Iester et al., 2000), but worse than those with CMC (Sanchez et al., 2010).
- Carbomer-containing artificial tears might be more effective than those based on PVA (Marner et al., 1996) or CMC (Xiao et al., 2008) or cellulose/ mineral oils (Wang et al., 2007), but less (Baeyens et al., 2012, Johnson et al., 2008) or as effective (Miháltz et al., 2018) as sodium hyaluronate.
- Most studies recommend 4x/day use, but reported/measured use is generally less than that advised (Pinto-Bonilla et al., 2015).
- Long-term compliance is needed to improve ocular surface signs, rather than just symptoms (Craig et al., 2021), and symptoms benefit from 4x/day compared to “as needed” dosing (Asbell et al., 2018).

- Higher liposomal concentration increases effectiveness (Dausch et al., 2006, Pult et al., 2021).
- Lower osmolarity increases the effectiveness of an artificial tear drop (Troiano and Monaco, 2008).
- Higher concentration (viscosity) CMC is more effective in reducing corneal and conjunctival staining, but cause more reports of visual disturbance (Simmons and Vehige, 2007).
- While drops targeting individual layers of the tear film seem equally effective (Calvao-Santos et al., 2011, Simmons et al., 2015a), studies have shown that the most effective drop for an individual can be predicted from their baseline classification; drops containing phospholipids are more effective in those with evaporative dry eye (Craig et al., 2021, Essa et al., 2018) and osmoprotectants benefit those with high tear film osmolarity (Essa et al., 2018).
- Artificial tears may not be effective for as much as one-third of patients, but this can be predicted by one month of compliant use (Craig et al., 2021).

These findings can inform clinical dry eye practice. In summary: non-preserved or soft preserved artificial tears are appropriate to prescribe to patients, regardless of the severity of their DED; patients with evaporative dry eye should be prescribed artificial tears containing a high concentration of liposomes; one month's compliant use 4x/day is recommended to determine whether an artificial tear can manage the patients' symptoms in the longer-term; signs of ocular surface disease typically take up to 4 months to start improving so patience is needed; artificial tears with multiple active ingredients (especially with PEG) seem to outperform more basic previous generation drops; ability to use different types of artificial tear bottles/sprays varies (Drew and Wolffsohn, 2015) and should also be part of the prescribing consideration. While the efficacy of artificial tears is well established for managing DED, their use in ocular surface disease without symptoms, to improve post-surgical symptomology and to reduce refractive 'surprises' from poor ocular biometry (Röggla et al., 2021) is less well established. The data available as reviewed in this study is limited by the definition of DED applied in published studies being variable, as well as the disease severity examined and compliance with artificial tears being rarely quantified.

3.5.1. Other therapeutic functions of artificial tears

As well as being a management option for DED and the ocular surface, artificial tears can also be utilised for a wide range of therapeutic functions such as in the treatment of anterior eye trauma, infection, inflammation and disease, as well as contact lens management.

3.5.1.1. Corneal abrasion and wound healing

Corneal abrasions can be caused by foreign bodies, trauma, and trichiasis, and may result in pain, redness, lachrymation, and photophobia. Artificial tears improve epithelial healing (Prinz et al., 2021). Ideally, preservative-free drops are used, as they tend to be associated with better ocular surface health and tolerability (Walsh and Jones, 2019). The most common treatment for perioperative corneal abrasions is artificial tears, followed by a combination of artificial tears and antibiotic ointment (Segal et al., 2014). Most artificial tears contain hydrogels; these are known to activate the epidermal growth factor receptor which promotes the healing of corneal epithelial wounds (Lozano et al., 2008).

3.5.1.2. Pain and inflammation management

Artificial tears are commonly used in the management of ocular pain and inflammation. In the treatment of episcleritis, the combination of artificial tears and cold compresses provide symptomatic relief (Salama et al., 2018). No significant differences have been observed in the signs or symptoms of idiopathic episcleritis when either artificial tears or topical ketorolac (NSAID) is used (Williams et al., 2005). Following photorefractive keratectomy surgery, the application of preservative-free artificial tears reduces postoperative ocular discomfort and increases visual recovery (Mohammadpour et al., 2021). Cooled artificial tears have been shown to reduce corneal and conjunctival sensation, with 4°C being the most comfortable temperature (Fujishima et al., 1997). In contrast to this, Bitton et al found no improvement in perceived patient comfort when refrigerated Systane Ultra artificial tears were used for mild to moderate dry eye sufferers (Bitton et al., 2018). It is also worth noting that pain complaints can be associated with contrasting subjective responses (Galor et al., 2016), and in some patients artificial tears are not effective in relieving uncomfortable symptoms (Kim et al., 2021).

3.5.1.3. Conjunctivitis

Allergic conjunctivitis causes ocular itching, watery discharge, lid oedema and conjunctival chemosis. Bilkhu et al exposed 18 participants (with known allergy) to grass pollen, and found that artificial tears and cold compresses improved the signs of allergic conjunctivitis and provided symptomatic relief (Bilkhu et al., 2014). However, if symptoms are persistent, short-

term use of topical antihistamines and mast cell stabiliser drops is recommended (Castillo et al., 2015).

Viral (non-herpetic) conjunctivitis causes redness, discomfort, and watering. Follicles on the palpebral conjunctiva and punctate epithelial lesions on the cornea may also be observed. It has been shown that 0.5% topical ketorolac (Shiuey et al., 2000), 0.45% ketorolac tromethamine (Lyra et al., 2014), and 1% prednisolone acetate (Santiago et al., 2019) are no better in relieving signs or symptoms of viral conjunctivitis compared to artificial tears.

Bacterial conjunctivitis causes redness, discomfort, and produces a sticky discharge with crusting of the eyelids. Bacterial conjunctivitis usually self-resolves, but the application of artificial tears and eye bathing aids ocular comfort and hygiene. If bacterial conjunctivitis persists after 3–4 days, the application of topical antibiotics is usually recommended (Messmer, 2012).

3.5.1.4. Keratitis

Keratitis is an inflammation of the cornea and has several different aetiologies including viral (Herpes Simplex), bacterial (marginal keratitis), fungal, contact-lens associated and unprotected exposure to ultraviolet radiation (photokeratitis). In dry eye and photokeratitis (Sengillo et al., 2021), the application of artificial tears has been recommended. In herpetic keratitis, marginal keratitis, fungal keratitis, and contact-lens associated keratitis, artificial tears are advised (for lubrication and symptomatic relief) alongside additional treatment such as topical antivirals, topical and/or oral antibiotics, and antifungals.

3.5.1.5. Contact lens rewetting and removal

Contact lens wearers commonly use preservative- free artificial tears for ocular lubrication, comfort and contact lens rehydration (Choy et al., 2013, Pucker, 2020, Pucker et al., 2021). Towards the end of wear, contact lenses become drier and fit tighter. The application of artificial tears reduces friction against the cornea and can facilitate safe lens removal.

3.5.1.6. Foreign body removal

Corneal foreign bodies can cause irritation, lachrymation, blurred vision, and redness. Loose foreign bodies can be irrigated away with normal saline or artificial tears. Upon successful removal of a foreign body, prophylactic antibiotics (Chou et al., 2021), analgesia and artificial tears may be advised (NICE, 2022).

3.5.2. Conclusion

Artificial tears are the mainstay of DED management, but also have a role in corneal abrasion and wound healing, pain and inflammation management, conjunctivitis, keratitis, contact lens rewetting and removal, and foreign body removal. A review of randomised controlled trials comparing artificial tears identified 64 papers. There is good evidence that artificial tears improve symptoms of DED within a month of regular use, applied around 4x per day, but signs generally take several months. Not all patients with DED benefit from artificial tears, so if there is no benefit over one month, alternative management should be considered. Combination formulations are more effective than single active-ingredient artificial tears. PEG-containing artificial tears are more effective than those containing CMC and HPMC. Those classified as having evaporative DED, benefit from artificial tears with liposomes, especially of higher concentration.

This systematic review, and the work of other authors in the field of DED therapy, highlighted a need for further research into the issue of molecular weight in artificial tears. The following chapter describes a randomised clinical trial, in which participants were treated with artificial tears containing sodium hyaluronate of different molecular weights, to identify differences in clinical efficacy, in the treatment of DED.

4. Clinical impact of molecular weight in hyaluronic acid-based artificial tears – A randomised crossover trial

This chapter was presented at the Association for Research in Vision and Ophthalmology 2023, as:

Semp, D, Dutta, D and Wolffsohn, JS. The clinical efficacy of higher molecular weight sodium hyaluronate in artificial tears: A randomised clinical trial. ARVO New Orleans, 26th Apr 2023.

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Semp, D, Dutta, D and Wolffsohn, JS, 2023. The clinical efficacy of higher molecular weight sodium hyaluronate in artificial tears: A randomised clinical trial. *Investigative Ophthalmology & Visual Science*, *64*(8), pp.3970-3970.

4.1. Introduction

DED is a common condition characterised by unpleasant symptoms of discomfort and visual disturbance and is one of the most frequent causes of visits to eyecare practitioners (Bradley et al., 2019). Estimates of the prevalence of DED vary considerably, due to the differing diagnostic criteria adopted by each research study, but generally range from 5-50% in studies involving symptoms and/or signs, and up to 75% when only signs have been considered (Stapleton et al., 2017). However, TFOS DEWS II advocated a standardised system for the diagnosis of DED based on validated symptoms questionnaires and key clinical signs (Wolffsohn et al., 2017). The high prevalence, and symptomatic nature of DED, result in considerable human and economic burden – due to loss of productivity, and healthcare costs to individuals and health systems (Luo et al., 2021, McDonald et al., 2016, Morthen et al., 2021). It is also reported that the quality of life impact of severe cases equates to chronic systemic conditions such as angina (Schiffman et al., 2003).

DED is broadly divided into evaporative and aqueous deficient subclasses, with some sufferers having a combination of both, but EDE is usually more predominant (Craig et al., 2017a). Regardless of the subtype and aetiology, artificial tears are typically included in first-line management options, being easily accessible in a wide range of formulations, and having a low risk-profile (Jones et al., 2017). Most artificial tear preparations have been found to be effective in reducing the symptoms and signs of DED, however there have been few high quality randomised controlled trials comparing them with each other (Jones et al., 2017, Pucker et al., 2016). Although drops designed for specific layers of the tear film appear to be equally effective (Calvao-Santos et al., 2011, Simmons et al., 2015a), research indicates that the optimal drop for a person can be anticipated based on their initial diagnosis. Drops with phospholipids are more beneficial for individuals with evaporative dry eye (Craig et al., 2021, Essa et al., 2018) whereas osmoprotectants are advantageous for those with elevated tear film osmolarity (Essa et al., 2018).

Aqueous-based drops often contain viscosity enhancing agents, such as carbomer 940 (polyacrylic acid), carboxymethyl cellulose, dextran, hyaluronic acid, HP-guar, hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone and polyethylene glycol, which lubricate and increase their retention time in the eye (Jones et al., 2017). Originally isolated from the vitreous humour of bovine eyes (Meyer and Palmer, 1934), hyaluronic acid is a long-chain natural biopolymer, consisting of disaccharide units of glucuronic acid and acetylglucosamine, classified as a non-sulphated glycosaminoglycan (Chang et al., 2021). Sodium hyaluronate is a

smaller, semi-synthetic compound commercially produced using bacteria, such as Streptococcus equi and Streptococcus zooepidemicus (Rah, 2011).

In the human body, hyaluronic acid performs vital functions, such as joint and tendon lubrication, and intercellular communication (Hynnekleiv et al., 2022). Although it is often broadly categorised into low, medium and high molecular weights, the actual sizing of these categories varies between different literature, with high being quoted as ranging from ≥3000 kDa to ≥6000 kDa, medium ranging between >1500 to <3000 kDa and ≥1500 to <6000 kDa, and low being ≤1500 kDa, <1500 kDa and 500 to 730 kDa (Hummer et al., 2020). Regardless of these disparities, higher molecular weight formulations have consistently demonstrated greater efficacy in orthopaedic medicine compared to lower molecular weight products (Hummer et al., 2020). Its use in ophthalmology was pioneered by Andre Balazs in the late 1960s (Balazs et al., 1972), with Polack and McNiece (1982) being the first to report its use in dry eye.

Hyaluronic acid is water soluble and is capable of binding large quantities of water, compared to its own weight, but its physical properties vary depending upon its molecular weight (Müller-Lierheim, 2020). There is evidence to suggest that high molecular weight hyaluronic acid is clinically superior in the treatment of DED compared to its low molecular weight counterpart (Kojima et al., 2020). Furthermore, HMWHA has been found to be protective against corneal cell apoptosis due to benzalkonium chloride toxicity, ultraviolet light radiation and chemical burns (Pauloin et al., 2008, Pauloin et al., 2009, Wu et al., 2013), as well as being anti-inflammatory and having a role in reducing pain sensation (Kojima et al., 2020, Gomis et al., 2004a).

It is important that artificial tears behave in a similar way to natural tears. One aspect of this is rheology, which refers to the way fluids and soft solids flow. The viscosity of human tears is capable of reducing during each blink cycle, in order to protect the ocular surface from damage due to fluid turbulence (Jones et al., 2017). Similarly, hyaluronic acid has been shown to exhibit non-Newtonian shear-thinning properties (Pisarcik et al., 1995), making it suitable for use in artificial tears (Arshinoff et al., 2021).

Few previous clinical trials have compared the efficacy of different artificial tear products, for patients with DED, in order to aid management decisions (Essa et al., 2018, Craig et al., 2021). The purpose of this trial was to compare drops containing different molecular weights of sodium hyaluronate – and hence displaying different rheological properties – in terms of patient comfort and ocular surface outcomes. It is hoped that this will inform practitioners when choosing which products to recommend for their patients.

Table 4.1. Properties of the three artificial tears used by each patient.

Drop	Brand Name	Other Ingredients	Molecular Weight
1	HydraMed	Tamarind seed polysaccharide, mannitol, sodium citrate & citric acid monohydrate	Medium
2	Evolve	Sodium chloride, boric acid & borax	Low
3	Hylo-Forte	Citric acid anhydrous, sodium citrate & sorbitol	High

4.2. Methods

4.2.1. Interventions

The study compared the effects of three commercially available sodium hyaluronate-containing artificial tears on dry eye symptoms, the tear film and ocular surface. Table 4.1 summarises the properties of the formulations used. An unmasked investigator removed the product labels and replaced them with customised labels, to achieve double masking. At each of the three study visits, participants received a single randomised application of drop one, two or three to both eyes. Participants were instructed not to use other eye drops, or any other treatments such as warm compresses or lid hygiene, on the day of testing. Prior to the start of the trial, each drop was weighed. It was determined that two drops of Hylo-Forte would be required for one application, due to its low mass and volume (average 0.017g / drop), compared with the other drops (0.044 and 0.040g / drop). All participants received all three artificial tears, with outcome measurements taken seven times during each study visit: at baseline and 5, 15, 30, 45, 60 and 90 minutes after drop instillation.

Solution rheology testing was performed by the Centre for Industrial Rheology (Warnford, Hampshire, UK), using a research rheometer (DHR2, TA Instruments, New Castle, Delaware, USA) fitted with a 60mm aluminium flat plate measuring system, at 31°C. A solvent trap cover was employed, to minimise drying of the sample at the exposed edges. Shear rate profiling was performed across a wide range of shear rates. This encompassed zero-shear viscosity plateau behaviour, of relevance to residence time on the eye, and very high shear rates, of relevance to blink conditions. Following a 30s equilibration time at 31°C, the samples were exposed to a shear rate sweep (1.0 s^{-1} to a nominal 50000 s^{-1} logarithmically scaled; 5 points per decade of shear rate, shear applied for 30 s at each rate), with viscosity calculated over the final 10 seconds of

each step. In addition, normal stress measurement (when an elastic fluid is sheared a stress is generated normal to the direction of shear) was measured on a research rheometer through a force transducer fitted in the rheometer head. The magnitude of this force is strongly associated with film-forming ability, a prerequisite for thick-film lubrication. A good film-former typically generates a high normal stress compared to a poor one, at a given shear rate. Following a 60s equilibration time at 31 °C, the samples were exposed to a linear sweep (0.0 to 150 rad/s, at 10 rad/s increments; 5 s equilibration, 15 s averaging).

4.2.2. Participants

This prospective, double-masked, randomised crossover trial adhered to the tenets of the Declaration of Helsinki and received favourable ethical clearance from Aston University Research Ethics Committee (REC ID: 1831). Visits were completed between January and April 2022 at Aston University. Participants were required to be 18 years or older, with manifest symptoms and signs of DED according to the TFOS DEWS II diagnostic criteria (Ocular Surface Disease Index score ≥13 or 5-Item Dry Eye Questionnaire ≥6, with at least one positive indicator of homeostatic imbalance based on non-invasive tear film breakup time, tear osmolarity and/or ocular surface staining) (Wolffsohn et al., 2017). In addition, participants were required not to wear contact lenses during the study, report no history of major ocular conditions; report no ophthalmic surgery in the previous three months or during the treatment period. Therapeutic measures were allowed during the study period, however, no changes to any treatment courses or routines (such as warm compresses) were permitted during the study, and not within two hours of study visits. Eligible participants were enrolled for baseline screening after providing written informed consent to participate. A total of 25 eligible participants (80% females; mean ± SD age 23.6 ± 9.2 years, range 19 to 65 years) were recruited and completed all three visits. Symptom severity (assessed with a visual analogue scale) was designated as the primary outcome measure, with tear breakup time, tear meniscus height and ocular redness as secondary outcome measures.

Randomisation was achieved via a pre-determined Latin square system, so that each sequence of drops occurred an equal number of times. The minimum required sample size was calculated to be 13 with a two-tailed repeated measures ANOVA, to detect clinical significance with 95% power, at a significance level of 0.05 (G*Power v3.1; Franz Faul, Universität Kiel, Germany). This was increased to 25, in order to make it more comparable to similar larger studies (Johnson et al., 2008, Park et al., 2017) and to increase the robustness of the statistical tests.

4.2.3. Measurements

All participants were assessed at the same site, by the same masked investigator (the author), in the same facility, with a room temperature of approximately 21°C and relative humidity of around 30%. Ocular measurements were taken from the right eye only, to prevent bias due to the strong correlation between an individual's eyes, which could result in falsely narrow confidence intervals if both eyes were included (Armstrong, 2013). Clinical tests were conducted in accordance with the recommendations of the TFOS DEWS II Diagnostic Methodology subcommittee (Wolffsohn et al., 2017): to reduce the impact on tear film physiology, the tests were ordered from least to most invasive at each study visit (TMH, NIBUT, conjunctival hyperaemia). Ocular comfort was assessed at each time point, using a visual analogue scale. All tear film and ocular surface measurements were assessed using the Keratograph 5M (Oculus Optikgeräte, Wetzlar, Germany). Conjunctival hyperaemia was evaluated by automated objective evaluation of high magnification digital imaging (nasal and temporal regions averaged), benchmarked against the JENVIS grading scale, ranging from 0 to 4 (Sung et al., 2018). The lower tear meniscus height was assessed by capturing a high magnification digital image and applying pre-calibrated digital callipers taking an average of 3 readings below the cornea. NIBUT was measured using automated detection of first breakup, while the participant maintained fixation, and was requested to refrain from blinking. Two breakup time readings were averaged from each time point, due to the limited time between measurements, and to minimise the impact on subsequent ocular comfort and tear measurements.

4.2.4. Statistical analysis

Data analysis was conducted using SPSS Statistics (v29; IBM, New York, USA). As the measures were all continuous and not restricted by a ceiling or floor effect, repeated measures ANOVA was applied with artificial tear and time as within-participant variables. This reduced the number of statistical tests and hence the chance of a type I error. T-tests post-hoc testing was applied to compare between artificial tears at a particular time point when a difference had been detected.

4.3. Results

Hylo-Forte showed a less Newtonian relationship between viscosity and sheer force ($r^2 = 0.295$) compared to HydraMed ($r^2 = 0.485$) and Evolve ($r^2 = 0.521$; Figure 4.1).

Comfort improved with drop instillation and then declined with time ($F = 12.460$, $p < 0.001$), with all drops following a similar profile ($F = 0.814$, $p = 0.636$; Figure 4.2). While there was no significant difference between drops ($F = 0.048$, $p = 0.953$), comfort was highest with Hylo-Forte at most time points.

Tear stability improved with drop instillation and then declined with time ($F = 7.182$, $p < 0.001$), with all drops following a similar profile ($F = 1.472$, $p = 0.134$; Figure 4.3). HydraMed was unable to maintain tear stability ($F = 4.198$, $p = 0.021$).

Tear volume increased with drop instillation and then declined with time ($F = 18.643$, $p < 0.001$), with Evolve having a reduced initial effect compared to HydraMed and Hylo-Forte ($F = 4.045$, $p < 0.001$; Figure 4.4). Overall, there was no statistically significant difference between drops ($F = 1.875$, $p = 0.164$).

Average bulbar redness was not significantly affected over time ($F = 1.721$, $p = 0.120$) with any of the artificial tears ($F = 1.249$, $p = 0.296$; Figure 4.5). However, the average redness grade at baseline was just 0.63 ± 0.44.

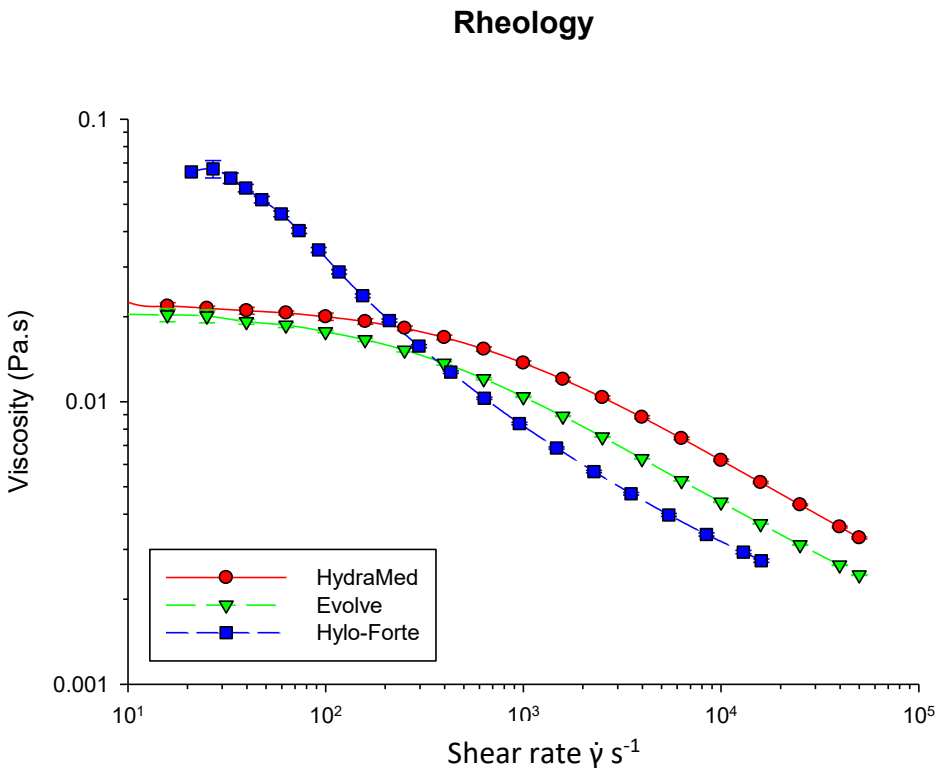

Figure 4.1. Artificial tear rheology – average of three readings. Error bars = ±1 S.D.

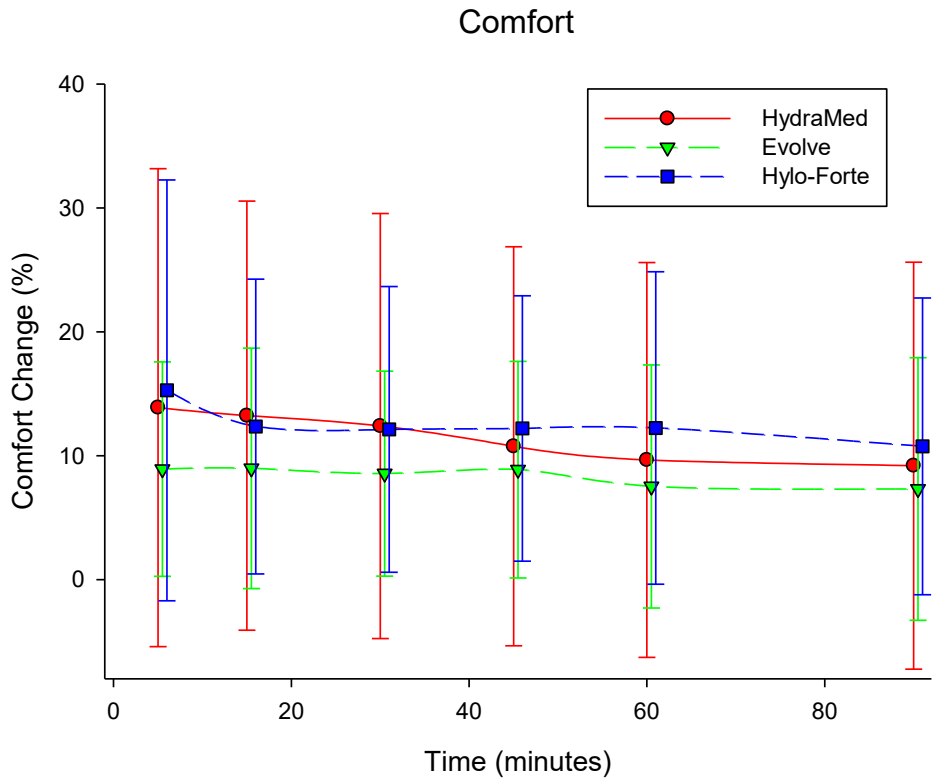

Figure 4.2. Comfort change compared to baseline over time with 0.2% sodium hyaluronate-based artificial tears of different molecular weights. N=25. Error bars = ±1 S.D.

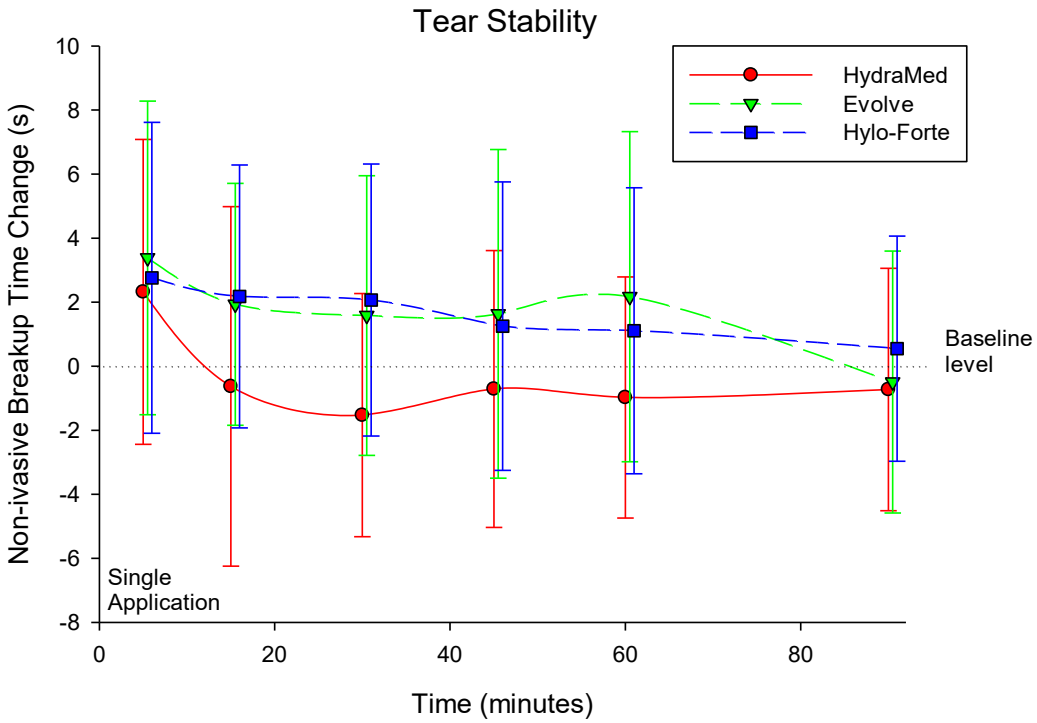

Figure 4.3. Tear stability change compared to baseline over time with 0.2% sodium hyaluronate - based artificial tears of different molecular weights. N=25. Error bars = ±1 S.D.

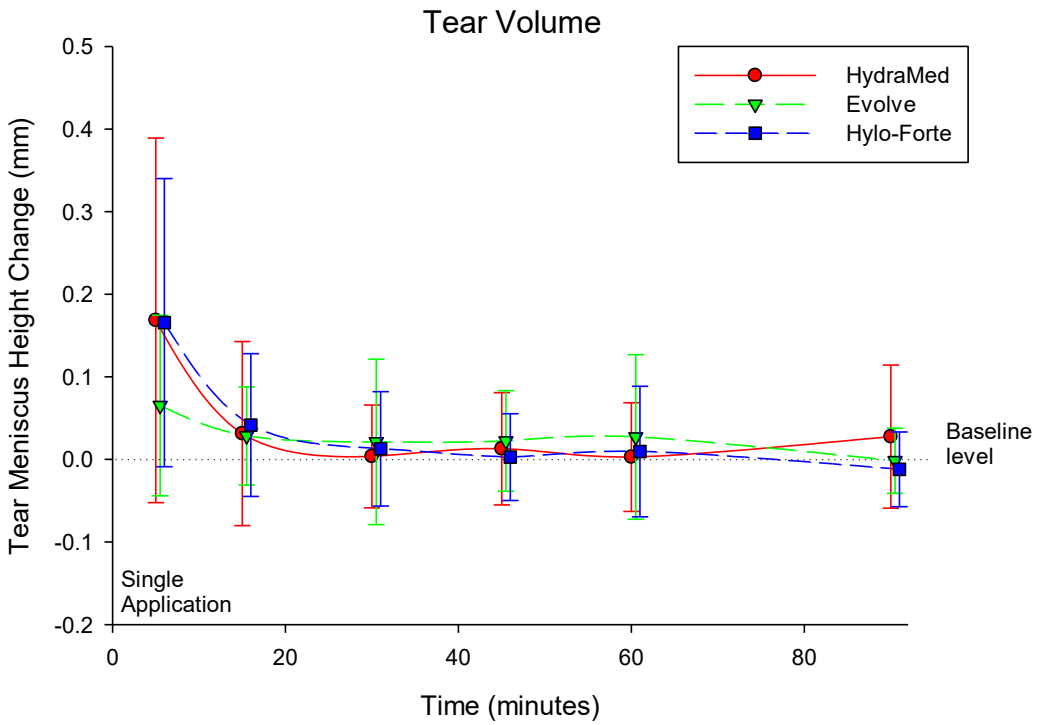

Figure 4.4. Tear volume change compared to baseline over time with 0.2% sodium hyaluronate-based artificial tears of different molecular weights. N=25. Error bars = ±1 S.D.

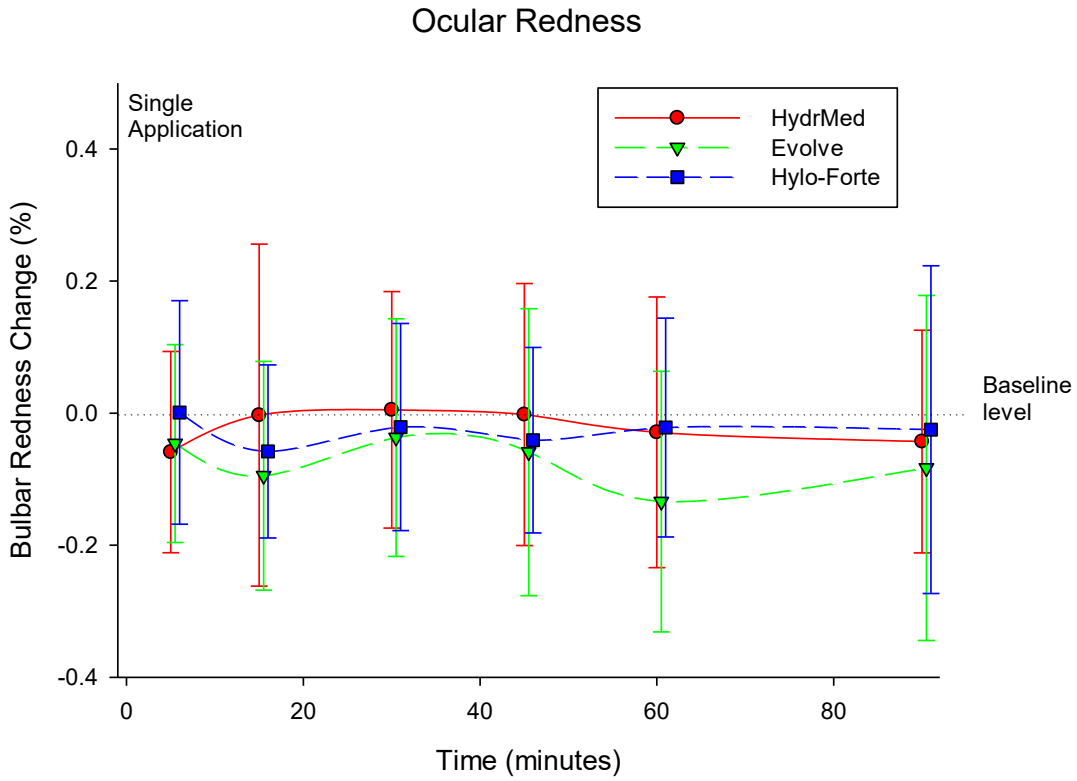

Figure 4.5. Ocular redness change compared to baseline over time with 0.2% sodium hyaluronate-based artificial tears of different molecular weights. N=25. Error bars = ±1 S.D.

4.4. Discussion

The key purpose of this study was to compare different molecular weights of 0.2% sodium hyaluronate-based artificial tears, to ascertain their relative efficacy, and hence whether practitioners should recommend one product over another. Previous studies have compared drops containing different concentrations of hyaluronate (Johnson et al., 2006, Park et al., 2017). Conversely, this study evaluated the effects of molecular weight and hence rheology of hyaluronate, in formulations of the same concentration. The volume was matched, to remove this as a confounding factor. The premise of this study is that molecular weight of hyaluronate should be taken into account when comparing different products. Molecular weight has previously been shown to significantly affect the rheology of different formulations (Aragona et al., 2019), and hence the viscosity between (ideally high) and during (ideally low) a blink (Figure 4.1). Hence, results of clinical trials may not be directly comparable without knowing the molecular weight of hyaluronate used (Müller-Lierheim, 2020).

With regard to the primary outcome measure of dry eye symptoms (VAS), the results demonstrated that whilst all of the study drops reduced symptoms, the drop containing high molecular weight sodium hyaluronate was the most comfortable at most time points. Secondary outcome measures were tear breakup time, tear volume, and ocular redness. All three drops improved tear stability, however HydraMed's initial effectiveness was short lived. For tear volume, there was no significant difference between the drops overall, however, Evolve (low molecular weight) had a reduced effect initially. There was no difference between drops in terms of ocular redness, but as noted previously, this was low at baseline in the study sample.

As with other trials of artificial tears, all the studied drops produced improvements in the symptoms and signs of dry eye, with differences between formulations on a single application being relatively small. This adds to the weight of evidence showing that artificial tears are beneficial for the majority of patients with DED. As is common in dry eye, signs and symptoms did not correlate closely (Sullivan et al., 2014, Begley et al., 2003). For example, in this study, HydraMed performed considerably worse in terms of tear stability, however it performed relatively well in terms of subjective comfort. The relative merits of recommending artificial tear formulations containing HMWHA warrants further investigation.

In the present study, participants received each drop only once; however, even after just this single instillation, some differences were observed. One limitation was the presence of other ingredients in each formulation, aside from sodium hyaluronate, which may have influenced its relative performance. However, this did allow for the comparison of commercially available

artificial tear products. The sample size was modest, and participants were mainly young females, however this may have made the results more comparable than had the study population been more heterogenous. Future trials expanding on this research would be useful, with a larger sample size and repeated instillations of each drop over weeks or months, followed by a washout period and repeat measurements with other drops. Ideally this would take the form of a large, high-quality Level 1 randomised controlled clinical trial.

In conclusion, this study enhances our current understanding of how molecular weight, and the resultant rheological properties, affects the clinical performance of artificial tear preparations. This is important, because it fills a knowledge gap and has practical applications in helping to inform prescribing decisions, which is beneficial to eye care providers, medical and other prescribers, and not least their patients. High molecular weight hyaluronate has rheological properties similar to the natural tear film (Yokoi et al., 2008) and this study demonstrates this may positively impact its clinical effectiveness compared to low molecular weight formulas.

Artificial tears have long been the mainstay of DED treatment, however, there is growing awareness that the majority of cases of DED are evaporative in nature. It is therefore necessary to examine the treatment of MGD, as the root cause of evaporative DED. The following chapter evaluates a novel device for the treatment of MGD, in the form of a randomised clinical trial, comparing a new device to established traditional techniques.

5. MGrx versus standard debridement and expression for meibomian gland dysfunction: A randomised clinical trial

The work in this chapter has been submitted to a peer-reviewed journal as:

David A. Semp, Debarun Dutta, James S. Wolffsohn (2024). Randomized clinical trial: MGrx versus standard debridement and expression for meibomian gland dysfunction, Optometry and Vision Science.

It has also been accepted for presentation at the American Academy of Optometry:

David A. Semp, Debarun Dutta, James S. Wolffsohn. Randomized clinical trial: MGrx versus standard debridement and expression for meibomian gland dysfunction. AAO Academy, 7th Nov 2024, Indianapolis, USA.

5.1. Introduction

DED is a common condition characterised by unpleasant symptoms of discomfort and visual disturbance and is one of the most frequent causes of visits to eyecare practitioners (Bradley et al., 2019). Once a diagnosis of DED is established, the management is dependent on causal factors and subclassification as evaporative or aqueous deficient dry eye. Some patients present with mixed dry eye, however the majority of cases are evaporative (Craig et al., 2017a), caused predominantly by meibomian gland dysfunction; where changes in meibomian gland physiology result in a defective tear lipid layer, insufficient surface protection and excessive evaporation of the aqueous phase of the tear film (Craig et al., 2017a). MGD has been defined as:

> "a chronic, diffuse abnormality of the meibomian glands, commonly characterised by terminal duct obstruction and/or qualitative/ quantitative changes in the glandular secretion, which may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease" (Nelson et al., 2011).

Meibum secreted by healthy meibomian glands is clear, oily and fluid at body temperature, enabling a small quantity to be expressed with each blink (Knop et al., 2011). In MGD, the phase-transition temperature is higher, and the consistency of the gland contents is more viscous at physiological temperatures, hence meibum becomes cloudy or inspissated, is harder to express and can cause gland blockage (Magno et al., 2022). The combination of increased melting point and viscosity of meibum, and excessive keratinisation of the ductal epithelium in MGD, results in the blockage of the terminal ducts and impedes meibum secretion (Asbell et al., 2011). Meibum from individuals with MGD typically needs to be raised to 38.5 °C to reach a comparable degree of fluidity to healthy meibum at 36 °C (Borchman, 2019). Practitioners have traditionally advised the use of warm compresses and lid massage, however patients often struggle to adhere to the recommended twice daily regime (Alghamdi et al., 2017). Therefore, in-office treatments can be advantageous, especially in more severe cases, which may require more intense and precisely directed therapy than would typically be achieved at home.

A variety of methods for meibomian gland expression have been described and utilised in the treatment of MGD for many years (Geerling et al., 2011, Jones et al., 2017). Expulsion of meibum can be achieved by pressing the eyelid against the eyeball, by squeezing the eyelids together, or by employing a solid object such as a metal paddle on the inner side of the eyelid, and a thumb, finger, or another solid object on the outer lid (Geerling et al., 2011, Jones et al., 2017). This can also be conducted in addition to at-home lid warming, massage and cleansing by the patient themselves. However, the amount of force a practitioner can apply to the eyelids is patient-

dependent, with only a small proportion of patients being able to tolerate full gland evacuation without heating (Korb and Blackie, 2011). Although topical anaesthesia is employed to numb the ocular surface and allow patients to keep their eyes open during treatment, numbing of the eyelids themselves is not adequate to provide relief. Heating of the glandular contents results in expression being achieved at lower pressure, allowing more complete treatment, and facilitating normal gland function.

Little is known about the exact nature of physiological effects brought about by meibomian gland expression. Recently, Swiderska et al. (2023) demonstrated contrast changes in meibography images after gland expression, and recovery back to baseline within 24 hours, suggesting that meibography imaging reveals functional, as well as physical gland properties. A study by Bilkhu et al. (2022b) examined the effects of debridement and expression, on meibomian glands of varying length, width and tortuosity. They found that warm compresses improved the quality of expressed meibum in all glands, except those of less than 10% length, which did not express. Additionally, baseline gland length had a major bearing on meibum quality.

Another significant factor in MGD is hyperkeratinisation and terminal duct obstruction, which can progress to complete occlusion of the meibomian gland orifices (Knop et al., 2011). Excess keratinised tissue and other debris, such as solidified meibum, plugs gland orifices and prevents the egress of meibum onto the ocular surface. The resultant build-up of pressure within the glands, due to continual meibum production, then leads to progressive damage and atrophy (Knop et al., 2011). To address this, mechanical debridement-scaling of the line of Marx and lid margin can be performed, in order to unblock the meibomian gland orifices (Korb and Blackie, 2013). It has been shown that debridement, using a corneal epithelial spatula, increases meibomian gland output in patients with MGD and DED (Bilkhu et al., 2022b). A small pilot study, involving patient's with Sjögren Syndrome, also found improvements in symptoms and some signs, following debridement-scaling (Ngo et al., 2015). A retrospective case series involving both eyes of 24 MGD sufferers also found significant improvements in symptom and ocular surface metrics, as well as MMP-9 levels, 4 weeks after debridement and expression (Moon et al., 2021). However, to date, no randomised trials have been conducted utilising a heated debridement tool, such as the thermal debridement tool of the MGrx device (OcuSci Inc., California, USA) (see Table 5.1).

In recent years, electronic treatment devices have emerged, such as the LipiFlow Thermal Pulsation System (TearScience/J&J Vision, Morrisville, NC), which was the first commercially available device of its kind (Lane et al., 2012). Other such systems include TearCare (Sight

Sciences, Inc., Menlo Park, CA) (Badawi, 2018), the iLux MGD Treatment System (Alcon, Fort Worth, TX) (Tauber et al., 2020) and MiBo ThermoFlo (MiBo Medical Group, Dallas, TX) (Li et al., 2022). Multiple randomised controlled trials have demonstrated the efficacy of such systems (Lane et al., 2012, Badawi, 2018, Tauber et al., 2020, Li et al., 2022), however the cost and availability of treatments may be prohibitive to some patients, mainly due to the high cost of equipment and consumables incurred by practitioners, being passed on to patients (Beining et al., 2022).

The MGrx system (McMurren et al., 2023) consists of a handheld device, with three reusable treatment instruments (Figure 5.2A), and therefore has the advantage of requiring no expensive consumables. The reusable treatment instruments – for debridement, lid warming and expression – are attached to the MGrx device during use, and then detached to be disinfected using alcohol wipes or autoclaving between patients. This negates the need for warm compresses and a microwave in the consulting room, providing a time and space-saving alternative to standard debridement and expression. An open-label trial of the MGrx device was recently published, involving 36 participants with symptoms and/or signs of DED (McMurren et al., 2023). Statistically significant improvements were found in symptoms (SPEED questionnaire), tear breakup time and meibomian gland score at the 30-day follow-up.

The aim of the current study was to assess the efficacy of the MGrx device for meibomian gland debridement and expression, compared to conventional treatment. This was planned in a randomised-sequence trial, comparing MGrx and a standard method for debridement and expression, in participants with both EDE and MGD.

Table 5.1. Studies of the effectiveness of debridement-scaling and/or meibomian gland expression.

Study	Study Design	Participants	Comparators	Results
Bilkhu et al. (2022b)	Interventional case series	N = 15 Age: 31.6 ± 13.1	MG metrics pre & post: -Warming alone -Warming + debridement -Warming + debridement + expression	-MG function correlated with MG length & tortuosity, but not width -Warm compresses improved meibum quality -Debridement further improved expression in partial MGs, but not forcible expression
Korb & Blackie (2011)	Interventional case series	N = 28 Age: 42.4 ± 14.2	Lower eyelid expression & pain by pressure: -First expression -Complete evacuation of expressible gland contents	-Three participants could not tolerate enough pressure to yield any expression -Expression began at 5-40 psi (N = 25; mean 16.1 ± 8.2 psi) -Partial therapeutic expression of any glands began at 10-40 psi (N = 16; mean 25.6 ± 11.4 psi) -93 % of participants unable to tolerate complete treatment
Korb & Blackie (2013)	Randomised controlled trial	N = 28 (16 test, 12 control) Age: 55.9 ± 15.0 (test) 53.7 ± 15.3 (control)	Symptoms (SPEED) & MG function (MG Evaluator): -Before & ~1 month post debridement-scaling (Control group received no treatment)	-Significant decrease in symptoms in test group -Significant increase in number of diagnostically expressable MGs in test group -Control group showed no significant difference in symptoms or MG function over the same period
McMurren et al. (2023)	Interventional case series	N = 36 Age: 57 ± 14	Symptoms (SPEED), TBUT and MG score (MG Evaluator score x meibum quality score): -Before & 1 month post MGrx treatment	-Significant decrease in symptoms -Significant increase in TBUT -Significant increase in product of MGS & meibum quality (N = 26)
Moon et al. (2021)	Retrospective case series	N = 24 Age: 63.1 ± 10.6	TBUT, corneal & conjunctival NaFl staining, Schirmer 1, lid margin & MG slit-lamp exam, OSDI score, & MMP-9: -Pre & 4 weeks post debridement (BlephEx) & MGX	Significant changes: -Increased TBUT -Reduced SICCA OSS & Oxford staining -Reduced lid margin abnormality scores -Reduced MGD scores -Reduced OSDI & ocular irritation symptom scores -Reduced MMP-9 immunoassay positivity rate
Ngo et al. (2015)	Randomised controlled trial	N = 13 SS sufferers (7 treatment, 6 control) Age: 60.0 ± 9.7 (58.0 ± 8.1 treatment, 62.3 ± 11.6 control)	OSDI, SANDE, SICCA OSS, TBUT, MGS, MGYLS, line of Marx position: -Pre & 1 month post debridement-scaling	- Significant decrease in symptoms & signs in test group but only with OSDI scores & SICCA OSS -Significant reduction in MGS only in test group -Control group: no significant change in any test variable
Swiderska et al. (2023)	Interventional case series	N = 15 Age: 21.5 ± 1.73	MG metrics at: -Baseline -Immediately post expression -2 weeks post expression	-Michelson contrast decreased 10.39% (immediate) -Simple contrast decreased 11.54% (immediate) -Gland length ratio decreased 7.79% (immediate) -No significant change in meibomian gland area, tortuosity & any of the width metrics -All metrics returned to baseline within 24hrs

TBUT = fluorescein breakup time, MG = meibomian gland, MGD = meibomian gland dysfunction, MGS = meibomian gland score, MGX = meibomian gland expression, MGYLS = meibomian gland yielding liquid secretions score, MMP-9 = matrix metalloproteinase-9, NaFl = sodium fluorescein, OSDI = ocular surface disease index, PSI = pounds per square inch, SANDE = symptom assessment in dry eye visual analogue scores, SICCA OSS = Sjögren's International Collaborative Clinical Alliance ocular staining score, SPEED = standard patient evaluation of eye dryness questionnaire.

5.2. Methods and materials

5.2.1. Participants

This research was reviewed by an independent ethical review board and conforms with the principles and applicable guidelines for the protection of human subjects in biomedical research (Research Registry: 10340) and followed the guidelines set out in the consolidated standards of reporting trials 2010 statement (Moher et al., 2010). The prospective trial was conducted between January 2023 and January 2024 at Aston University. Participants were required to be aged 18 years or older, with manifest symptoms and signs of DED, according to the second Tear Film and Ocular Surface Society Dry Eye Workshop diagnostic criteria (Ocular Surface Disease Index score ≥13 or 5-Item Dry Eye Questionnaire ≥6, with at least one positive indicator of homeostatic imbalance based on non-invasive tear film break up time, tear osmolarity and/or ocular surface staining) (Wolffsohn et al., 2017). Participants were also required to have manifest signs of MGD at baseline, according to the Tear Film and Ocular Surface Society International Workshop on Meibomian Gland Dysfunction diagnostic criteria (Tomlinson et al., 2011). Pre-existing therapeutic measures were allowed during the study period, however no changes to any treatment courses or routines (such as warm compresses) were permitted. Exclusion criteria included diagnosed systemic diseases that may have affected the ocular surface, prior ocular surgery and trauma. Eligible participants were enrolled for baseline screening after providing written informed consent to participate. A total of 30 eligible participants (mean age 36.4 ± 15.4 years, 77% female) were recruited and received treatment and follow-up, with 15 participants being randomised to each treatment arm, using a Latin square method devised by the principal investigator (JSW; Figure 5.1). This provided 95% power to detect a clinically significant OSDI difference of 10.35 (the midpoint of 7.3 to 13.4 for severe symptoms (Miller et al., 2010)), at a significance level of 0.05. Sample size calculation was conducted using G*Power software (v3.1; Franz Faul, Universität Kiel, Germany) for a two-tailed ANOVA test. A further 2 patients were enrolled but did not meet the symptomology criteria in order to participate.

5.2.2. Interventions

The study compared the effects of the MGrx device, and ‘traditional’ debridement and expression, on dry eye symptoms, and the tear film and ocular surface. Fifteen patients each were treated with the MGrx device, and a traditional lid warming and debridement and expression protocol.

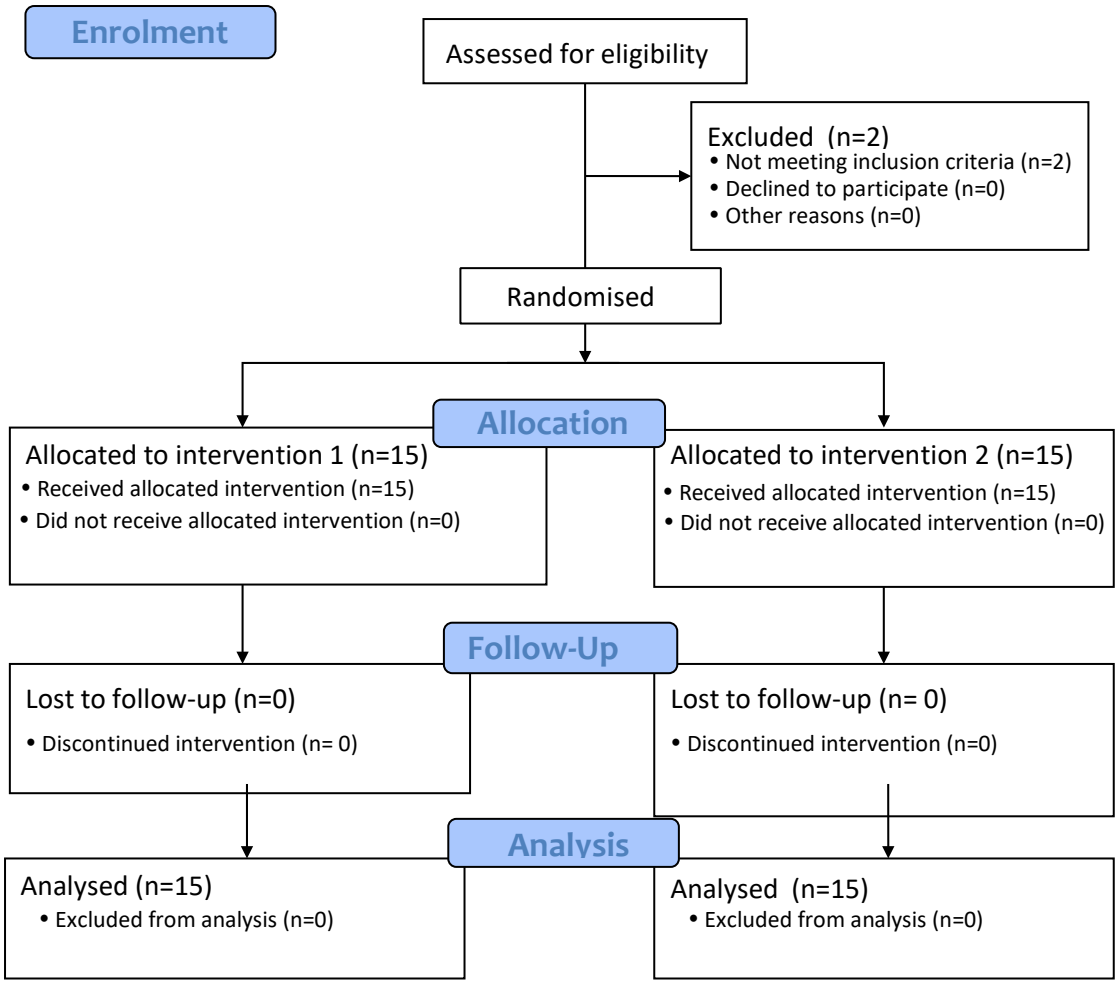

Figure 5.1. Consolidated standards of reporting trials 2010 flow diagram.

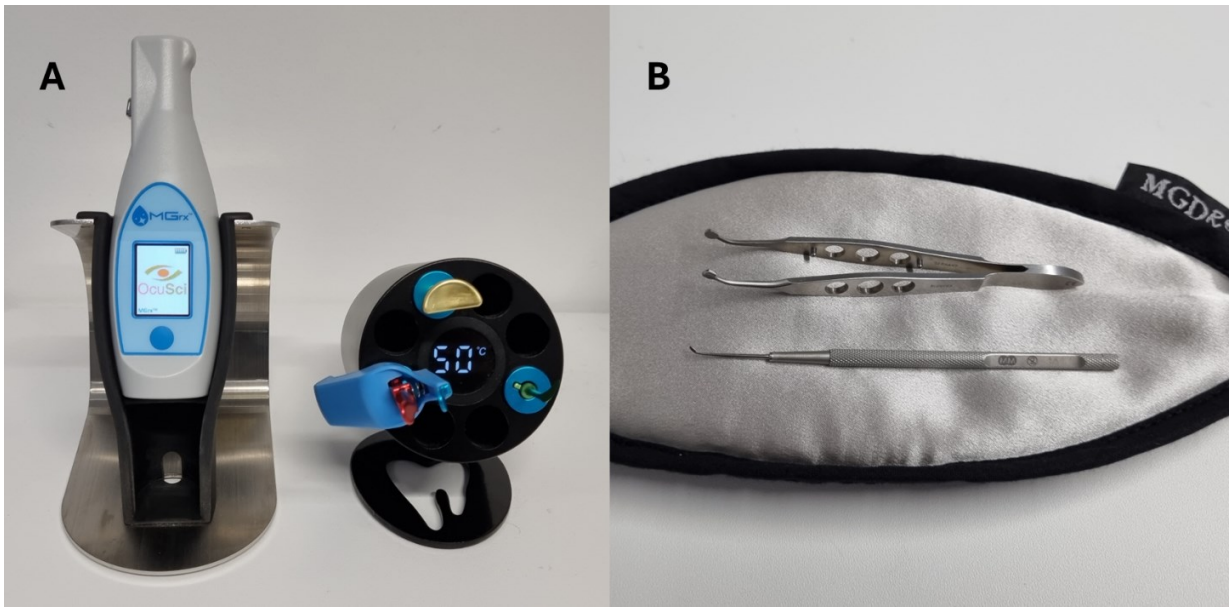

Figure 5.2. (A) The MGrx device, alongside its treatment instruments and heating unit. (B) Golf club spud and Arita tweezers, with the MGDRx warm compress.

For the MGrx device, the manufacturer-supplied instruction manual and 'In-Service Video' (OcuSci Inc., 2022) were followed. The three treatment instruments were pre-heated, with the instrument heater set to 50 °C, and the handheld MGrx device fully charged prior to use (Figure 5.2A). The debridement instrument was inserted into the MGrx, and one drop of 0.5% proxymetacaine was instilled into each eye, before sweeping the full width of each lid margin, from nasal to temporal and temporal to nasal. Next the thermal massage instrument was inserted, and gel applied to it, before warming and massaging the upper and lower lids for 120 seconds per eye. Finally, the thermal expression instrument was mounted and a further drop of 0.5% proxymetacaine was instilled into each eye, followed by expression of the full length of the upper and lower lids of both eyes. The manufacturer recommends that the MGrx treatment is not conducted at the slit-lamp, but suggests the use of magnifying loupes.

Fifteen control patients received 'standard' lid warming, debridement and expression. First, the MGDRx EyeBag (The EyeBag Company Ltd., Halifax, UK; Figure 5.2B) warm compress was placed in an 800 W microwave for 30 seconds, and the eyelids were warmed for 10 minutes. Next, one drop of 0.5% proxymetacaine was instilled into each eye, before debriding the full width of each lid margin, from nasal to temporal and temporal to nasal, using a golf club spud (Storz Ophthalmic Instruments, Bausch and Lomb, Rochester, New York, USA; Figure 5.2B). Finally, expression of the full length of the upper and lower lids of both eyes was conducted, using Arita tweezers (CorzaMedical, Parsippany, New Jersey, USA; Figure 5.2B). Debridement and expression were performed at the slit-lamp, to aid visualisation and precision.

5.2.3. Measurements

All participants were enrolled and assessed in the same dry eye clinic, by the same investigator (DS), at all baseline and follow-up visits. Ocular symptoms were assessed at each visit, using the OSDI, DEQ-5 and SANDE questionnaires. Clinical tests were conducted in accordance with the recommendations of the TFOS DEWS II Diagnostic Methodology subcommittee (Wolffsohn et al., 2017). To reduce the impact on tear film physiology, tests were ordered from least to most invasive at each study visit. All tear film and ocular surface measurements were assessed using the Keratograph 5M (Oculus, Optikgeräte, Wetzlar, Germany). Blink rate was measured by doubling the number of blinks counted during a 30 second video recording, taken once the patient was settled but before any instructions were given. Conjunctival hyperaemia was evaluated by automated objective evaluation of high magnification digital imaging (nasal and temporal regions averaged), benchmarked against the JENVIS grading scale, ranging from 0 to 4 (Sung et al., 2018). The lower tear meniscus height was assessed by capturing a high magnification digital image and applying pre-calibrated digital callipers, taking an average of 3

readings below the cornea. NIBUT was measured using automated detection of first breakup, while the participant maintained fixation and was requested to refrain from blinking, and the average of three readings was calculated for each eye (Wolffsohn et al., 2017). Inferior eyelid meibomian glands were expressed with the Meibomian Gland Evaluator (TearScience, North Carolina, USA). The number of meibomian gland orifices yielding lipid secretions was recorded for each eye.

5.2.4. Statistics

The data between groups were compared using SPSS Statistics (v29; IBM, New York, USA). Those measures (symptoms and objective redness grade) that produced normally distributed data (Shapiro-Wilk test; Table 5.3) were assessed by repeated measure Analysis of Variance, with technique as a between subject factor, and time as a within subject factor. Measures (blink rate, TMH, NIBUT, LLT grade, corneal and conjunctival staining grades, LWE grade and meibomian gland expression grade) that significantly differed from a normal distribution were analysed with a Friedman test, chi-square test, or Mann-Whitney *U* test where applicable. Values below p = 0.05 were taken as significant, and Bonferroni corrections were applied for multiple comparisons.

5.3. Results

A total of 30 participants (mean age 36.4 ± 15.4 yrs, range 20-65, 77% female) completed the study. No adverse reactions were reported, and all participants were able to tolerate treatment. Baseline characteristics were similar between the two treatment technique groups (Table 5.2).

Table 5.3 details which data produced normal distributions. In the Shapiro-Wilk test, a result of 0.05 or more indicates a normal distribution. Where both groups had normally distributed data at baseline, parametric tests were used, and where one or both groups had non-normally distributed data, non-parametric tests were used.

Table 5.2. Baseline participant characteristics, by treatment group. Normally distributed data is presented as a mean ± 1 standard deviation. Other data is presented as a median and (range).

	MGrx Group (n = 15)	**Traditional Group (n = 15)**	**Significance (p)**
Demographics			
Age (yrs)	33.0 ± 15.2	39.8 ± 15.3	0.11[a]
Sex (% female)	87	93	0.20[a]
Ethnicity (% Asian)	53	53	<0.99[a]
Measures			
OSDI	38.9 ± 18.1	35.7 ± 11.8	0.87[b]
DEQ-5	12.0 ± 3.3	12.3 ± 3.8	0.87[b]
SANDE frequency	61.8 ± 24.1	60.7 ± 27.8	0.97[b]
SANDE severity	52.1 ± 21.4	46.9 ± 24.3	0.57[b]
Blink rate (per min)	20 (18-26)	24 (12-28)	0.78[b]
TMH (mm)	0.28 (0.24-0.34)	0.30 (0.24-0.35)	0.57[b]
NIBUT (s)	6.76 (4.41-8.56)	6.63 (5.10-8.65)	0.74[b]
Lipid layer grade	3.0 (2.5-4.5)	3.0 (2.5-4.0)	0.87[b]
Conjunctival redness grade (Jenvis)	0.72 ± 0.20	0.81 ± 0.26	0.37[b]
Corneal staining grade (Oxford)	0.0 (0.0-0.2)	0.0 (0.0-0.2)	0.60[b]
Conjunctival staining grade (Oxford)	0.0 (0.0-0.3)	0.0 (0.0-0.5)	0.97[b]
LWE grade	1.0 (0.0-2.0)	0.0 (0.0-2.0)	.65[b]
Expression grade	4.0 (2.0-5.0)	2.0 (0.0-4.0)	.09[b]

a - Chi-square test, b - Mann-Whitney *U* test. DEQ-5 = 5-item dry eye questionnaire, LWE = lid wiper epitheliopathy, NIBUT = non-invasive tear breakup time, OSDI = ocular surface disease index, SANDE = symptoms assessment in dry eye.

Table 5.3. Normality of baseline participant characteristics (Shapiro-Wilk test).

Characteristic	MGrx Group (n=15)	Traditional Group (n=15)
OSDI	p = 0.349*	p = 0.983*
DEQ-5	p = 0.917*	p = 0.602*
SANDE frequency	p = 0.463*	p = 0.723*
SANDE severity	p = 0.357*	p = 0.652*
Blink rate	p = 0.005	p = 0.004
TMH	p = 0.584	p = 0.01
NIBUT	p = 0.333	p = 0.003
Lipid layer grade	p = 0.975	p = 0.04
Conjunctival redness	p = 0.625*	p = 0.287*
Corneal staining	p = <0.001	p = <0.001
Conjunctival staining	p = <0.001	p = <0.001
Lip wiper epitheliopathy	p = 0.011	p = 0.001
Expression grade	p = 0.005	p = 0.045

*Normal distribution.

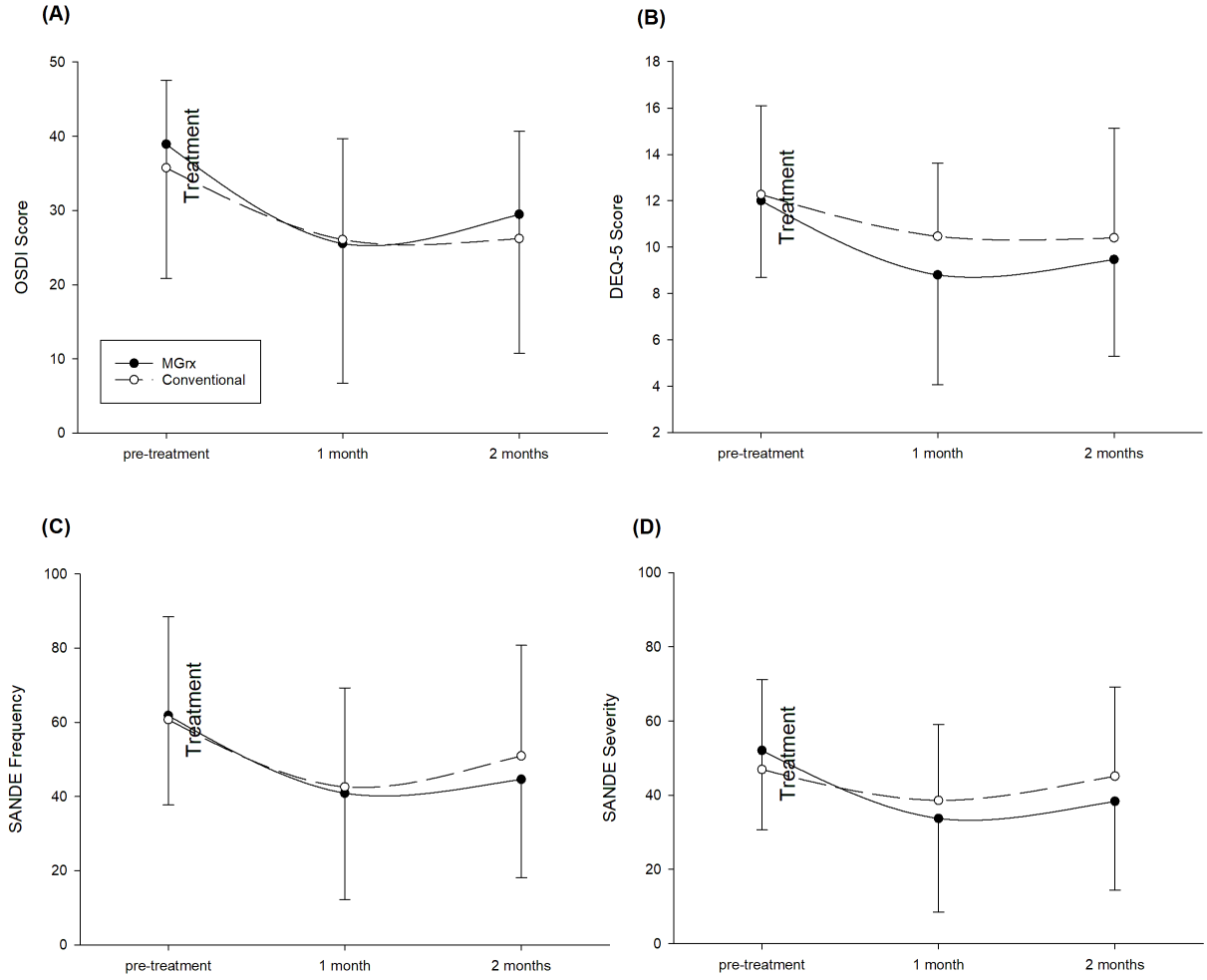

Figure 5.3. Improvement in symptoms post treatment with the (A) Ocular Surface Disease Index (OSDI); (B) 5-Item Dry Eye Questionnaire (DEQ-5); (C) Symptom Assessment iN Dry Eye (SANDE) Frequency; and (D) SANDE severity questionnaires using the MGrx device compared to conventional debridement of the eyelid margin and therapeutic expression of meibum. Error bars = 1 standard deviation.

5.3.1. Symptomology

All symptom questionnaire scores improved with treatment (Figure 5.3). OSDI reduced at 4 weeks post- MGrx (34%) and traditional treatment (27%; $F = 12.035$ $p < 0.001$). DEQ-5 reduced at 4 weeks post- MGrx (27%) and traditional treatment (15%: $F = 10.969$ $p < 0.001$). SANDE frequency score reduced 4 weeks post- MGrx (34%) and traditional treatment (28%; $F = 17.385$ $p < 0.001$). SANDE severity score reduced 4 weeks post- MGrx (35%) and traditional treatment (18%; $F = 9.514$ $p < 0.001$). There was no significant decline in symptomology over the 2 months post treatment (OSDI: $F = 1.236$ $p = 0.28$; DEQ-5: $F = 0.274$ $p = 0.61$; SANDE frequency: $F = 3.278$ $p = 0.08$; SANDE severity: $F = 3.322$ $p = 0.08$). There was no significant interaction between treatment and time for symptomology (OSDI: $F = 0.647$, $p = 0.531$; DEQ-5: $F = 0.728$, $p = 0.492$; SANDE

frequency: F = 0.681, p = 0.514; SANDE severity: F = 2.023, p = 0.152). The improvement was similar with MGrx and conventional treatment (OSDI: F = 0.647 p = 0.53; DEQ-5: F = 0.728 p = 0.49; SANDE frequency: F = 0.681 p = 0.51; SANDE severity: F = 2.023 p = 0.15).

5.3.2. Blink rate

Blink rate did not change after the MGrx (χ^2 = 1.483, p = 0.48) or conventional (χ^2 = 2.151, p = 0.34) treatment and there was no significant difference between the techniques (χ^2 = 3.045, p = 0.22). Post-hoc testing also showed similar blink rates in each treatment group, both one month (p = 0.37) and two months (p = 0.90) post treatment.

5.3.3. Tear film quality and quantity

Tear meniscus height did not change after the MGrx (χ^2 = 0.414, p = 0.81) or conventional (χ^2 = 3.170, p = 0.21) treatment and there was no significant difference between the techniques (χ^2 = 1.514, p = 0.47). Post-hoc testing also showed similar TMH in each treatment group both one month (p = 0.31) and two months (p = 0.44) post treatment. Non-invasive tear breakup time was stable after the MGrx (χ^2 = 0.533, p = 0.77), but deteriorated with conventional treatment (χ^2 = 10.133, p = 0.006) between one and two months post treatment, resulting in a significant difference between the techniques (χ^2 = 7.200, p = 0.03). Lipid layer thickness grade did not change after the MGrx (χ^2 = 1.187, p = 0.55) or conventional (χ^2 = 4.65, p = 0.10) treatment and there was no significant difference between the techniques (χ^2 = 4.778, p = 0.09). Post-hoc testing also showed similar lipid thickness grades in each treatment group, both one month (p = 0.33) and two months (p = 0.78) post treatment.

5.3.4. Ocular surface characteristics

Conjunctival redness grade did not change with treatment (F = 0.660, p = 0.53), with no difference between MGrx and conventional treatment (F = 0.711, p = 0.41). Post-hoc testing showed similar grades between 1 and 2 months post treatment (F = 0.938, p = 0.34). Corneal staining grade did not change after the MGrx (χ^2 = 0.813, p = 0.67) or conventional (χ^2 = 2.150, p = 0.34) treatment and there was no significant difference between the techniques (χ^2 = 2.861, p = 0.24). Post-hoc testing showed similar staining grades in each treatment group, both one month (p = 0.65) and two months (p = 0.29) post treatment. Conjunctival staining grade did not change after the MGrx (χ^2 = 2.438, p = 0.30) or conventional (χ^2 = 3.622, p = 0.16) treatment and there was no significant difference between the techniques (χ^2 = 5.594, p = 0.06). Post-hoc testing showed similar staining grades with MGrx and conventional treatment, at both one month (p = 0.94) and two months (p = 0.65) post treatment. Lid wiper epitheliopathy grade did not change after the MGrx (χ^2 = 0.378, p = 0.83) or conventional (χ^2 = 0.111, p = 0.95) treatment and there was no significant difference

between the techniques (χ^2 = 0.255, p = 0.88). Post-hoc testing showed similar LWE grades with MGrx and conventional treatment at both one month (p = 0.16) and two months (p = 0.46) post treatment.

5.3.5. Meibomian gland expressibility

Expression grade did not change after the MGrx (χ^2 = 0.419, p = 0.81) or conventional (χ^2 = 3.00, p = 0.22) treatment and there was no significant difference between the techniques (χ^2 = 1.520, p = 0.47). Post-hoc testing showed similar expression grades with MGrx and conventional treatment at both one month (p = 0.22) and two months (p = 0.41) post treatment.

5.4. Discussion

Previous studies have investigated traditional in-office treatments for MGD, such as forceful expression, with (Bilkhu et al., 2022b) and without (Korb and Blackie, 2011, Moon et al., 2021, Swiderska et al., 2023) lid warming, and/or debridement-scaling (Bilkhu et al., 2022b, Korb and Blackie, 2013, Moon et al., 2021, Ngo et al., 2015). Other studies have examined the efficacy of recently developed electronic devices (Badawi, 2018, Lane et al., 2012, Li et al., 2022, Tauber et al., 2020), which provide automated or standardised eyelid treatment procedures, however the cost of consumables may render some patients unable to access treatment. To date, no data have been available to compare the novel MGrx device to traditional meibomian gland debridement and expression. Therefore, a randomised controlled trial was conducted, to compare these treatment techniques in patients with meibomian gland dysfunction and evaporative DED.

The key findings of this study were significant improvements in dry eye symptoms, following either MGrx or traditional debridement and expression, as shown by reduced OSDI and DEQ-5 questionnaire scores, and both frequency and severity sub-scores of the SANDE visual analogue scales, which lasted for at least 2 months post treatment. There were no statistically significant differences in symptoms between the two treatment groups at both one and two months post treatment. Ocular surface measures of blink rate, tear meniscus height, lipid layer thickness grade, conjunctival redness grade, corneal and conjunctival staining grades, lid wiper epitheliopathy grade and meibomian gland expression grade were unchanged with either treatment. Non-invasive tear breakup time did not improve after MGrx treatment; however, it deteriorated in the traditional treatment group, perhaps due to progressive disease or environmental changes, suggesting the MGrx may have a protective effect compared to traditional treatment. These findings corroborate previous research findings (see Table 5.1), adding to the evidence that meibomian gland debridement and expression is an effective

treatment for MGD. There were, however, significant inter-study differences, for example treatment regimes, inclusion criteria, diagnostic criteria, age, severity and ethnicity of participants, diagnostic equipment and techniques differed between studies.

McMurren et al. (2023) conducted an open-label trial, also using the MGrx device, and found statistically significant improvements in symptoms (SPEED), tear breakup time and the product of meibomian gland score multiplied by meibum quality score, at 30 days post treatment. Similarly to this trial, the majority of participants were female, both upper and lower lids were treated, and symptoms improved substantially. Conversely, participants in the current trial did not demonstrate improvements in any clinical signs. However, there were some significant disparities in materials and methods between the two studies. For example, McMurren et al. did not employ the TFOS DEWS II diagnostic methodology in their inclusion criteria, opting instead for a SPEED score of over 12 or TBUT of less than 6 seconds in either eye. They excluded patients with more than 66% lower lid gland atrophy and recruited an older age group (mean age 54 years, compared to 36 in this trial) so it may be that their participants had more advanced MGD at baseline, and hence more scope for improvement in clinical signs. It is also known that signs take longer to change than symptoms post treatment, so improvements in signs may have been seen with longer follow-up or after repeated treatment (Craig et al., 2021).

While another debridement and expression study reported improvements in both signs and symptoms at one month post treatment (Moon et al., 2021), it was an unmasked retrospective case series of patients with more advanced disease. Furthermore, debridement involved BlephEx, and participants performed daily warm compresses and lid scrubs, and instilled artificial tears during follow-up, likely enhancing the treatment efficacy.

In terms of randomised controlled trials, Korb and Blackie (2013) reported improvements in symptoms and diagnostic (not forced) meibomian gland expression after debridement of the lower lid alone, in a double-masked randomised-controlled trial. Another small randomised but unmasked trial of debridement on both lids also found similar results to this study, with no improvement in tear stability or ocular surface signs (Ngo et al., 2015).

Other studies summarised in Table 5.1 aimed to improve the understanding of the relationship between meibomian gland structure and function, rather than examining clinical treatment effects on symptoms and ocular signs such as TBUT (Bilkhu et al., 2022b, Korb and Blackie, 2011, Swiderska et al., 2023). Bilkhu et al. (2022b) conducted debridement and expression in separate steps, but without symptom assessment or follow-up. Korb and Blackie (2011) investigated the amount of pressure required for partial and full meibomian gland expression, and the resulting

pain, but likewise did not assess treatment effectiveness. Devices designed to deliver automated or standardised lid heat and massage treatments have been shown to be effective (Badawi, 2018, Lane et al., 2012, Li et al., 2022, Tauber et al., 2020), but they do not debride keratinised tissue from the lid margin which is likely to impact their effectiveness (Bilkhu et al., 2022b).

This study sheds light on a novel device for in-office thermal meibomian gland debridement and expression. The results affirm that debridement and expression are useful in reducing dry eye symptoms in patients with EDE, which accounts for the vast majority of sufferers (Lemp et al., 2012). The heated tools of the MGrx reduce the procedure time by approximately 6 minutes compared to lid warming with warm compresses, and are reusable, adding per-treatment cost savings. The heat can be applied more directly to the lid margin and there is no delay between heating the second eye and performing the expression. The tools can be autoclaved and reused indefinitely. Furthermore, all the study participants found treatment to be effective and tolerable.

This was a randomised controlled trial, which is widely considered to be the gold standard clinical trial design, as it generates the highest level of experimental evidence. There were, however, some limitations. Baseline characteristics were well matched between treatment groups (Table 5.2), however the study was not powered to examine differences in effect with participant demographics such as ethnicity, or with meibomian gland disease severity. There was no masking of investigators (due to the need for consistency of treatment) or participants (due to the invasive nature of the procedure), which could have resulted in bias. However, the effectiveness measurements were obtained using objective techniques, for example the automated detection of first tear breakup on the Oculus K5M, generated independently of investigator input. This trial involved three visits: at baseline, one month and two months. Therefore, it is possible that changes in symptoms and signs could have occurred between visits. Confounding factors, such as hay fever, lack of sleep and intense digital device use, may have affected some participants, however this was likely to have affected both groups equally. Further research, addressing the above limitations, would therefore be beneficial.

In conclusion, the MGrx device provides an effective, safe and tolerable means of conducting in-office treatments for DED. It has time, space and cost-saving benefits compared to conventional debridement and expression approaches.

A key principle of evidence-based medicine is the use of current best evidence in clinical care. It is important to know if practitioners are adopting the best practice in DED therapy, based upon the available evidence. In order to determine if this is the case, a unique series of global surveys has been conducted, and the results analysed and compared to track changes in management

patterns over time. The following chapter is based upon the second, and most recent, in this series, which was coordinated by the thesis author.

6. Clinical practice patterns in the management of dry eye disease: A TFOS international survey 2023-4

The work in this chapter has been submitted for publication in a peer-reviewed journal as:

James S Wolffsohn, David A Semp, Debarun Dutta, Lyndon Jones, Jennifer P Craig and the TFOS ambassadors (2024). Clinical practice patterns in the management of dry eye disease: A TFOS international survey 2023-4. The Ocular Surface.

It has also been accepted for presentation at the American Academy of Optometry:

James S Wolffsohn, David A Semp, Debarun Dutta, Lyndon Jones, Jennifer P Craig and the TFOS ambassadors. Clinical practice patterns in the management of dry eye disease: A TFOS international survey 2023-4. AAO Academy, Indianapolis USA, 7th Nov 2024.

6.1. Introduction

DED is common and symptomatic, affecting many millions of individuals worldwide (Stapleton et al., 2017). It is a multifactorial condition characterised by a loss of tear film homeostasis, perpetuated by a vicious cycle of tear film instability, hyperosmolarity, and ocular surface damage and inflammation (Craig et al., 2017a). The nature and severity of symptoms vary widely, and can significantly impair quality of life (Schiffman et al., 2003) and increase anxiety and depression (Li et al., 2011). This results in considerable human and economic burden, through loss of productivity, and healthcare costs incurred by individuals and healthcare systems (Luo et al., 2021, McDonald et al., 2016, Morthen et al., 2021). Considered in totality, the appropriate diagnosis and management of DED has a far-reaching impact and, as such, is of high importance.

As with other diseases, the type and severity of DED should be identified, in order to formulate an effective management plan (Craig et al., 2017a, Jones et al., 2017). DED can be subclassified into evaporative, aqueous deficient, or a combination of these elements (Craig et al., 2017a). Features of EDE include changes in meibomian gland secretions and morphology, and abnormal lipid layer thickness on interferometry, suggesting meibomian gland dysfunction (Wolffsohn et al., 2017). In ADDE, there is reduced aqueous tear volume, apparent as a reduction in tear meniscus height (Craig et al., 2021).

Artificial tears are the mainstay management option for DED, being easily accessible in a wide range of formulations, and having a low risk-profile (Jones et al., 2017), with the addition of lipid-containing products being preferential in EDE management (Craig et al., 2021, Essa et al., 2018). With numerous products on the market, it can be difficult for patients and practitioners to ascertain the best option, which can result in a trial-and-error approach, accompanied by mounting frustration and expense (Semp et al., 2023). Other common strategies may include patient education, modification of local environment, dietary modifications, such as oral essential fatty acid supplementation, modification/elimination of offending systemic and topical medications, and lid hygiene/ warm compresses (Jones et al., 2017). Numerous other treatments have been used in the management of DED, but as healthcare practitioners, it is essential that clinicians are guided by evidence from high quality research. The TFOS DEWS II Management and Therapy Report provided a staged management algorithm, with suggested treatments based on the best available evidence at the time (Jones et al., 2017). It is intended that this be used following a positive diagnosis and subclassification of DED, in conjunction with other available clinical information regarding its nature and severity.

The TFOS DEWS II reports provided expert consensus recommendations for the diagnosis and management of DED. However, there remains limited evidence to guide practitioners as to which

treatment may be expected to be most effective for each DED severity and subtype (Jones et al., 2017). Previous studies have compared management patterns between certain countries (Downie et al., 2016), between different professions working within the same country (van Tilborg et al., 2015, Williamson et al., 2014, Xue et al., 2017) and have evaluated differences between clinical patterns and evidence-based guidelines across Australia (Downie et al., 2013) (Table 6.1). A recent study looked at the evolving landscape of optometry in the United Kingdom, in light of its increasing scope (Casemore et al., 2023). Nonetheless, there is still a dearth of studies comparing global trends (Sy et al., 2015).

The purpose of relaunching the TFOS international survey after 5 years was to re-evaluate clinical DED prescribing and management patterns of dry eye practitioners (Wolffsohn et al., 2021a), and examine how this has changed since the reporting of TFOS DEWS II, with the aim of improving patient care. This allows practitioners to compare their practice to that of their peers, and understand how management varies in different locations across the world. This is also important for industry, in terms of product development and in the provision of professional education and support.

6.2. Methods

6.2.1. Survey design

The content of the survey (Figure 6.1) was chosen to reflect the dry eye management strategies reported by TFOS DEWS II (Jones et al., 2017). The wording of the questions was designed to ascertain which treatments a practitioner would select, depending on the subtype and severity of DED. It was first produced in English, and then translated into 14 languages (Brazilian Portuguese, Chinese/Mandarin Chinese, Czech, French, German, Italian, Spanish, Polish, Portuguese, Rumanian, Russian and Serbian). In every instance, the translation underwent a process of back-translation and was subsequently reviewed by a native speaking eye care professional, ensuring that the intended meaning of the questions was preserved in each case (Su and Parham, 2002). Once perfected, the anonymous survey was administered using the online Qualtrics platform (Utah/Seattle, Washington, USA).

Question Categories	Possible Responses
Practitioner demographics	Mode of practice; ophthalmologist, optometrist or other Years of clinical experience Country of practice
Type of dry eye patients managed (ranking)	1. No presenting specific symptoms: identified incidentally on questioning 2. Intermittent presenting symptoms: occasional effect on quality of life 3. Mild symptoms: low impact on quality of life 4. Moderate symptoms: frequent impact on quality of life 5. Severe symptoms: constant debilitating effect on quality of life
Are you LICENSED to use this within your scope of practice in your country? Do you ever PRESCRIBE this option? What SUBTYPE(S) of dry eye disease do you consider this treatment appropriate for (select as many as apply)? What SEVERITY(S) of dry eye disease do you consider this treatment appropriate for (select as many as apply)?	1. Advice 2. Essential fatty acid supplements 3. Artificial tears a. Low viscosity-enhancing lubricant PRESERVED b. High viscosity-enhancing lubricant PRESERVED c. Low viscosity-enhancing lubricant UNPRESERVED d. High viscosity-enhancing lubricant UNPRESERVED 4. Ointments 5. Lipid containing lubricants (drops/spray) 6. Lid hygiene a. Lid wipes/scrubs b. Demodex cleansing lid wipes c. In-office demodex lid control d. Lid margin debridement e. In-office lid hygiene (e.g. BlephEx) f. Therapeutic meibomian gland expression 7. Moisture chamber spectacles/ goggles 8. Punctal occlusion (with plugs) 9. Warm compresses a. Home-made warm lid compress, such as face-cloth b. Commercially available warm lid compress/face mask c. In-office thermal pulsation of lids (e.g. LipiFlow) 10. In-office techniques (e.g. intense pulsed light therapy) 11. Topical antibiotics (e.g. azithromycin) 12. Systemic antibiotics a. Systemic azithromycin b. Oral antibiotics (e.g. doxycycline) 13. Topical anti-inflammatory/ immunosuppression a. Topical corticosteroids b. Topical cyclosporine c. Topical tacrolimus d. Topical lifitegrast 14. Secretagogues a. Topical secretagogues b. Oral secretagogues 15. Biologics a. Autologous/allogeneic serum b. Amniotic membrane 16. Therapeutic contact lenses 17. Surgical approaches a. Intraductal probing b. Other surgical approaches

Figure 6.1. Summary of questions presented in the survey. Modified from (Wolffsohn et al., 2021a).

6.2.2. Ethics

This study adhered to the tenets of the Declaration of Helsinki and received ethical clearance from the respective ethics committees at Aston University and the University of Auckland (REC ID: 019870). Data were gathered anonymously and were handled confidentially. Prior to survey completion, a statement detailed the survey's duration, that submission of the questionnaire signified their consent to participate, and that due to the anonymity of the data, no modifications could be made once the responses were submitted. Participants could submit responses only once each, from a single device.

6.2.3. Participants

The online survey link was disseminated through various channels, including email, TFOS Ambassadors, conference seminars, professional colleges, and alumni university communities and by word-of-mouth. The survey remained accessible from July 2023, until data extraction in May 2024.

6.2.4. Data analysis

For the purpose of statistical analysis, countries were grouped into continents; Europe and the United Kingdom (EU), North America (NA), Latin America (LA), Australasia (AA), Asia/Middle East (AME) and Africa (A). In the 2018-19 survey, insufficient responses were received from participants in Africa to allow for statistical analysis of data from this continent.

SPSS Statistics (version 29, New York, USA) was employed for data analysis, and incomplete surveys were excluded. Descriptive statistics, such as median and range, or mean and standard deviation, were utilised to portray the clinical severity and subtype of DED when examining practitioners' therapy approaches. Given the ordinal nature of the data, the Mann-Whitney U test was used to compare data between continents. For usage data, the chi-square test was applied. For categorical data, Fisher’s exact test was employed. Regarding statistical significance, a p-value of 0.003 or less was considered significant when comparing approaches to dry eye management between continents, based on a Bonferroni adjustment.

Table 6.1. Previous studies on patterns of clinical diagnosis and management of dry eye disease (all anonymous internet surveys).

Study	Comparison	Topics	Surveyed	Professionals	Results	Comments
Downie et al., (2013)	Australian practice versus international guidelines	- Practitioner demography - Dx & Mg for each severity - Research evidence basis	144	Optoms	- DED practitioners utilise more Dx techniques & newer treatments - Mg: - Mild: ATs & lid hygiene - Moderate: Pres. free lubricants - Severe: Gels	- EFA recommended if more severe. - Steroids & anti-inflammatories also used in moderate & severe cases.
Downie et al., (2016)	UK versus Australian practice patterns	- Practitioner demography - Dx & Mg at each severity - Research evidence basis	317	Optoms	- Symptoms, MGE & FBUT key in UK & Australia for Dx - Mg: - Mild: Lid hygiene & lubricants - Moderate: Pres. free gels - Severe: Ointments & punctal plugs	- Dx: UK more use of TMH, LIPCOF, grading of conj. LG stain & OSDI - Dx: Australia FBUT often used - Severity: UK evaluation of symptoms - Mg: UK advise more EFA & more unpreserved ATs in mild dry eye. Australia uses steroids in moderate & severe dry eye
Sy et al., (2015)	Global practice patterns	- Practitioner demography - mg of ADDE (case study) - Treatment availability - Mg algorithms	115	Cornea specialists (66 %), general ophthalmol (16 %), non-clinical research (6 %), optoms (6 %) & other (6 %)	Commonest mg included ciclosporin, FML, loteprednol & autologous serum. Commonest oral treatments included EFA supplements, weak doxycycline & flaxseed products, and punctal plugs	Treatment efficacy measured with corneal NaFl stain, symptoms of foreign body & burning.
Van Tilborg et al., (2015)	Optometry & general practice in Holland	- Awareness - Dx methodology - Preferred Mg	231	Optoms (138) & GPs (93)	- Dx: Variable GPs: Dx testing uncommon. - Mg: Agreement limited to gel/ointment products	- Mg: Optoms: use more pres. free ATs, eyelid hygiene & heat therapies GPs: use more preserved ATs

Study	Comparison	Topics	Surveyed	Professionals	Results	Comments
Williamson et al., (2014)	Perceptions of optoms & ophthalmologists in North Carolina	- Awareness of symptoms - Dx - Mg used	100	Optoms & Ophthalmol	- Dx: BUT, NaFl stain - Mg: ATs, warm comps & eyelid cleansing	- Dx: combined BUT, NaFl & LG stain Optoms: NaFl stain & history Ophthalmol: Schirmer
Xue et al., (2017)	Protocols for diagnosis & management in New Zealand	- Practitioner demography - Dx methodology - Mg at each severity - Research evidence basis	203	Optoms (174) & Ophthalmol (29)	- Dx: Symptoms, MGE, FBUT Optoms: MGE Ophthalmologists: NaFl stain - Mg: Mild: Preserved & pres. free ATs & lid hygiene Moderate: Lid hygiene, EFAs, pres. free ATs & gels Severe: Lid hygiene, pres. free ATs & gels	For severe DED pres. free gels, ointments, ciclosporin, steroids, oral tetracyclines, punctal plugs & autologous serum used by both professions
Casemore et al. (2023)	Diagnosis & management patterns of UK optometrists in light of increased role in therapeutic management	- Practitioner demographics - Diagnostic techniques - management & patterns of intervention - Therapeutic qualification & implementation	131	Optoms in primary care setting, excluding secondary & tertiary practice	Optoms in primary care setting have inadequate time treating DED. Therapeutically qualified Optometrists felt more confident treating DED. - Dx: Symptomatology, NaFl staining, MGE, FBUT, TMH, screen use - Mg: Mild: Environmental modification, dietary advice, lid hygiene, unpreserved ATs Moderate: Ointments, liposomal sprays, light therapies, Severe: topical corticosteroids, punctal plugs, systemic tetracyclines	Increase in therapeutic management of DED in UK, & stepwise approach is being implemented

AT – Artificial Tears, DED – Dry Eye Disease, GP – General Practitioner, Dx – Diagnosis, Mg – Management, MGE – Meibomian Gland Examination, FBUT – Fluorescein BreakUp Time, LG – Lissamine Green, NaFl – Sodium Fluorescein, BUT – BreakUp Time (method not defined), TMH – Tear Meniscus Height, LIPCOF – Lid Parallel Conjunctival Folds, OSDI – Ocular Surface Disease Index Questionnaire.

6.3. Results

6.3.1. Practitioner demographics

Completed questionnaires were submitted by a total of 905 eye care professionals, (42% ophthalmologists, 52% optometrists and 6% opticians) from 56 countries across 6 continents:

• Europe/UK and Scandinavia (n = 410): Albania (n = 1), Austria (n = 6), Bulgaria (n = 42), Czech Republic (n = 4), Denmark (n = 4), France (n = 2), Germany (n = 14), Ireland (n = 4), Italy (n = 24), Moldova (n = 1), Netherlands (n = 13), Poland (n = 13), Portugal (n = 23), Romania (n = 5), Serbia (n = 3), Slovakia (n = 1), Spain (n = 26), Sweden (n = 2), Switzerland (n = 3), United Kingdom (n = 219).

• North America (n = 81): Canada (n = 57), United States of America (n = 24).

• Latin America (n = 169): Argentina (n = 17), Brazil (n = 8), Chile (n = 18), Colombia (n = 5), Dominican Republic (n = 1), Ecuador (n = 4), Guatemala (n = 1), Mexico (n = 67), Paraguay (n = 1), Peru (n = 46), St. Vincent and the Grenadines (n = 1).

• Australasia (n = 81): Australia (n = 34), New Zealand (n = 47).

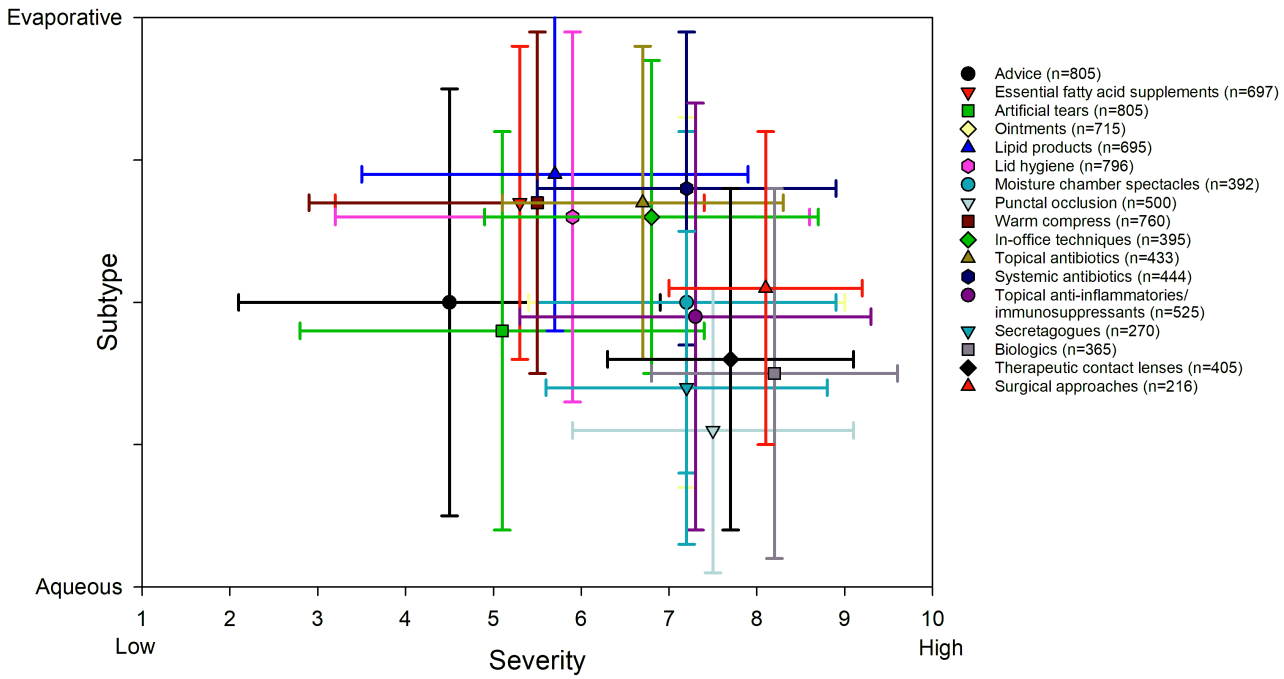

Figure 6.2. Global management of dry eye disease based on severity and subtype. Symbol positioned at median value and bars indicate average range.

• Asia and the Middle East (n = 114): China (n = 44), Georgia (n = 9), Hong Kong (n = 5), India (n = 10), Malaysia (n = 1), Philippines (n = 1), Russia (n = 1), Saudi Arabia (n = 1), Singapore (n = 2), South Korea (n = 14), Thailand (n = 26).

• Africa (n = 50): Botswana (n = 1), Cameroon (n = 1), Ethiopia (n = 2), Ghana (n = 9), Kenya (n = 1), Madagascar (n = 1), Nigeria (n = 15), Seychelles (n = 1), South Africa (n = 16), Uganda (n = 3).

The average years of clinical experience was 14.9 ± 7.8, being similar between professions (p = 0.573).

6.3.2. Types of patients examined

Of those who responded (n = 905), 827 practitioners detailed the severities of dry eye they manage; patients with mild (28%, n = 229/827) and moderate (26%, n = 210/827) symptoms were the most common. Although 11% (n = 89) predominantly managed those with severe symptoms, some 51% (n = 410) found these to be the least common.

6.3.3. Global management and therapeutic approach

Out of all the respondents, 7% (n = 62) stated they were unable to prescribe for DED but, of those, 21% (n = 13 / 62) were providing advice, such as diet, water intake and office conditions.

Numerous dry eye therapies (Jones et al., 2017) were found to be in usage. The commonest management approaches globally are advice (82%), low (82%) and high (81%) viscosity unpreserved lubricants and lid wipes/scrubs (79%). Figure 6.2 presents, the average, and range of severities and subtypes practitioners identified each treatment to be most suitable for.

Trends in management strategies were observed worldwide. Unpreserved products were prescribed more commonly than preserved (1.45:1; n = 738 to 509, p<0.001). Unpreserved artificial tears with low and high viscosity were prescribed by similar numbers of practitioners (1.01:1; n = 628 to 619, p=0.646). Ointments were given more commonly (1.13:1; n = 691 to 612, p<0.001) than lipid-containing lubricants, and unpreserved high viscosity lubricants were used more than ointments (1.06:1; n = 733 to 691, p=0.016). Prescriptions for general lid wipes/scrubs outnumbered those with anti-Demodex properties (1.33:1; n = 719 to 541, p<0.001). Patient applied anti-Demodex wipes were given more commonly than in-office anti-Demodex therapies (1.73:1; n = 541 to 313, p<0.001). Commercially available warm lid compresses/face masks are now recommended by more practitioners than homemade alternatives (e.g. hot flannels) (1.11:1; n = 603 to 541, p=0.003). With regard to in-office lid hygiene, for example BlephEx or debridement, lid debridement was used by similar numbers (1.01:1; n = 320 to 318, p=0.921), however, therapeutic meibomian gland expression is still used by more practitioners (1.47:1; n = 466 to

318, p<0.001). Intense pulsed light therapy was used by more practitioners than LipiFlow (by 1.48 times; n = 245 vs 166, p<0.001). For tear preservation, punctal occlusion was utilised more frequently than moisture chamber spectacles/goggles (by 1.41 times; n = 364 to 259, p<0.001).

A similar number of prescriptions were written for topical compared to oral antibiotics (1.09:1; n = 419 to 385, p=0.108). There was an equal split between topical and oral azithromycin (1.01:1; n = 235 to 232, p=0.872). Topical secretagogues were used more than systemic forms (1.79:1; n = 145 to 81, p<0.001). Prescriptions for topical immunomodulatory agents, e.g. tacrolimus, greatly outnumber those for lifitegrast (1.90:1; n = 169 to 89, p<0.001), however corticosteroids were favoured much more than tacrolimus (2.83:1; n = 478 to 169, p<0.001). Clinicians fit therapeutic contact lenses in favour of autologous/allogeneic serum (1.36:1; n = 363 to 267, p<0.001) and amniotic membrane (1.70:1; n = 363 to 214, p<0.001). Autologous/allogeneic serum was reported to be prescribed more commonly than amniotic membrane (1.25:1; n = 267 to 214, p=0.005). Finally, other surgical approaches are now performed by more responding clinicians than intraductal probing (1.32:1; n = 91 to 69, p=0.071).

The large number of treatments were divided into the categories shown in Figure 6.1, in order to simplify visualisation. Numbers (percentage) of respondents prescribing specific treatments are listed below:

- Advice; n=805 (89%) such as on sleep or diet.
- Essential fatty acid supplements; n=697 (77%) in oral form.
- Artificial tears; n=805 (89%) – low and high viscosity, preserved and unpreserved.
- Ointments; n=715 (79%).
- Lipid containing lubricants (drops/spray); n=695 (77%).
- Lid hygiene; n=796 (88%).
- Moisture chamber spectacles /goggles; n=392 (43%).
- Punctal occlusion (with plugs); n=500 (55%).
- Warm compresses; n=760 (84%) reported offering both in-office thermal pulsation as well as patient-administered lid warming.
- In-office techniques (e.g. intense pulsed light therapy); n=395 (44%).
- Topical antibiotics (e.g. azithromycin); n=433 (48%).
- Systemic antibiotics; n=444 (49%).
- Topical anti-inflammatory/immunosuppressant medications; n=525 (58%) prescribed dual anti-inflammatory options.
- Secretagogues; n=270 (30%) were prescribed both topically and orally.

- Biologic products; n=365 (40%) gave serum in addition to membranes.
- Therapeutic contact lenses; n=405 (45%).
- Surgical approaches; n=216, (24%) administered intraductal probing and/or other surgical approaches.

6.3.4. Severity

The choice of treatments deemed suitable for each disease severity are presented in Figure 6.2. Some therapies were applied roughly equally for all severity levels (scaled from 1 – mild to 10 – extreme), such as advice (median 4.5, range 4.8), artificial tears (median 5.1, range 4.6) and nutritional supplements (median 5.3, range 4.2). Others were reserved for patients with more severe disease, for example biologics (median 8.2, range 2.8) and surgical approaches (median 8.1, range 2.2).

The analysis of the proportion of practitioners selecting a particular management approach based on varying severity levels revealed statistically significant differences across continents (Table 6.2). Advice was offered to patients with lower levels of disease severity in Africa, Asia/Middle East, Australasia and Europe/UK, than in Latin America. Practitioners in Latin America also reported reserving artificial tears for patients with higher DED severity than in North America, Asia/Middle East and Europe. Practitioners in Australasia prescribed lipid-containing lubricants for dry eye of lower severity than did their counterparts in Asia/Middle East, Latin America and Africa; as did those in Europe. Topical and systemic antibiotics were prescribed more readily in Africa, Latin America and Asia/Middle East than Europe; topical antibiotics more so in Latin America than in Australasia and systemic antibiotics more so in North America than in Europe. Topical anti-inflammatories/immunomodulators were used for dry eye of lower severity in Asia/Middle East and North America than in Europe and Australasia; and in Latin America compared to Europe. Secretagogues were favoured for milder disease in Asia/Middle East and Latin America, than in Europe and Australasia.

Table 6.2. Differences in treatment choice between continents, by severity and subtype of DED.

Treatment	Severity	Sig. (p)	Subtype	Sig. (p)
Advice	A ⇨ LA	**0.001**	Not significant	
	AME ⇨ LA	**<0.001**		
	AA ⇨ LA	**0.001**		
	EU ⇨ LA	**<0.001**		
Essential fatty acid supplements	Not significant		Not significant	
Artificial tears	NA ⇨ LA	**<0.001**	Not significant	
	AME ⇨ LA	**<0.001**		
	EU ⇨ LA	**0.002**		
Ointments	Not significant		LA → EU	**<0.001**
			LA → A	**<0.001**
Lipid containing lubricants (drops/ spray)	AA ⇨ AME	**0.001**	Not significant	
	AA ⇨ LA	**<0.001**		
	AA ⇨ A	**<0.001**		
	EU ⇨ AME	**0.008**		
	EU ⇨ LA	**<0.001**		
	EU ⇨ A	**0.006**		
Lid hygiene	Not significant		A → AME	**<0.001**
			EU → AME	**<0.001**
			NA → AME	**0.001**
Moisture chamber spectacles/ goggles	Not significant		Not significant	
Punctal occlusion (with plugs)	Not significant		Not significant	
Warm compresses	Not significant		Not significant	
In-office IPL therapy	Not significant		Not significant	
Topical antibiotics (e.g. azithromycin)	A ⇨ EU	**<0.001**	Not significant	
	LA ⇨ AA	**0.008**		
	LA ⇨ EU	**<0.001**		
	AME ⇨ EU	**<0.001**		
Systemic antibiotics	A ⇨ EU	**<0.001**	A → LA	**<0.001**
	LA ⇨ EU	**<0.001**	A → EU	**<0.001**
	NA ⇨ EU	**0.006**	A → NA	**<0.001**
	AME ⇨ EU	**0.004**	A → AME	**<0.001**
			A → AA	**<0.001**
Topical anti-inflammatory / immunomodulators			NA → AME	**<0.001**
	AME ⇨ EU	**<0.001**	NA → EU	**<0.001**
	AME ⇨ AA	**<0.001**	NA → AA	**<0.001**
	NA ⇨ EU	**<0.001**	LA → AME	**<0.001**
	NA ⇨ AA	**0.001**	LA → EU	**<0.001**
	LA ⇨ EU	**<0.001**	LA → AA	**<0.001**
Secretagogues	AME ⇨ EU	**<0.001**	LA → AME	**<0.001**
	AME ⇨ AA	**<0.001**		
	LA ⇨ EU	**<0.001**		
	LA ⇨ AA	**<0.001**		
Biologics	Not significant		Not significant	
Therapeutic contact lens approaches	Not significant		Not significant	
Surgical approaches	Not significant		EU → NA	**<0.001**

EU=Europe/UK & Scandinavia, NA=North America, LA=Latin America, AA=Australasia, AME=Asia/Middle East, A=Africa. Black arrow (⇨) points towards more severe & orange arrow (→) points towards more evaporative DED.

6.3.5. Subtype

Worldwide, practitioners appear to have clearly established management algorithms for treating dry eye of each subtype. While practitioners reported prescribing advice, artificial tears and anti-inflammatories for both DED subtypes, the key approach for aqueous deficient DED involved punctal occlusion, therapeutic contact lenses and secretagogues, whereas, products containing essential fatty acids, lipids, lid hygiene, lid warming, in-office treatments and antibiotics were central to the treatment of evaporative DED Table 6.3.

Table 6.3. Proportion of practitioners that only use each therapy for a particular subtype of DED.

	ADDE	EDE
Essential fatty acids	2%	18%
Artificial tears	15%	7%
Ointments	7%	9%
Lipid-based products	1%	23%
Lid hygiene	2%	6%
Moisture chamber goggles	13%	11%
Punctal occlusion	32%	4%
Eyelid warming	2%	13%
In-office treatments	1%	14%
Topical antibiotics	2%	12%
Systemic antibiotics	1%	8%
Anti-inflammatories/Immunosuppressants	7%	3%
Secretagogues	7%	1%
Biologics	9%	8%
Therapeutic contact lenses	17%	2%
Other surgical approaches	4%	3%

ADDE = pure aqueous deficient dry eye; EDE = pure evaporative dry eye.

Some patients present with mixed DED, and display elements of both ADDE and EDE (Wolffsohn et al., 2017). These patients can be located anywhere along a continuum between the two extremes of pure ADDE or EDE. Between continents (Table 6.2), practitioners in Latin America reported prescribing ointments for patients with a greater aqueous deficient element, compared to those practising in Europe and Africa. Those in Africa, Europe and North America, recommended lid hygiene for patients with less severe evaporative disease than respondents in Asia/Middle East. Systemic antibiotics were prescribed for ADDE more in Africa, than in any other continent. Practitioners in North America and Latin America reported prescribing topical anti-inflammatories/ immunomodulators for patients with a greater degree of ADDE than those in Asia/Middle East, Europe and Australasia. Secretagogues were prescribed for aqueous deficient

patients more in Latin America than in Asia/Middle East. Finally, surgical approaches were performed for ADDE more commonly in Europe than in North America.

6.3.6. Management trends

Preservation of the survey format used in the original analysis allowed comparison of global practice patterns over time. Data extraction for the first survey took place in August 2019, and that of the current survey took place in May 2024.

Table 6.4 provides a summary of the changes in practice patterns over nearly 5 years, many of which were statistically significant. A higher proportion of respondents reported prescribing ointments, lipid containing lubricants, lid hygiene, warm compresses and in-office therapies, as well as pharmaceuticals, such as systemic antibiotics, topical anti-inflammatories/ immunosuppressants, secretagogues and biologics, compared to 2018-19. Practitioners are also prescribing systemic antibiotics for lower severities of DED than previously, but overall the severity at which treatments are being prescribed had changed by less than 5%. There were no statistically significant changes in the DED sub-classification each treatment was considered to be appropriate for.

Table 6.4. Overall change in prescribing patterns & changes in DED severity & subtype for which each treatment was considered appropriate, between 2019 & 2024 analyses. P<0.003 considered significant with Bonferroni correction for multiple testing.

Treatment	Change in use (%)	Significance (p)	Severity change (%)	Significance (p)	Subtype change (%)	Significance (p)
Advice	-4	0.059	+5	0.121	-1	0.753
Essential fatty acid supplements	+3	0.456	0	0.639	+1	0.696
Artificial tears	-4	0.014	+1	0.339	-2	0.236
Ointments	+11	**<0.001**	-2	0.179	-2	0.149
Lipid containing lubricants	+12	**<0.001**	-5	0.050	0	0.964
Lid hygiene	+18	**<0.001**	+1	0.923	0	0.117
Moisture chamber spectacles/ goggles	+5	0.482	0	0.698	-4	0.152
Punctal occlusion	+9	0.132	+1	0.843	-2	0.330
Warm compresses	+31	**<0.001**	0	0.450	+1	0.642
In-office therapies	+175	**<0.001**	-2	0.123	-1	0.338
Topical antibiotics	+10	0.055	-3	0.120	-2	0.178
Systemic antibiotics	+19	**<0.001**	-5	**0.002**	0	0.208
Topical anti-inflamm./ immunosupp.	+36	**<0.001**	-1	0.364	0	0.825
Secretagogues	+43	**<0.001**	-3	0.513	0	0.808
Biologics	+30	**<0.001**	-4	0.004	-1	0.264
Therapeutic CLs	+9	0.125	-2	0.294	-5	0.234
Surgical approaches	+11	0.329	-1	0.826	-1	0.601

For subtype change, '–' indicates more aqueous deficient dry eye and '+' more evaporative.

6.4. Discussion

The aim of this study was to determine how clinical management patterns differed depending on disease severity and subtype. Data collected from practitioners across the globe also allowed differences in dry eye management approaches between continents to be identified (Wolffsohn et al., 2021a). Furthermore, as the survey was conducted twice, it became possible to compare datasets, and reveal evolution in management strategies over time. Survey responses encompassed a broad spectrum of clinicians from over 50 countries, across 6 continents, ranging from newly qualified to seasoned practitioners with decades of experience. To our knowledge, this is a first series of studies to have tracked and compared the dry eye management patterns of eye care professionals around the world.

Completed surveys were received from 905 practitioners from across the globe, with a balance between optometrists and ophthalmologists, each with around 15 years of clinical practice experience, on average. The reason practitioners from some countries participated more in this unpaid survey than others is uncertain, and could be due to workload and how frequently they receive other survey invites. As found previously (Wolffsohn et al., 2021a), the most commonly seen patients were those with mild symptoms, and the least common were those with severe symptoms.

Many treatment options for DED were observed to be utilised by respondents. As environment and iatrogenic factors, such as air conditioning and contact lens wear can disrupt the homeostasis of the tear film, advice is critical at all levels of DED severity, as identified in the TFOS DEWS II Management and Therapy Report (Jones et al., 2017). Indeed, independent of severity and subtype, the most common management approaches were offering advice (82%) and recommending over-the-counter, low and high viscosity unpreserved lubricants and lid wipes/scrubs. “Step 1” interventions in the TFOS DEWS II management algorithm include patient education/advice, dietary advice, artificial tears and warm compresses (Jones et al., 2017), as they are conventional, low risk, and widely available management approaches suitable for early-stage disease. This study identifies these as the most commonly recommended management approaches, as reported in other studies (Downie et al., 2016, Williamson et al., 2014, Xue et al., 2017, Downie et al., 2013).

There was an increase in the preference for unpreserved artificial tears, versus preserved, with the ratio of prescriptions increasing from 1.3:1 in the 2018-19 survey, to 1.5:1 in 2023-24. This is supported by TFOS DEWS II guidance, which advises the use of preservative-free products where possible (Jones et al., 2017), and is facilitated by a wider range of unpreserved artificial tears having come to market in recent years. A greater proportion of lid wipes/scrubs was made up by

those developed specifically for Demodex control, rather than those for general lid cleansing. This may reflect greater product availability. There was also an increase in the use of commercial warm compresses, over homemade alternatives such as hot flannels which have been shown to rapidly fall below an effective temperature (Bitton et al., 2016, Borchman, 2019), to the point where these are now advised by the majority of practitioners. The number of practitioners using mechanical spinning brush tools for lid hygiene increased, matching that of lid margin debridement, which was previously favoured, however therapeutic expression was still used by more respondents. Another change was seen in the relative adoption of in-office treatments such as intense pulsed light therapy and combined inner lid warming and massage devices. Five years ago, a slightly greater proportion of practitioners were performing the latter, but this has reversed, and the balance is now 1.5 times in favour of light therapies. Intense pulsed light and low-level light therapies (Giannaccare et al., 2023) have been shown to be effective in improving symptoms and signs of DED (Xue et al., 2020), and an increasing number of clinics appear to be offering light therapies to their patients.

Practitioners licensed to prescribe ocular therapeutics appear to have refined their prescribing profiles since the previous survey. The global use of topical tacrolimus increased significantly, relative to lifitegrast (1.9:1 in 2024 versus 1.2:1 in 2019) and topical steroids (0.4:1 in 2023-24 versus 0.2:1 in 2018-19), which is presumed to be due to its favourable risk/benefit profile and availability. Therapeutic contact lenses were still used by more respondents than autologous/allogeneic serum and amniotic membrane, but the gap has closed somewhat, again possibly due to greater availability of biologic therapies. Finally, a greater number of respondents reported performing surgical procedures rather than intraductal probing, compared to the previous survey.

Some treatments were prescribed across all severity levels (scaled from 1 mild to 10 severe), such as advice (median 4.5, range 4.8), artificial tears (median 5.1, range 4.6) and nutritional supplements (median 5.3, range 4.2). Others were prescribed more frequently with increasing disease severity, for instance, biologics (median 8.2, range 2.8) and surgical approaches (median 8.1, range 2.2). This aligns with the principles of conservative medicine, where invasive and higher risk treatments are reserved for incalcitrant cases, or for those patients most debilitated by their symptoms.

While a similar number of practitioners reported prescribing advice, artificial tears and anti-inflammatories, regardless of DED subtype, the major reported approaches for managing aqueous deficient DED were punctal occlusion, therapeutic contact lenses and secretagogues.

In contrast, the use of oral essential fatty acids, topical lipid-containing products, lid hygiene and lid warming were the preferred management choices for evaporative DED (Table 6.3). Although some patients present with mixed dry eye, the vast majority are predominantly evaporative in nature, due to meibomian gland dysfunction (Craig et al., 2017a, Vidal-Rohr et al., 2024, Lemp et al., 2012). The combination of increased melting point/viscosity of meibum (Borchman, 2019), and excessive keratinisation of the ductal epithelium in meibomian gland dysfunction (Dietrich et al., 2021), results in terminal duct obstruction (Asbell et al., 2011) and a defective tear lipid layer. Treatments which address this deficiency are therefore important, in order to facilitate the normal functioning of the meibomian glands, restore tear film and ocular surface homeostasis and reduce evaporation of the underlying aqueous tear film.

Differences in management that respondents felt were appropriate for each severity and subtype of DED were noted between continents (Table 6.2), most notably with respect to less common advice or artificial tear prescribing in Latin America, lesser use of lipid-based products (shown to be beneficial in those with more EDE (Essa et al., 2018, Craig et al., 2021) outside Europe and Australasia and fewer prescriptions for antibiotics in Europe and anti-inflammatories along with secretagogues in Europe and Australasia. There were less intercontinental differences in prescribing according to subtype, with ointments used more for ADDE in Latin America, lid hygiene being used more for EDE in Asia and the Middle East, systemic antibiotics being used less commonly for evaporative dry eye in Africa and topical anti-inflammatories and immunomodulators being used less frequently for EDE in North and Latin America.

Retention of the original survey format allowed direct comparison of new data with the 2018-19 survey outcomes. It was found in the current survey that more respondents reported prescribing ointments, lipid containing lubricants, lid hygiene, warm compresses and in-office therapies, as well as pharmaceuticals, such as systemic antibiotics, topical anti-inflammatories/immunosuppressants, secretagogues and biologics. It may be that practitioners, increasingly, are attempting to treat the root causes of DED, in addition to the symptoms. Examples include treating meibomian gland dysfunction with warm compresses, lid hygiene and with systemic antibiotics, such as low dose doxycycline. Lipid-containing drops and sprays have gained greater popularity and enjoyed more widespread availability in recent years, as the importance of meibomian gland dysfunction and evaporative DED has become clearer (Essa et al., 2018, Craig et al., 2021). Practitioners are also prescribing systemic antibiotics at a lower DED severity threshold than previously, but largely the severity for which treatments are being prescribed experienced less than 5% change. There were no statistically significant changes in the treatments considered appropriate for specific DED sub-classification

categories, suggesting that clinicians consistently have a battery of treatments suited to each dry eye subtype.

Surveys are intrinsically susceptible to selection bias, as those choosing to respond are likely to be practitioners with more knowledge and experience of managing the condition, compared to their peers. There will always be significant variation in management approaches between practitioners, not least because each patient presents with their own unique challenges. In addition, the practitioner cohort will have differed between 2018-19 and 2023-24, creating noise in the comparison over time. It is also known that social desirability bias can affect the validity of questionnaires (King and Bruner, 2000). However, despite this, the findings significantly enhance our understanding of an important research area, and allow clinicians to benchmark their clinical practice against world norms, for the benefit of their patients.

7. Thesis summary, conclusions and future research directions

7.1. Thesis summary

There has been a great deal of advancement in the field of DED research, and interest and awareness has also increased markedly since the publication of the TFOS DEWS II reports in 2017. However, there are still gaps in the literature, as highlighted in chapter 1. For example, there are still relatively few RCTs comparing different artificial tear formulations to one another, as opposed to a placebo or vehicle (Jones et al., 2017, Pucker et al., 2016). There has been increasing interest in the molecular weight of hyaluronic acid, and its smaller semi-synthetic counterpart, sodium hyaluronate in artificial tears (Kojima et al., 2020). As previously identified by Hynnekleiv et al. (2022), there is a need for more research into the molecular weight of hyaluronan in artificial tears.

It was also necessary to establish which tests and diagnostic equipment were most appropriate for clinical data collection. To this end, an international prospective randomised clinical trial was conducted (chapter 2), which compared dry eye outputs generated by the novel Topcon MYAH device, to those from the Oculus K5M and traditional methods, such as the slit-lamp. One hundred and fifty participants symptomatic of DED were recruited and received detailed assessment. Thousands of individual images were analysed, taking many weeks. A key finding was that first non-invasive tear breakup time measured by the MYAH was grossly underestimated, resulting in wholesale overdiagnosis of DED, when using this metric. Meibomian gland loss was also overestimated, again indicating inaccuracy. It was therefore decided that the K5M, which had previously been validated for use in dry eye (Tian et al., 2016, Best et al., 2012), would be utilised for the collection of clinical data for the remainder of the thesis.

It was also necessary to evaluate the existing evidence specific to artificial tears, in order to identify knowledge gaps, and plan research to address them. Therefore, a systematic review of randomised controlled trials comparing artificial tear formulations to one another was conducted in chapter 3 (Semp et al., 2023). This established what was currently known, and where further work was warranted. Sixty-four RCTs were examined, analysed and evaluated, including conducting a Cochrane risk of bias analysis (appendix 2).

Studies showed that unpreserved artificial tears can be prescribed for patients with any subtype and severity of DED, with the addition of high-concentration liposomal formulations being beneficial for those with evaporative disease. Adherence to four times per day instillation is recommended to determine whether an artificial tear can manage patients' symptoms in the longer term. Signs of ocular surface disease typically take up to 4 months to start improving so

patience is needed. The most effective drop for an individual can be predicted from their baseline classification; drops containing phospholipids are more effective in those with evaporative dry eye (Craig et al., 2021, Essa et al., 2018) and osmoprotectants benefit those with high tear film osmolarity (Essa et al., 2018). As previously identified by Hynnekleiv et al. (2022), there was a lack of research evidence for molecular weight in artificial tears.

A prospective double-masked randomised crossover trial was conducted (chapter 4), in order to examine the clinical impact of molecular weight of sodium hyaluronate, which is commonly found in artificial tear formulations. Solution rheology testing was performed at the Centre for Industrial Rheology, using a research rheometer and shear rate profiling was performed across a wide range of shear rates. Twenty-five participants with DED were enrolled, and attended three visits each, where a single instillation of each drop was applied, and data was gathered at seven time points. The drop containing high molecular weight sodium hyaluronate demonstrated more non-Newtonian shear thinning properties. Comfort improved with all three drops, with no significant different between formulations, however Hylo-Forte performed best at most time points. Tear stability improved with drop instillation and then declined with time with all drops following a similar profile, however, HydraMed was unable to maintain tear stability after the first five minutes. Tear volume increased with drop instillation and then declined with time, with Evolve having a reduced initial effect compared to HydraMed and Hylo-Forte. Hence, although all three drops performed relatively similarly, some trends were identified, which warrant further investigation.

Artificial tears have long been the mainstay of DED management (Jones et al., 2017), however, in preventative medicine, it is important to target the root causes of disease, as well as the alleviation of symptoms. There is a growing understanding that most DED is predominantly evaporative in nature, mainly due to MGD (Craig et al., 2017a). This led to a study to compare a novel device for treating MGD to traditional debridement and expression techniques, in a prospective randomised controlled trial (chapter 5). Thirty participants with EDE and MGD were recruited and attended three visits each, one month apart, with fifteen each being randomised to treatment with either the MGrx device or traditional debridement and expression. Symptom questionnaire scores (OSDI, DEQ-5 and SANDE) all improved significantly with both treatments, with no subsequent deterioration for at least 8 weeks. Clinical signs (blink rate, tear film quality and quantity, ocular surface characteristics and meibomian gland expressability) were all unchanged in both treatment groups except for NIBUT, which deteriorated after conventional treatment, between four and eight weeks post treatment. No adverse reactions were reported, and all participants were able to tolerate treatment. The MGrx device was found to be an effective

option for the management of EDE, with potential time, space and cost savings, which could make treatment more accessible to patients.

Utilising the best currently available research evidence is central to evidence-based medicine; however, it is important to know how widely the latest and most effective treatments are being adopted by clinicians. Five years on from the original study (Wolffsohn et al., 2021a), and in light of recent developments and increased interest in DED, a second TFOS global survey was launched, allowing trends in clinical management patterns to be reassessed and tracked over time (chapter 6). Nine hundred and five clinicians were recruited in over fifty countries, across six continents. Clinical management patterns in DED were assessed, by severity, subtype and location. It was also possible to track trends in management in recent years, because the same questionnaire had been administered twice.

Some significant changes were identified, for example, there has been an increase in the popularity of lipid-containing artificial tears and lubricants, facilitated by greater product availability in the marketplace. Light therapies, such as IPL and LLLT have become more widely adopted, and now outnumber treatments with LipiFlow. More respondents report prescribing lid hygiene, warm compresses and in-office therapies, as well as pharmaceuticals, such as systemic antibiotics, topical anti-inflammatories/immunosuppressants, secretagogues and biologics. It may be that practitioners are increasingly attempting to treat the root causes of DED, in addition to the symptoms. There is still a need for more clinicians to adopt a more evidence-based mode of practice, in order to improve patient care.

7.2. Limitations

This thesis was not without its limitations. Ethically, it is generally accepted that the number of research participants should be limited to that which is necessary to power a study, based on sample size calculations (Sheppard and Shah, 2021). This was the case in this thesis, however the availability of suitable participants, willing to take part in clinical research, may have limited the number of participants with certain severities and subtypes of DED, resulting in underrepresentation in the study samples. This can impact generalisability to patients with differing disease characteristics. It could, however, be argued that this mirrors the relative prevalences found in the wider population, where less common presentations will, by definition, be fewer and further between.

Strict inclusion and exclusion criteria can also limit the generalisability of research findings to real-world clinical settings. It is therefore important to strike a balance between the need to exclude certain participants who are likely to induce confounding factors, for example those suffering from hay fever or infection, but including a range of clinical presentations commonly encountered in practice.

Bias and confounding factors can affect any research, for example, surveys are often prone to selection bias, as practitioners choosing to respond are likely to be those with more interest, knowledge and experience of DED, compared to their peers.

It is recognised that masking can reduce bias, but is not always practical to achieve, for example when conducting therapeutic treatments such as debridement and expression. However, where masking was not possible, effectiveness measurements were obtained using objective techniques, for example the automated detection of first tear breakup on the Oculus K5M, generated independently of investigator input.

7.3. Future research directions

As mentioned, the research in this study was subject to some limitations. It may, therefore, be beneficial to conduct further studies involving larger numbers of participants, for example to increase numbers of presentations from different severities and subclasses of DED.

In the case of artificial tear molecular weight, only a single instillation of each drop was used by each participant. This may have contributed to the resulting similarities seen in the performance of each formulation. For this reason, it would be desirable to increase the follow-up time, for example, to 4 weeks per drop, followed by a washout period, before switching to the next formulation.

In addition to artificial tears, one study examined to efficacy of a device for treating MGD. As this was found to be effective, it would be interesting to compare the MGrx treatment to, for example, intense puled light, low-level light therapy and/or a combination of the two. This could also be compared in participants using at-home self-treatments, such as warm compresses or chambered warm moist air devices, e.g. Blephasteam. It would also be desirable to establish whether debridement and expression makes other treatments more effective, if conducted prior to their commencement.

Of interest is whether DED management can be better tailored to the disease features presenting in a specific patient (Essa et al., 2018). The ability to predict the most effective treatment for a

given patient would be beneficial for both patients and practitioners. It would therefore be desirable to conduct treatments on patients with particular tear film and ocular surface biomarkers, in order to ascertain who receives the greatest treatment effect.

Furthermore, the principles of preventative medicine could be applied to patients with risk factors such as MGD, female sex and Asian race, to examine whether it would be appropriate to treat at-risk individuals before they become symptomatic. This could, for example take the form of eyelid warming and massage, or dietary supplements such as essential fatty acids. Longitudinal data from such a trial could be analysed to show whether the development of DED could be avoided, or future severity reduced.

7.4. Conclusions

DED results in a substantial burden, which is likely to increase, due to aging populations and environmental/lifestyle factors, such as increasing VDU use. The appropriate assessment and management of DED has a far-reaching impact, and is of high importance, yet adequate management of symptoms and signs remains challenging for practitioners and their patients. The overall aim of this thesis was to expand the research evidence-base, and translate it into patient care.

The definition of DED alludes to its complexity, and also the variety of aetiologies, symptoms and signs which it encompasses. It therefore follows that a single treatment is often insufficient in providing consistent and effective control of symptoms and signs. Good long-term control requires accurate diagnosis, subclassification and a tailored stepwise approach to management and therapy, as well as patient adherence to treatment.

Clinicians are rightly investing in an ever-increasing suite of electronic equipment to enhance their practice. When manufacturers develop new diagnostic devices, it is essential that practitioners can rely upon the accuracy and usability of their features. Prior to the release of a product, it would be helpful if there was greater collaboration between designers, researchers and practitioners, who will ultimately be the end-users.

Artificial tears are still the mainstay of DED management. The work in this thesis has confirmed that high molecular weight sodium hyaluronate has more non-Newtonian shear thinning properties, and that further research into its role in artificial tears is warranted. In EDE, which is by far the commonest form of DED, the addition of lipid-based products, such as unpreserved high-concentration liposomal drops, is also beneficial.

MGD is key in the pathophysiology of EDE and can lead to progressive loss of meibomian gland function. Lid warming, massage and cleansing, to facilitate the return towards normal physiology, is an important part of its management. The MGrx device has been shown to be effective and potentially advantageous for this purpose.

High quality research evidence is key to informing clinical practice, yet the rapid uptake of best practice does not necessarily follow. Time lags of around 17 years for the adoption of research findings in clinical practice have been suggested (Morris et al., 2011). It is therefore important that clinicians practice evidence-based medicine, and are kept informed of advances and research findings.

The work in this thesis has filled knowledge gaps and added to the evidence for artificial tears, which are still the mainstay of DED management, and treatments for MGD – the leading cause of evaporative DED. It has also added to the understanding of clinical management patterns globally. Furthermore, the dissemination of its findings, has ensured that they can be translated into clinical care. This has resulted in a significant contribution to the field of evidence-based management of dry eye, for the benefit of clinicians and their patients.

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Appendices

Appendix 1: PROSPERO registration for systematic review of artificial tears

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Systematic review

*Fields that have an **asterisk (*)** next to them means that they **must be answered. Word limits** are provided for each section. You will be unable to submit the form if the word limits are exceeded for any section. Registrant means the person filling out the form.*

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The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

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Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None

Grant number(s)

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13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

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Professor Wolffsohn receives research funding or consultancy from Alcon, Rayner, Scope and Thea

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Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Do the constituents of an artificial tear change its effectiveness in reducing ocular symptoms and signs related to dry eye?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

Web of Science, PubMed and MEDLINE from inception

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Dry eye disease

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Patients with dry eye disease, according to the TFOS DEWS II criteria or equivalent

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Artificial tear products: these are ocular lubricants and unmedicated comforting eye drops, gels, sprays etc

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

They are compared to each other

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

RCT, crossover, repeated measures

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Ocular symptoms and surface/tear film measures

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

None

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Questionnaires, tear film stability in seconds, Schirmer's strip length in mm and corneal staining grade

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Included if compare efficacy of one product to others. Data extracted will include symptom scores, tear breakup time, tear meniscus height, ocular redness, tear lipid layer grade, Schirmer test. This will be tabulated and presented in the paper

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

The Cochrane Risk of Bias 2 tool (Sterne et al., 2019) will be used for quality appraisal. As all dry eye symptoms are frequently assessed using the same assessment method, they will be considered a single outcome for the appraisal. The standard Risk of Bias parallel-group or crossover trial tool will be used as appropriate. Risk of Bias assessments will be completed independently by two assessors and discrepancies resolved through discussion. Where a competing interest is present (e.g. listed as an author), the remaining assessor will appraise the article alone.

Sterne JAC, Savovi? J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:I4898-I.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If metaanalysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

This is a systematic review of artificial tear products and their efficacy, compared to each other, in terms of improvements in symptoms and ocular surface signs. Studies comparing artificial tears with the same constituents will be grouped and the findings considered in terms of the effect size and risk of bias

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach. Some trials may sub-group participants by disease severity or type of dry eye (e.g. evaporative or aqueous deficient)

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

No

Individual patient data (IPD) meta-analysis

Intervention

No

Living systematic review

No

Meta-analysis

No

Methodology

No

Narrative synthesis

No

Network meta-analysis

No

Pre-clinical

No

Prevention

No

Prognostic

No

Prospective meta-analysis (PMA)

No

Review of reviews

No

Service delivery

No

Synthesis of qualitative studies

No

Systematic review

Yes

Other

No

Health area of the review

Alcohol/substance misuse/abuse

No

Blood and immune system Cancer

No

Cardiovascular

No

Care of the elderly

No

Child health

No

Complementary therapies

No

COVID-19

No

Crime and justice

No

Dental

No

Digestive system

No

Ear, nose and throat

No

Education

No

Endocrine and metabolic disorders

No

Eye disorders

Yes

General interest

No

Genetics

No

Health inequalities/health equity

No

Infections and infestations

No

International development

Mental health and behavioural conditions

No

Musculoskeletal

No

Neurological

No

Nursing

No

Obstetrics and gynaecology

No

Oral health

No

Palliative care

No

Perioperative care

No

Physiotherapy

No

Pregnancy and childbirth

No

Public health (including social determinants of health)

No

Rehabilitation

No

Respiratory disorders

No

Service delivery

No

Skin disorders

No

Social care

No

Surgery

No

Tropical Medicine

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

England

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Artificial tears, dry eye disease, keratoconjunctivitis sicca

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

None

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Appendix 2: Cochrane risk of bias analysis for systematic review of artificial tears

Registered articles: Outcomes registered vs reported (selective reporting analysis)

Paper	Title	Registration ID	Outcomes registered	Outcomes reported
Baudouin et al. 2012	Randomized, phase III study comparing osmoprotective carboxymethylcellulose with sodium hyaluronate in dry eye disease	NCT00987727	**Primary:** Change From Baseline in Global Ocular Staining Score at Day 35 **Secondary:** Change From Baseline in Ocular Surface Disease Index Questionnaire Score at Day 35	OSDI **TBUT (s)** **Schirmer I test (mm/5 min)** **Tear osmolarity (mOsm/L)** Total staining score Corneal staining score Nasal conjunctival staining score Temporal conjunctival staining score Data presented from 35 days and **3 months**
Chiambaretta et al. 2017	A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome	NCT02023268	Global Ocular Staining (With Oxford Scale - Ranges : 0-15)	A questionnaire on dry eye and symptoms, Schirmer test, tear break-up time, conjunctival hyperaemia, and global performance were assessed as secondary efficacy criteria at baseline, day 35, and day 84

Craig et al. 2021	Developing evidence-based guidance for the treatment of dry eye disease with artificial tear supplements: A six-month multicentre, double-masked randomised controlled trial	ACTRN12619000390189	**Primary:** Change in symptom score according to the Symptom Assessment iN Dry Eye questionnaire [Baseline, and 1, 2, 3, 4, 5 and 6 months (primary timepoint)] Change in symptoms according to the Ocular Surface Disease Index Questionnaire[Baseline, and 1, 2, 3, 4, 5 and 6 months (primary timepoint)] Change in tear film stability measured objectively as the non invasive keratograph break up time [Baseline, and 1, 2, 3, 4, 5 and 6 months (primary timepoint)] **Secondary:** Change in blink quality (blink completeness) by masked observation of infrared videos captured under infrared illumination[1, 2, 3, 4, 5 and 6 months from baseline] Change in blink rate (blinks per minute) by masked observation of infrared videos captured under infrared illumination[Baseline, and 1, 2, 3, 4, 5, and 6 months]	OSDI SANDE **DEQ-5** **BCVA** Blinking assessment Conj. redness TMH NITBUT Lipid layer grade Osmolarity Slit-lamp exam Surface staining LWE MG expressibility Meibography **Lid margin thickening grade** **Lid margin rounding grade** **Lid margin notching grade** **Lid margin foaming grade** **Lid margin telangiectasia grade** **Meibomian gland capping grade** **Staphylococcal lash crusting grade** **Seborrhoeic lash crusting grade** **Demodex lash cylindrical dandruff grade** **Meibum quality**

			Change in bulbar hyperemia measured objectively by the Oculus Keratograph 5M [Baseline, and 1, 2, 3, 4, 5, and 6 months] Change in lid wiper epitheliopathy visualised with slit-lamp biomicroscopy following application of vital dyes (sodium fluorescein, lissamine green)[Baseline, and 1, 2, 3, 4, 5, and 6 months] Change in meibomian gland expressibility evaluated with the application of a consistent pressure from the Meibomian Gland Evaluator[1, 2, 3, 4, 5 and 6 months from baseline] Change in ocular surface staining highlighted by application of vital dyes (sodium fluorescein, lissamine green) and visualised by slit-lamp biomicroscopy[Baseline, and 1, 2, 3, 4, 5, and 6 months] Change in percentage meibomian gland drop out, assessed by a masked observed from infrared images captured with the Oculus	

			Keratograph 5M.[6 months from baseline] Change in tear meniscus height measured with digital callipers from a still image captured under infra red illumination with the Oculus Keratograph 5M[Baseline, and 1, 2, 3, 4, 5, and 6 months] Change in tear osmolarity evaluated with the TearLab Osmometer [Baseline, and 1, 2, 3, 4, 5, and 6 months] Lipid layer grade (LLG) evaluated from masked grading of interferometric patterns recorded with the Oculus Keratograph 5M [Baseline, and 1, 2, 3, 4, 5, and 6 months]	
Downie et al. 2020	An artificial tear containing flaxseed oil for treating dry eye disease: A randomized controlled trial	NCT02553772	OSDI change, TBUT change, corneal stain change, conj stain change, Schirmer change	**Match**
Essa et al. 2018	Can the optimum artificial tear treatment for dry eye disease be predicted from presenting signs and symptoms?	NCT02420834	OSDI, NIBUT, TMH, LIPCOF, surface staining (NaFl and lissamine), phenol red test	**Match**

Fogt et al. 2019	Changes in Tear Lipid Layer Thickness and Symptoms Following the Use of Artificial Tears with and Without Omega-3 Fatty Acids: A Randomized, Double-Masked, Crossover Study	NCT03380624	Change in Tear Lipid Layer Thickness [Time Frame: 15 minutes]	Reported at 15 mins **and 60 mins**
Fondi et al. 2018	Effect of Hyaluronic Acid/Trehalose in Two Different Formulations on Signs and Symptoms in Patients with Moderate to Severe Dry Eye Disease	NCT02980913	Primary: Number of drops of Thealoz Duo® eye drops and Thealoz Duo® gel instilled during the day (patient diary) [Time Frame: 4 weeks] Secondary: 1. Tear Break Up Time [Time Frame: 4 weeks] 2. Schirmer I test [Time Frame: 4 weeks] 3. Conjunctival and corneal staining [Time Frame: 4 weeks] 4. OSDI questionnaire [Time Frame: 4 weeks] 5. Quality of life of patients (VAS) [Time Frame: 4 weeks]	Corneal and conj staining, TBUT, instillation frequency and quality of life, Schirmer – reported as one week, but this was due to crossover design?

Jerkins et al. 2020	A Comparison of Efficacy and Safety of Two Lipid- Based Lubricant Eye Drops for the Management of Evaporative Dry Eye Disease	NCT02776670	**Primary:** Mean Change From Baseline in Tear Film Break-Up Time (TFBUT) at Day 35 **Secondaries:** Change From Baseline in TFBUT at Day 35. Lipid Layer Thickness (LLT) Area Under the Curve (AUC120) at Day 35. Mean Change From Baseline in Global Ocular Discomfort Visual Analog Scale Score at Day 35.	**Primary:** TFBUT **Secondary:** VAS **'Exploratory':** **LWE** **IDEEL scores for treatment effectiveness and treatment inconvenience scores**
Labetoulle et al. 2018	Efficacy and safety of dual-polymer hydroxypropyl guar- and hyaluronic acid-containing lubricant eyedrops for the management of dry-eye disease: a randomized double-masked clinical study	NCT02470429	Primary: Change From Baseline in Total Ocular Surface Staining (TOSS) Score at Day 42. Secondary: Change From Baseline in IDEEL Treatment Effectiveness Score at Day 42. Change From Baseline in IDEEL Treatment Inconvenience Score at Day 42. Change From Baseline in Tear Film Break-up Time (TFBUT) at Day 42.	Match **Exploratory end points also reported in subset of 30 participants**

Laihia et al. 2020	Disease aetiology-based design of multifunctional microemulsion eye drops for moderate or severe dry eye: a randomized, quadruple-masked and active-controlled clinical trial	NCT03569202	**Primary:** Change From Baseline OSDI Change From Baseline Tear Osmolarity Change From Baseline TBUT **Secondary:** Change From Baseline Blink Rate Change From Baseline Ocular Protection Index (OPI) Change From Baseline Corneal Staining Change From Baseline Conjunctival (Temporal) Staining Change From Baseline Conjunctival (Nasal) Staining **Other:** Change From Baseline Visual Acuity Change From Baseline Conjunctival Redness	TBUT OPI Tear osmolarity Corneal, conj staining Lid redness OSDI VA (ETDRS) IOP Match

			Change From Baseline Lid Redness Change From Baseline Intraocular Pressure	
Lievens et al. 2019	Evaluation of an enhanced viscosity artificial tear for moderate to severe dry eye disease: A multicenter, double-masked, randomized 30-day study	NCT02280473	**Primary:** Change From Baseline in the Ocular Surface Disease Index Score [day 7] **Secondary:** Change From Baseline in the OSDI Score [day 30] Change From Baseline in Tear Break-up Time [day 30] Change From Baseline in the Combined Corneal and Conjunctival Staining Scores [day 30] Change From Baseline in the Schirmer Test [day 30]	OSDI, 7 and 30 days TBUT Staining Schirmer Match

Muntz et al. 2020	Prophylactic action of lipid and non-lipid tear supplements in adverse environmental conditions: A randomised crossover trial	ACTRN12619000361101	**Primary:** Lipid layer grade evaluated by a masked observer from interferometric video images captured on the Ocular Keratograph 5M[Baseline 10 minutes after drop instillation Within 5 minutes of adverse environment exposure (primary endpoint)] Non-invasive tear film stability measured objectively by the Oculus Keratograph 5M[Baseline 10 minutes after drop instillation Within 5 minutes of adverse environment exposure (primary endpoint)] **Secondary:** Bulbar hyperaemia quantified objectively by the Oculus Keratograph 5M[Baseline 10 minutes after drop instillation Within 5 minutes of adverse environment exposure] Lid Wiper Epitheliopathy [At screening Following adverse environment exposure]	SANDE NITBUT Lipid layer grade TMH Bulbar & limbal redness Match

			Symptom severity evaluated on a visual analogue scale[Baseline 10 minutes after drop instillation Within 5 minutes of adverse environment exposure] Tear Meniscus Height quantified using the digital callipers of the Oculus Keratograph 5M[Baseline 10 minutes after drop instillation Within 5 minutes of adverse environment exposure]	
Park et al. 2017	A Randomized Multicenter Study Comparing 0.1%, 0.15%, and 0.3% Sodium Hyaluronate with 0.05% Ciclosporin in the Treatment of Dry Eye	KCT0001796	**Primary:** Changes in corneal staining score **Secondary:** Changes in conjunctival staining score Changes in corneal staining score Changes in meibomian gland dysfunction grading score Changes in OSDI score Changes in Schirmer's I test score Changes in TBUT (tear break-up time)	NaFl corneal staining Lissamine conj. staining TBUT Schirmer OSDI MGD **Match**

Perez-Balbuena et al. 2016	Efficacy of a fixed combination of 0.09 % xanthan gum/0.1 % chondroitin sulfate preservative-free vs polyethylene glycol/ propylene glycol in subjects with dry eye disease: a multicenter randomized controlled trial	NCT01657253	**Primary:** Ocular Surface Disease Index Questionnaire **Secondary:** Schirmer Test Tear Film Break up Time	OSDI Schirmer TBUT **Match**
Postorino et al. 2018	Efficacy of eyedrops containing cross-linked hyaluronic acid and coenzyme Q10 in treating patients with mild to moderate dry eye	NCT03074344	**Primary:** OSDI Corneal & conj staining **Secondary:** VA IOP Fundus exam TBUT Corneal esthesiometry	OSDI Staining **MGD assessment** Corneal aesthesiometry TBUT **IVCM** VA IOP Fundus
Robert et al. 2016	Efficacy and safety of a cationic emulsion in the treatment of moderate to severe dry eye disease: a randomized controlled study	EudraCT database: 2011-A00955-36 with the protocol code number NVG11F120	Could not find registry entry	

Simmons et al. 2015a	Comparison of novel lipid-based eye drops with aqueous eye drops for dry eye: a multicenter, randomized controlled trial	NCT01459588	**Primary:** OSDI **Secondary:** Change in TBUT Change From Baseline in Corneal Staining Change From Baseline in Conjunctival Staining Change From Baseline in Schirmer Test Results	OSDI TBUT Schirmer Corneal stain Conj stain **Match**

Simmons et al. 2015c	Efficacy and safety of two new formulations of artificial tears in subjects with dry eye disease: a 3-month, multicenter, active-controlled, randomized trial	NCT01294384	**Primary:** Change From Baseline in Ocular Surface Disease Index Score **Secondary:** Change From Baseline in Visual Analog Symptom Scale: Dryness Percentage of Participants Much Better or Better in Near Visual Acuity (Low Contrast) Percentage of Participants Much Better or Better in Near Visual Acuity (High Contrast) Change From Baseline in Tear Break-Up Time Change From Baseline in Corneal Staining Change From Baseline in Conjunctival Staining Change From Baseline in Schirmer Test	OSDI Corneal staining Conj staining VAS **Visual disturbance questionnaire** Schirmer High and low contrast reading TBUT

Szegedi et al., 2018	Effect of Single Instillation of Two Hyaluronic Acid-Based Topical Lubricants on Tear Film Thickness in Patients with Dry Eye Syndrome	NCT03161080	**Primary:** Change in tear film thickness [Time Frame: 1 day] **Secondary**: Change in lipid layer thickness [Time Frame: 1 day] Tear Break Up Time [Time Frame: 2 weeks] Visual Analogue Scale [Time Frame: 2 weeks] Schirmer I test [Time Frame: 2 weeks] Ocular Surface Disease Index score [Time Frame: 1 day] Corneal fluorescein staining [Time Frame: 2 weeks] Visual acuity [Time Frame: 2 weeks] Intraocular pressure (IOP) [Time Frame: 1 day]	Tear film thickness time course BUT Corneal stain LLT VAS Schirmer I OSDI Corneal fluorescein staining VA IOP

Waduthantri et al. 2012	Lubricant with Gelling Agent in Treating Dry Eye in Adult Chinese Patients	NCT00796926	**Primary:** VAS **Secondary:** Corneal Fluorescein Staining Score Tear Break Up Time Schirmer I Reading Meibography Grading Tear Osmolarity (TearLab) Superior and Inferior Tear Meniscus Height (AS OCT)	VAS TBUT Schirmer Corneal stain **Not reported:** **Meibography** **Tear osmolarity** **TMH (AS OCT)** One outlier was excluded due to SANDE score deteriorating very significantly

Cochrane risk of bias ratings

Paper	Random sequence generation (R)	Allocation concealment (C)	Blinding of Px and personel (M)	Blinding of outcome assessment (O)	Incomplete outcome data (I)	Selective reporting (S)	Other bias (B)
Baudouin et al. 2012	Unspecified randomisation RATED: ?	Not mentioned RATED: ?	Masking only of investigators RATED: -	No RATED: ?	Yes RATED: –	35 day data not reported RATED: –	Compliance etc not reported RATED: ?
Chiambaretta et al. 2017	Unspecified randomisation: ?	"lack of blinding of the patients to their treatment allocation": -	'investigator masked' only: -	?	No ITT analysis?: ?	See outcomes registered vs reported: -	Compliance etc not reported: ?
Craig et al. 2021	"Computer-generated random number allocation": +	"Investigator involved in baseline participant assessment had no involvement in treatment allocation" +	"Product labels were removed, and customised labels applied to obscure contents" +	+	ITT analysis, 0 excluded from analysis: +	See outcomes registered vs reported: -	"Returned eyedrop bottles were weighed at each visit to determine patient compliance" +
Downie et al. 2020	"Randomisation scheme was prepared by the sponsor's biostatistics group": +	"Managed using an interactive response technology system": +	"Products were supplied by the study sponsor in identical 0.4-mL unit-dose vials": +	"Treatment allocation(s) were concealed from the site investigators & Study subjects": +	ITT analysis: +	See outcomes registered vs reported: +	Compliance etc not reported: ?

Paper	Random sequence generation (R)	Allocation concealment (C)	Blinding of Px and personel (M)	Blinding of outcome assessment (O)	Incomplete outcome data (I)	Selective reporting (S)	Other bias (B)
Essa et al. 2018	Unspecified randomisation: ?	?	Single-masked: -	?	No missing data: +	See outcomes registered vs reported: +	Compliance etc not reported: ?
Fogt et al. 2019	?	?	'Px masked, examiner not masked, but analysis masked': -	?	+	See outcomes registered vs reported: -	compliance etc not reported ?
Fondi et al. 2018	Unspecified randomisation: ?	?	'observer-masked' -	?	"Statistical analysis was done "per protocol." ?	See outcomes registered vs reported: +	compliance etc not reported ?
Jerkins et al. 2020	"randomization codes were generated using an interactive response technology system" +	+	Method not stated ?	?	No ITT analysis -	See outcomes registered vs reported: +	compliance etc not reported ?
Labetoulle et al. 2018	"interactive response technology system" +	+	Method not stated ?	?	"All randomized patients were included in the intent-to-treat and safety analyses" +	See outcomes registered vs reported: +	compliance etc not reported ?

Paper	Random sequence generation (R)	Allocation concealment (C)	Blinding of Px and personel (M)	Blinding of outcome assessment (O)	Incomplete outcome data (I)	Selective reporting (S)	Other bias (B)
Laihia et al. 2020	"Randomization lists for Parts 2 and 3 were prepared by a randomization expert (4Pharma, Turku, Finland)" +	+	"complete masking of product identity from participants, healthcare providers, data collectors and statisticians" +	+	"Statistical analyses were performed primarily on the intention-to-treat (ITT) population of Part 3 comprising all randomized subjects who received a study treatment at least once and from whom subsequent efficacy measurements were available" +	See outcomes registered vs reported: +	Compliance reported +

Paper	Random sequence generation (R)	Allocation concealment (C)	Blinding of Px and personel (M)	Blinding of outcome assessment (O)	Incomplete outcome data (I)	Selective reporting (S)	Other bias (B)
Lievens et al. 2019	"automated Interactive Voice Response System" +	+	"identical 15-mL bottles"+	+	"The intent-to-treat (ITT) population consisting of all randomized subjects was used for efficacy analysis based on the randomized treatment."+	See outcomes registered vs reported: +	Compliance reported+
Muntz et al. 2020	"computer-generated randomised schedule determined prior to participant enrolment"+	+	"identically concealed bottles+"	+	All patients completed the study +	See outcomes registered vs reported: +	Compliance etc not reported ?

Paper	Random sequence generation (R)	Allocation concealment (C)	Blinding of Px and personel (M)	Blinding of outcome assessment (O)	Incomplete outcome data (I)	Selective reporting (S)	Other bias (B)
Park et al. 2017	"Central randomization was adopted for assigning patients to each group using a dynamic allocation of stratified centers" +	?	"masked conditions for the investigators; the perfect masked conditions could not be accomplished.." -	?	"All patients who were enrolled in the study were included in the efficacy and safety analyses" +	See outcomes registered vs reported: +	Compliance etc not reported ?
Perez-Balbuena et al. 2016	"random numbers software" +	"investigators were masked" ?	'instilled away from investigators.' 'labels removed etc' +	?	"An intent-to-treat analysis was performed." +	See outcomes registered vs reported: +	Compliance reported +
Postorino et al. 2018	"randomization scheme, corresponding to allocation codes generated for the 2 treatments using the permuted block method" +	"subjects were randomly divided into 2 groups and assigned to a treatment by personnel not involved with the patients' examination" +	Single-masked -	?	6 failed screening and no ITT reported ?	See outcomes registered vs reported: -	Compliance partially reported ?

Paper	Random sequence generation (R)	Allocation concealment (C)	Blinding of Px and personel (M)	Blinding of outcome assessment (O)	Incomplete outcome data (I)	Selective reporting (S)	Other bias (B)
Robert et al. 2016	"Treatments were allocated according to a sequential randomization list, by blocks, prepared in advance by the clinical supplies distributor LC2"+	"the investigator (who distributed the treatments) masked to treatment allocation"?	'investigator masked'-	?	All efficacy analyses were carried out on the full analysis set (FAS) and the per protocol (PP) set. +	See outcomes registered vs reported: +	Compliance etc not reported ?
Simmons et al. 2015a	"computer-generated randomization scheme" +	Not reported ?	'investigator masked' -	?	"The intent-to-treat population consisted of all randomized subjects and was used for all efficacy analyses" +	See outcomes registered vs reported: +	Compliance etc not reported ?

Paper	Random sequence generation (R)	Allocation concealment (C)	Blinding of Px and personel (M)	Blinding of outcome assessment (O)	Incomplete outcome data (I)	Selective reporting (S)	Other bias (B)
Simmons et al. 2015c	"computer-generated random allocation scheme" +	"Treatment kits were dispensed to subjects as directed by an automated response system" +	"virtually identical 15-mL bottles and cartons" +	?	"The primary efficacy analysis used the ITT population of all randomized subjects and last observation carried forward (LOCF) for missing values." +	See outcomes registered vs reported: +	Compliance etc not reported ?
Szegedi et al., 2018	Randomisation method not specified ?	Not specified ?	"Single-masked, observer blinded" -	-	"Statistical analysis was done as a "per protocol" analysis." No drop-outs etc.+	See outcomes registered vs reported : +	"At baseline, TFT was significantly higher in the NaCl group" ?

Paper	Random sequence generation (R)	Allocation concealment (C)	Blinding of Px and personel (M)	Blinding of outcome assessment (O)	Incomplete outcome data (I)	Selective reporting (S)	Other bias (B)
Waduthantri et al. 2012	"A simple randomization process of picking the participants for each group from 30 blinded stubs was used" +	Not reported ?	"Both study examiners and patients were masked to the type of treatment received by each patient. Masking was done by putting the bottles in a paper bag and removing the commercial labels" +	+	No missing data? +	See outcomes registered vs reported: -	"Amount of study eye drops used were monitored throughout the period" +

Appendix 3: Publications, conferences and awards

Publications

David A Semp, Danielle Beeson, Amy L Sheppard, Debarun Dutta & James S Wolffsohn (2023) Artificial Tears: A Systematic Review, Clinical Optometry, 9-27, DOI: 10.2147/ OPTO.S350185

Semp, D, Dutta, D. and Wolffsohn, JS, 2023. The clinical efficacy of higher molecular weight sodium hyaluronate in artificial tears: A randomised clinical trial. *Investigative Ophthalmology & Visual Science*, *64*(8), pp.3970-3970

James S Wolffsohn, David A Semp, Debarun Dutta, Lyndon Jones, Jennifer P Craig and the TFOS ambassadors. Clinical practice patterns in the management of dry eye disease: A TFOS international survey 2023-4 (in print)

Michael TM Wang, Jennifer P Craig, Lyndon Jones, David A Semp, Sonia T Huarte, James S Wolffsohn and the TFOS Ambassadors. Clinical practice patterns in the diagnosis of dry eye disease: a TFOS international longitudinal survey (in print)

Conferences

- Interdisciplinary Postgraduate Research Conference 2022: Delegate
- ARVO 2023: Oral presentation
- IACLE World Congress 2023: Delegate and volunteer representing Aston University
- BCLA 2023: Oral presentation
- Interdisciplinary Postgraduate Research Conference 2023 (poster presentation & organising committee member)
- 100% Optical 2024: Data collection for TFOS practice patterns survey
- Optometry Tomorrow incorporating BCLA 2024: Data collection for TFOS practice patterns survey
- AAO 2024: Poster presentation and Ezell Followship Award recipient

Awards

- American Academy of Optometry 2024 Merton C. Flom Leadership Ezell Fellowship
- Inspiring Success 2024 Optometry Hero Finalist